RESEARCH ARTICLE

A case-control study and meta-analysis reveal the association between COX-2 G-765C polymorphism and primary end-stage hip and knee osteoarthritis

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Background: Osteoarthritis (OA) is a popular arthrosis featured as pain, limited joint activity, and deformity. Cyclooxygenase-2 (COX-2) has been reported to be up-regulated in arthritic tissues and is integral to the progression of osteoarthritis (OA). Previous studies showed the COX-2 promoter G-765C polymorphism could influence COX-2 expression. However, the relationship between the variant and OA risk is contrasting.

Methods: We conducted a case-control study with 196 primary end-stage hip and knee OA cases and 196 controls in a Chinese Han population. Subsequently, we integrated this case-control study in a meta-analysis to acquire greater statistical power. The results from our case-control study using MassARRAY genotyping technology and binary logistic regression statistical methods.

Results: The variant carriers in the Chinese Han population had a lower primary end-stage hip and knee OA susceptibility (C vs G: OR = 0.350, 95%CI: 0.154-0.797, $P = .012$; GC vs GG: adjusted OR = 0.282, 95%CI: 0.118-0.676, $P = .005$). Stratification studies indicated that a higher GC frequency in women decreased not only knee OA susceptibility but also unilateral knee OA risk. The meta-analysis showed that the variant exhibited a significantly decreased OA risk through comparisons involving allelic, homozygous, heterozygous, and dominant models.

Conclusion: Our findings suggest that the COX-2 G-765C polymorphism exerts a protective effect against primary end-stage knee osteoarthritis in a female Chinese Han population.

KEYWORDS

COX-2, G-765C, osteoarthritis, polymorphism, PTGS2

1 | INTRODUCTION

Osteoarthritis (OA) is the most prevalent chronic arthrosis in the elderly and affects approximately 9.6% of males and 18% of females over 60 years of age.^{1,2} Pathological features of OA involve progressive cartilage loss, subchondral bone sclerosis, bone cyst, and osteophyte formation, different degrees of synovitis as well as alterations

of the tissues in and surrounding the synovial joint.^{3,4} Pain, limitation of movement, and deformity are the main symptoms in OA patients; nowadays, we can only partially control the disease but have no disease-modifying therapeutics to slow OA progression until the end-stage, which is when joint replacement is necessary.⁵ Currently, obesity, female gender, old age, previous joint injuries, bone density, and hormonal status have been confirmed as risk factors for OA.⁶⁻⁸

Additionally, multiple genetic signals have also shown an association with OA, which provided clear evidence that genetics is involved in the onset and progress of OA.⁹⁻¹²

To date, there has been accumulating evidence from clinical, histological, and molecular studies that support the view that OA is a low-grade, chronic inflammatory disease rather than a wear and tear process.¹³⁻¹⁵ Among numerous risk genes involved in the inflammatory process, the gene COX-2 (also known as *PTGS2*) located on 1q31.1 contains 10 exons and encodes for COX-2, which is a key enzyme that participates in the process of converting arachidonic acid into prostaglandins (<http://ncbi.nlm.nih.gov/gene/5743>). Robust expression of COX-2, as well as its elevated downstream prostaglandin E2 (PGE2) level, has been confirmed in OA patients.^{16,17}

In addition to growing evidence indicating that the COX-2-PGE2 axis is involved in the pathogenesis of OA, several genetic single nucleotide polymorphisms (SNPs) in COX-2 have also shown an association with OA susceptibility.^{9,18} G-765C (rs20417) is one of the most investigated polymorphisms due to its location in the promoter of COX-2, and it may affect COX-2 expression by altering the transcription factor binding site.¹⁹ Additionally, the -765C allele possessed significantly lower promoter activity (30%) compared to the -765G allele.²⁰ The linkage between the COX-2 G-765C polymorphism and OA susceptibility has been studied in German and Turkish populations with conflicting results.^{21,22} However, there are no published studies about the relationship in a Chinese Han population.

To determine the precise relationship between the COX-2 G-765C polymorphism and OA risk, we performed a case-control study and then added the results to a meta-analysis to acquire higher statistical power to evaluate the impact.

2 | MATERIALS AND METHODS

2.1 | Case-control study

2.1.1 | Participants

In total, 196 cases with hip or knee OA from October 2016 to May 2017 were recruited from the Department of Orthopaedics at the First Affiliated Hospital of Anhui Medical University and the Department of Orthopaedics at the Anhui Provincial Hospital as a case group and 196 healthy subjects whose body mass index (BMI) was close to cases from volunteers were recruited as a control group. Inclusion and exclusion criteria were as follows: (i) the diagnosis of primary hip and knee osteoarthritis conformed to the criteria from the American College of Rheumatology,^{23,24} (ii) radiographic changes were grade III or IV according to the Kellgren and Lawrence classification method,²⁵ and (iii) rheumatoid arthritis, and patients suffering from OA induced by trauma, inflammation, tuberculosis, or sepsis were excluded.

Written informed consent was obtained from all subjects, and the research was authorized by the Ethics Committees of the two hospitals.

2.1.2 | Genomic DNA preparation and genotyping analyses

Two milliliters of peripheral venous blood was collected aseptically from every subject, and genomic DNA was extracted from every sample using the QIAamp[®] DNA Blood Mini Kit (Qiagen, Cat.No.51106) according to the manufacturer's guidelines. The quality of the genomic DNA was assessed through NanoDrop 2000 (Thermo Fisher, USA) at the optical density 260/280 nm. All the DNA samples were stored at -20°C until analysis. The primers used to identify rs20417 genotypes were 5'-ACGTTGGATGACTGTTCTCCGTACCTTCAC-3' as first-PCR, 5'-ACGTTGGATGACAGGGTAACTGCTTAGGAC-3' as second-PCR, and 5'-ccccTGAGGAGAATTACCTTTCCC-3' as UEP SEQ. The genotyping was performed using MassARRAYNanodispenser RS1000 (Agena Bioscience). The detailed methods were described by Stacey et al.²⁶ Finally, all the data were analysed using Typer 4.0 software (Sequenom).

2.1.3 | Statistical analyses

We analysed the data using a Pearson chi-square test or Independent-Samples *t* test to detect differences in age, gender, and body mass index (BMI) between the groups. The Hardy-Weinberg equilibrium (HWE) of the controls was calculated ($P = .405$) from goodness-of-fit chi-square statistics before analysis. Relationships between genotypes of rs20417 and OA susceptibility were assessed by odds ratios (ORs) with 95% Confidence intervals (CIs) using a binary logistic regression test with or without adjustments for age, gender, and BMI. The P value < .05 was deemed significant. All statistical analyses were conducted using SPSS 16.0 software (SPSS Inc., Chicago, IL, United States).

2.2 | Meta-analysis

2.2.1 | Literature search strategy, inclusion criteria, and data extraction

We searched PubMed, Embase, and Web of Science up to 1st August 2017 using the following search terms: ("osteoarthritis" OR "arthriti" OR "ostarthriti" OR "arthrophlogosis") AND ("cyclooxygenase-2" OR "COX-2" OR "PTGS2") AND ("polymorphism" OR "mutation" OR "variant" OR "variation" OR "SNP"). Additionally, we scanned reference lists of reviews and meta-analyses to identify other eligible studies. Identification and selection of the studies for meta-analysis were shown in PRISMA flow-diagram (Figure S1).

In our meta-analysis, the following criteria were used for selected studies: (i) the study should assess the linkage between the COX-2 G-765C polymorphism and hip or knee osteoarthritis; (ii) the study should concern primary hip and knee osteoarthritis with grade III or IV radiographic changes based on the Kellgren and Lawrence classification method; (iii) the study should be a case-control study; and (iv) the study should provide an OR and 95% CI directly or allow them to be calculated from sufficient data in the article.

Our case-control study conformed to the inclusion criteria, and the data were included in the meta-analysis.

Two reviewers (Wei Huang and Chen Deng) independently extracted the following information from every study: name of the first author, publication year, country, diagnosis criteria, and radiographic changes, numbers of patients and controls, the genotype of participants, and the consistency of genotype and allele frequencies with HWE. Additionally, conflicting results were referred to a third investigator.

2.2.2 | Statistical analysis

Five genetic models, including the allelic model, homozygous model, heterozygous model, dominant model, and recessive model were compared. A goodness-of-fit chi-square test was applied in a control group to evaluate HWE. The chi-square test based Q-test was adopted to evaluate heterogeneity²⁷ and the I squared value (I^2) for measuring inconsistency among studies.²⁸ A random-effects model was utilized for pooled results when high heterogeneity was observed ($P < .10$ or $I^2 > 50\%$).²⁹ Otherwise, a fixed model was adopted. Sensitivity analysis was assessed by removing each study in turn. $P < .05$ was deemed statistically significant, except for the specified conditions (statistical significance of chi-square test based Q-test was accepted for $P < .10$). We conducted meta-analysis using STATA software 12.0 (Stata Crop, College Station, TX).

3 | RESULTS

3.1 | Case-control study

Basic characteristics of the 196 OA cases and 196 controls are shown in Table 1. There was a significant difference ($P < .001$) in age between the case group (63.2 ± 9.6 years) and control group (56.6 ± 6.1 years), whereas there were no differences in the gender and BMI distributions ($P > .05$). The attributes of age, gender, and

TABLE 1 Basic characteristics of cases and controls in the study

Variable	Patients	Controls	P value
Sample size	N = 196	N = 196	
Age (years)	63.2 ± 9.6	56.6 ± 6.1	$P^a < .001^*$
Gender			
Female	128	118	$P^b = .296$
Male	68	78	
Body mass index (Kg/m ²)	25.6 ± 3.6	25.7 ± 3.2	$P^a = .741$
Type of OA			
Hip	62	/	
Knee	134	/	
Unilateral OA	109	/	
Bilateral OA	87	/	

Data of age and body mass index presented as mean $\pm$ SD.

P^a value from independent-samples T test and P^b value from Pearson chi-square test.

*P value indicates $P < .05$.

BMI were adjusted with the binary logistic regression method to eliminate confounding factors.

The genotypes and allele frequencies of the rs20417 are demonstrated in Table 2. Our present data showed that the frequency of the C allele was lower in cases (2.1%) compared to controls (5.6%), and there was a reduced OA risk (OR = 0.350, 95%CI: 0.154-0.797, $P = .012$). Furthermore, the distribution of heterozygous GC in OA cases also differed from controls (4.1% vs 11.2%) and GC carriers showed lower OA susceptibility (OR = 0.337, 95%CI: 0.146-0.776, $P = .011$) even after adjustment for age, gender, and BMI (OR = 0.282, 95%CI: 0.118-0.676, $P = .005$).

We also performed stratification studies to evaluate the linkage between the COX-2 G-765C polymorphism and different OA types based on gender, arthritic position (hip or knee), and unilateral or bilateral OA. GC frequency was lower in knee OA patients compared to control groups (5.2% vs 11.2%), and they showed decreased knee OA predisposition when adjusted for age, gender, and BMI (OR = 0.280, 95%CI: 0.102-0.769, $P = .014$). Furthermore, when stratified by gender, we saw in women that lower GC frequency increased not only knee OA susceptibility but also unilateral knee OA risk compared to the controls after adjusting for age, gender, and BMI (OR = 0.328, 95%CI: 0.116-0.922, $P = .035$, OR = 0.260, 95%CI: 0.037-0.925, $P = .037$, respectively). Other differences between male hip OA and bilateral OA from the control group were not significant regardless of whether there was an adjustment for confounding factors ($P > .05$). (Table 3).

3.2 | Meta-analysis

Overall, 2 published studies were extracted from databases and combined with our present case-control study (3 articles altogether) for the meta-analysis. Table S1 shows the characteristics of the 3 included studies. Of the three studies, two were performed in Caucasians, and our work was performed in Asians. Three genotyping methods, including pyrosequencing, chain reaction-restriction fragment length polymorphism (PCR-RFLP) and MassARRAY were applied in the studies. In addition, all studies conformed to HWE.

The results of the meta-analysis suggested there was no correlation between the COX-2 G-765C polymorphism and OA susceptibility (Table S2). In addition, when subgroup analysis was conducted by ethnicity, we still obtained negative results. We further conducted sensitivity and publication bias analyses to estimate the stability of these results; however, the sensitivity analysis indicated that Volkan et al's work significantly influenced the overall results. Additionally, the shape of the funnel plot also showed that Volkan et al's work was located outside of the funnel plot. Therefore, we decided to remove this study from the meta-analysis. Finally, 618 cases and 596 controls were incorporated into the meta-analysis, and the pooled results demonstrated the COX-2 G-765C polymorphism exhibited a significantly decreased OA risk through comparisons involving allelic, homozygous, heterozygous, and dominant models (C vs G: OR = 0.524, 95%CI: 0.403-0.682, $P < .001$; CC vs GG: OR = 0.330,

TABLE 2 Association of COX-2 G-765C polymorphism between OA patients and controls

	Patients	Controls	OR (95%CI) ^a /P ^a value	OR (95%CI) ^b /P ^b value
Genotype				
GG	188 (95.9%)	174 (88.8%)	Reference	Reference
GC	8 (4.1%)	22 (11.2%)	0.337 (0.146-0.776)/0.011*	0.282 (0.118-0.676)/0.005*
CC	0 (0%)	0 (0%)	/	/
GC/CC	8 (4.1%)	22 (11.2%)	0.337 (0.146-0.776)/0.011*	0.282 (0.118-0.676)/0.005*
Allele				
G	384 (97.9%)	370 (94.4%)	Reference	/
C	8 (2.1%)	22 (5.6%)	0.350 (0.154-0.797)/0.012*	/

OR, odd ratio; 95% CI: 95% confidence interval; OR (95% CI)^a and P^a values were calculated from binary logistic regression test; OR (95% CI)^b and P^b values were calculated from binary logistic regression test with adjustments for age, gender, and body mass index.

*P value indicates $P < .05$.

TABLE 3 Stratification analysis of the COX-2 G-765C polymorphism between different OA types and controls

Group	Gender	GG	GC/CC	OR (95%CI) ^a /P ^a value	OR (95%CI) ^b /P ^b value
Control	F&M (196)	174 (88.8)	22 (11.2%)	Reference	Reference
HOA	F&M (62)	61 (98.4%)	1 (1.6%)	0.130 (0.017-0.982)/0.048*	0.142 (0.018,1.101)/0.062
	F (21)	21 (100%)	0 (0%)	/	/
	M (41)	40 (97.6%)	1 (2.4%)	0.198 (0.026-1.510)/0.118	0.331 (0.034-3.186)/0.339
KOA	F&M (134)	127 (94.8%)	7 (5.2%)	0.436 (0.181-1.052)/0.065	0.280 (0.102-0.769)/0.014*
	F (107)	100 (93.5%)	7 (6.5%)	0.554 (0.228-1.342)/0.191	0.328 (0.116-0.922)/0.035*
	M (27)	27 (100%)	0 (0%)	/	/
UOA	F&M (109)	105 (96.3%)	4 (3.7%)	0.301 (0.101-0.898)/0.031*	0.232 (0.073-0.736)/0.013*
	F (70)	66 (94.3%)	4 (5.7%)	0.479 (0.159-1.443)/0.191	0.260 (0.073-0.925)/0.037*
	M (39)	39 (100%)	0 (0%)	/	/
BOA	F&M (87)	83 (95.4%)	4 (4.6%)	0.381 (0.127-1.142)/0.085	0.368 (0.012-1.127)/0.080
	F (58)	55 (94.8%)	3 (5.2%)	0.431 (0.124-1.496)/0.185	0.330 (0.087-1.251)/0.103
	M (29)	28 (96.6%)	1 (3.4%)	0.282 (0.037-2.180)/0.225	0.446 (0.049-4.032)/0.472

HOA, hip OA; KOA, knee OA; UOA, unilateral OA; BOA, bilateral OA; F, female; M, male; OR, odd ratio; 95% CI, 95% confidence interval.

OR (95%CI)^a and P^a values were calculated from binary logistic regression test. OR (95%CI)^b and P^b values were calculated from binary logistic regression test with adjustments for age, gender, and body mass index.

*P value indicates $P < .05$.

95%CI; 0.115-0.949, $P = .040$; GC vs GG: OR = 0.503, 95%CI: 0.373-0.678, $P < .001$; CC + GC vs GG: OR = 0.490, 95%CI: 0.366-0.655, $P < .001$ (Table S3).

4 | DISCUSSION

In the current study, we performed a case-control hospital-based study and a meta-analysis to investigate the association between COX-2 G-765C polymorphism and end-stage hip or knee OA susceptibility. In our case-control study, we found that the COX-2 G-765C polymorphism may decrease hip or knee OA risk. Furthermore, we conducted stratification analysis and observed heterozygous GC carriers possessed lower knee OA and unilateral OA predisposition in women but not in men. Additionally, data from our case-control study were added to the meta-analysis and the pooled results

indicated the COX-2 G-765C polymorphism exhibited a significantly decreased primary end-stage hip and knee OA risk.

OA is a prevalent chronic low-grade inflammatory disease with both environmental and genetic pathogenic factors.^{5,11,30} Genetic risk factors involved in OA pathogenesis stimulated the search for osteoarthritis relative risk alleles. The COX-2 protein is encoded by the COX-2 gene and can increase PGE2 synthesis, which plays a critical role in OA pathological process. There were many studies that reported the COX-2 G-765C polymorphism as a protective factor in a variety of diseases^{31,32}; however, some other articles had opposing views.³³⁻³⁵ For osteoarthritis, Schneider et al demonstrated that the COX-2 G-765C polymorphism reduced the end-stage hip and knee OA and bilateral OA susceptibility through a case-control study that included 531 cases and 400 controls in a German population.²¹ In contrast, in the same year, Volkan and colleagues analysed a population in

Turkey containing 100 OA patients and 100 controls, and they reported that there was no relationship between the COX-2 G-765C polymorphism and osteoarthritis.²² Our data derived from 196 cases and 196 controls in a Chinese Han population, after adjusting for confounding factors, demonstrated that the COX-2 G-765C polymorphism carriers had a lower hip and knee OA risk before stratification analysis, which was consistent with the work of Schneider et al. When we conducted further stratification analysis, the GG carriers showed higher knee OA and unilateral OA susceptibility in women but no significant differences between hip OA, male knee OA, bilateral OA and controls when they were adjusted for age, gender, and BMI. Although not statistically significant, these *P* values (hip OA group adjusted *P* = .062, bilateral OA group adjusted *P* = .080) were only slightly higher than the threshold value (0.05). Therefore, increasing the sample size may make the results of these groups statistically significant. The differences between ORs and adjusted ORs in our own data indicated that age, gender, and BMI may be related to OA risk. Comparing our data with others, the conflicting results could be caused by several differences between studies including the sample size of different OA types as well as statistical analysis of whether to adjust for confounding factors, genotyping methods, ethnic heterogeneity and others.³⁶

Due to inconsistent opinions from the available studies, we conducted a meta-analysis to obtain a comprehensive evaluation of the relationship between the COX-2 G-765C polymorphism and primary end-stage hip and knee OA susceptibility. In our meta-analysis study, we conducted a sensitivity analysis showing that the study of Volkan et al influenced the pooled results. It was also located outside of funnel plot. Therefore, we removed this study from the meta-analysis. Finally, one published study in a German population and our data in a Chinese population were combined, which included 618 primary end-stage hip and knee OA patients and 596 controls in the meta-analysis to evaluate the relationship between the COX-2 G-765C polymorphism and primary OA risk. The results of the meta-analysis revealed that the COX-2 G-765C polymorphism had a significantly lower primary end-stage hip and knee OA risk through comparing allelic, heterozygous, homozygous, and dominant models with controls.

The current study has a few limitations. First, the sample sizes of cases and controls were relatively small. Therefore, the CC genotype frequency in the case-control study was zero. Second, we should further detect the influence of the COX-2 polymorphism on PGE2 levels in blood. Finally, due to only two papers being included in the meta-analysis, the statistical power may be limited.

In conclusion, our study indicated that the COX-2 G-765C polymorphism may be a protective factor that could decrease the susceptibility of primary end-stage knee OA in a female Chinese Han population. This study provided further insight into how genetic factors are involved in OA pathogenesis. Studies with larger sample sizes and experiments to further explore the underlying mechanisms are required to confirm our findings.

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SUPPORTING INFORMATION

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