Association between the +104T/C polymorphism in the 5'UTR of GDF5 and susceptibility to knee osteoarthritis: A meta-analysis

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Abstract. Although the +104T/C polymorphism in the 5' untranslated region (UTR) of growth differentiation factor 5 (GDF5) plays a role in the pathogenesis of knee osteoarthritis, the results have been inconsistent. In this study, we performed a meta-analysis to assess the association of +104T/C polymorphism with knee osteoarthritis. Published literature from PubMed, Google Scholar and China National Knowledge Infrastructure data was retrieved. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using fixed- or random-effects models. A total of 6 case-control studies containing 2,744 patients and 4,518 controls were enrolled in this meta-analysis. Overall, a statistically significant association was found between the +104T/C polymorphism and risk of knee osteoarthritis (TT vs. CC: OR 1.68, 95% CI=1.41-2.01; TT vs. TC: OR 1.18, 95% CI=1.01-1.38; dominant model: OR 0.72, 95% CI=0.61-0.86). Taking into account the effect of ethnicity, further stratified analyses were performed. In the subgroup analysis, the same association was identified in Caucasian (TT vs. CC: OR 1.45, 95% CI=1.13-1.85) and Asian (TT vs. CC: OR 1.99, 95% CI=1.53-2.60; TT vs. TC: OR 1.33, 95% CI=1.16-1.52; dominant model: OR 0.64, 95% CI=0.56-0.72; recessive model: OR 1.77, 95% CI=1.37-2.29) populations. The meta-analysis results demonstrated that the +104T/C polymorphism in the 5'-UTR of GDF5 is associated with risk of knee osteoarthritis.

Introduction

Knee osteoarthritis, the most common type of osteoarthritis, is a chronic degeneration of the articular cartilage around a joint. This disease commonly affects individuals over 45 years of age but has been identified in all age groups. In a previous study, the prevalence of knee osteoarthritis was identified as 12.2% and was significantly higher in females (14.9%) than in males (8.7%). Prevalence was revealed to increase with age (1). A variety of risk factors have been correlated with knee osteoarthritis: age, obesity, female gender, trauma, repetitive knee trauma, muscle weakness, joint laxity, mechanical forces, kneeling, squatting and miniscal injuries (2,3). In addition, various genetic polymorphisms may be associated with knee osteoarthritis (4).

Previous studies have demonstrated that growth differentiation factor 5 (GDF 5), a member of the transforming growth factor-β (TGF-β) superfamily, is important in musculoskeletal processes, affecting endochondral ossification, synovial joint and bone formation (5,6). The +104T/C polymorphism (rs143383) in the 5' untranslated region (UTR) of GDF5 affects transcriptional activity in the GDF5 gene core promoter and transcriptional activity was found to be reduced in subjects carrying the T allele (6). An association between the +104T/C polymorphism and knee osteoarthritis was previously demonstrated (7-12). However, published results have been inconsistent. In this study, we performed a meta-analysis to investigate whether or not the +104T/C polymorphism is associated with knee osteoarthritis risk.

Materials and methods

Selection of studies. Data were independently gathered in duplicate by two investigators on the basis of a standard protocol. Discrepancies were settled by discussion until a consensus was reached. A literature search was conducted for studies that examined associations between the +104T/C polymorphism and knee osteoarthritis. A search was performed on PubMed, Google Scholar and the China National Knowledge Infrastructure database using the following keywords: '5'-UTR or GDF5', '+104T/C polymorphism or genotype' and 'knee osteoarthritis'.

Selection criteria. To be eligible for inclusion in this meta-analysis, the following criteria were established: i) case-control study that addressed knee osteoarthritis cases and healthy controls; ii) studies that evaluated the association between +104T/C polymorphism and knee osteoarthritis risk;

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Table I. Characteristics of the included studies for meta-analysis.

Study included	Year	Area	Ethnicity	Cases/ controls	Genotypes for cases			Genotypes for controls			HWE test
					TT	TC	CC	TT	TC	CC	
Miyamoto *et al* (8)	2007	China	Asians	313/485	197	97	19	244	193	48	0.28
Miyamoto *et al* (8)	2007	Japan	Asians	718/861	44	243	31	473	330	58	0.97
Southam *et al* (9)	2007	UK	Caucasians	509/822	219	238	52	324	372	126	0.26
Southam *et al* (9)	2007	Spain	Caucasians	274/1196	102	136	36	439	563	194	0.55
Tsezou *et al* (10)	2008	Greece	Caucasians	251/268	95	126	30	99	125	44	0.67
Yao *et al* (11)	2008	China	Asians	298/452	189	93	16	232	182	38	0.78
Zhang *et al* (12)	2010	Korea	Asians	276/298	150	115	11	159	113	26	0.36
Tawonsawatruk *et al* (13)	2011	Thailand	Asians	90/103	38	41	11	33	47	23	0.42

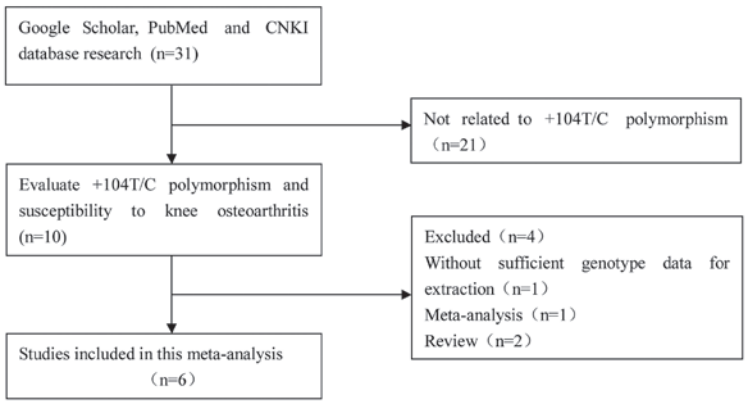

Figure 1. Flow diagram of study search and selection process. CNKI, China National Knowledge Infrastructure.

iii) studies that included sufficient genotype data for extraction; and iv) the genotype distribution among the control population in Hardy-Weinberg equilibrium (HWE).

Data extraction. The following information was extracted from the eligible studies: i) first author; ii) year of publication; iii) country; iv) ethnicity; v) sample size of subjects with and without CAD; vi) genotype distribution of subjects with and without knee osteoarthritis; and vii) P-value for HWE test in subjects without knee osteoarthritis.

Statistical analysis. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to estimate the strength of correlation between the +104T/C polymorphism and knee osteoarthritis risk. The pooled ORs were performed under a homozygote comparison (TT vs. CC), a heterozygote comparison (TT vs. TC), a dominant model (CC+TC vs. TT) and a recessive model (TT+TC vs. CC). In addition, we conducted a stratification analysis in Asian and European individuals to explore and explain diversity among the results of various studies (7). We tested whether genotype frequencies of controls were in HWE using the Chi-square test. Q- and I^2 tests were performed to evaluate whether the variation was due to heterogeneity or chance. If heterogeneity was identified among the studies (I^2<50%), the pooled OR was estimated by the fixed-effects model. Otherwise, the random-effects model was used to estimate the pooled OR. Sensitivity analysis was performed through the random-effects model values compared with the fixed-effects to ensure the stability of the results. Publication bias was assessed by Begg's test (P<0.05 was considered to indicate a statistically significant difference). Analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX, USA). All P-values were two-sided.

Results

Characteristics of studies. A total of 33 studies were obtained by the literature search, among which 6 fit the inclusion criteria (8-13). The flowchart of reviews demonstrates the detailed process of selection (Fig. 1). Of the 25 excluded studies, 21 were not associated with +104T/C polymorphism, 1 did not have sufficient genotype data for extraction, 1 was a meta-analysis and 2 were reviews. Data were collected from 2,744 knee osteoarthritis patients and 4,518 controls. Genotype distributions among the controls of all included studies were consistent with HWE. The 6 included studies contained 8 population studies of 5 Asian and 3 Caucasian groups. Information from these studies and the number of cases and controls with TT, TC and CC genotypes reported in each are shown in Table I.

Table II. Summary ORs and 95% CIs of the +104T/C polymorphism and knee osteoarthritis risk.

Subgroup	Genetic model	Sample size		Type of model	Test of heterogeneity		Test of association		Test of publication bias	
		Case	Control		I^2 (%)	P-value	OR	95% CI	z	P-value
Overall	TT vs. CC	2744	4518	Fixed	0.0	0.71	1.68	1.41-2.01	1.95	0.05
	TT vs. TC			Random	51.2	0.05	1.18	1.01-1.38	1.95	0.05
	Dominant model			Random	63.6	0.01	0.72	0.61-0.86	1.95	0.05
	Recessive model			Random	99.0	0.00	1.05	0.23-4.72	1.95	0.05
Caucasian	TT vs. CC	1034	2286	Fixed	0.0	0.63	1.45	1.13-1.85	0.00	1.00
	TT vs. TC			Fixed	0.0	0.84	1.00	0.85-1.18	0.00	1.00
	Dominant model			Fixed	0.0	0.75	0.92	0.79-1.07	0.00	1.00
	Recessive model			Random	99.4	0.00	0.41	0.03-6.20	0.00	1.00
Asian	TT vs. CC	1710	2232	Fixed	0.0	0.95	1.99	1.53-2.60	1.36	0.17
	TT vs. TC			Fixed	45.4	0.12	1.33	1.16-1.52	1.36	0.17
	Dominant model			Fixed	30.7	0.22	0.64	0.56-0.72	1.36	0.17
	Recessive model			Fixed	0.0	0.93	1.77	1.37-2.29	1.36	0.17

OR, odds ratio; CI, confidence interval.

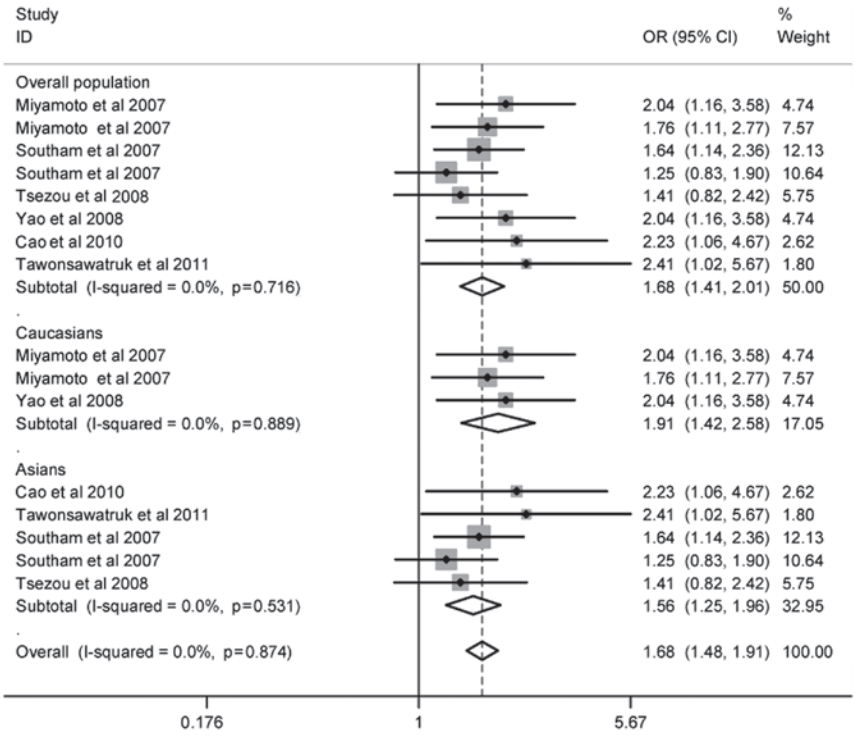

Figure 2. Meta-analysis with a fixed-effects model for the association between knee osteoarthritis risk and the +104T/C polymorphism (TT vs. CC) is shown in the subgroup analysis. OR, odds ratio; CI, confidence interval.

Results of meta-analysis. A summary of the meta-analysis findings of the association between +104T/C polymorphism and knee osteoarthritis risk is shown in Table II. Overall, we found a significant association of +104T/C polymorphism with knee osteoarthritis risk (TT vs. CC: OR 1.68, 95% CI=1.41-2.01; TT vs. TC: OR 1.18, 95% CI=1.01-1.38; dominant model: OR 0.72, 95% CI=0.61-0.86). In the subgroup analysis based on ethnicity, studies were divided into Caucasian and Asian populations. The same association was observed in the Caucasian (TT vs. CC: OR 1.45, 95% CI=1.13-1.85) and Asian (TT vs. CC: OR 1.99, 95% CI=1.53-2.60; TT vs. TC: OR 1.33, 95% CI=1.16-1.52; dominant model: OR 0.64, 95% CI=0.56-0.72; recessive model: OR 1.77, 95% CI=1.37-2.29) groups. Sensitivity analysis was performed through random-

effects model values compared with the fixed-effects, the results of which indicated no statistically significant difference, rendering the values of meta-analysis valid (TT vs. CC: OR 1.68, 95% CI=1.40-2.01; TT vs. TC: OR 1.19, 95% CI=1.07-1.32; dominant model: OR 0.74, 95% CI=0.67-0.81; recessive model: OR 0.28, 95% CI=0.25-0.32). Publication bias of the studies was assessed using the funnel plot and Begg's test. Publication bias was not observed in the funnel plot (all P>0.05, Table II and Fig 2).

Discussion

The association of genetic polymorphism and knee osteoarthritis has recently attracted growing attention. Miyamoto *et al* were the first study group to investigate the association between +104T/C polymorphism in the 5'-UTR of GDF5 and knee osteoarthritis in Asians. The results showed a significant correlation between +104T/C polymorphism and knee osteoarthritis risk in Japanese and Chinese populations. More recent studies have confirmed this correlation between +104T/C polymorphism and susceptibility to knee osteoarthritis. However, a number of studies have also demonstrated a conflicting correlation. In the present study, we quantitatively assessed the correlation between +104T/C polymorphism and knee osteoarthritis risk. Six studies were included with a total of 2,744 knee osteoarthritis patients and 4,518 controls. Overall, a significant correlation was observed between the +104T/C polymorphism and knee osteoarthritis risk in Caucasian (TT vs. CC: OR 1.45, 95% CI=1.13-1.85) and Asian (TT vs. CC: OR 1.99, 95% CI=1.53-2.60; TT vs. TC: OR 1.33, 95% CI=1.16-1.52; dominant model: OR 0.64, 95% CI=0.56-0.72; recessive model: OR 1.77, 95% CI=1.37-2.29) individuals. No evidence was found for publication bias in this meta-analysis for the +104T/C polymorphism. As the eligible study number was limited in the meta-analysis, these results require further investigation.

The mechanistic correlation between the +104T/C polymorphism and knee osteoarthritis risk remains unclear. GDF5 is involved in articular cartilage development, regeneration and maintenance and is a specific marker for synovial joints of appendicular skeletons (14). The +104T/C polymorphism regulates transcriptional activity in the GDF5 gene core promoter and the T allele reveals reduced transcriptional activity, this SNP may be the biological basis for the alteration in function (8). This evidence suggests that the +104T/C polymorphism is important in the development of knee osteoarthritis.

Several potential limitations of the present study should be noted. First, the results may be affected by additional confounding factors, including gender and age. We were unable to perform gender- and age-related subgroup analyses due to incomplete data. Second, the effect of genetic and environmental interactions was not addressed in our meta-analysis. Third, the number of studies and subjects in the studies included in the meta-analysis by specific subgroups was small. Therefore, additional studies with larger sample sizes are required.

In conclusion, the present study indicates that +104T/C polymorphism in the 5'-UTR of GDF5 is associated with risk of knee osteoarthritis. However, further studies of gene-gene and gene-environment interactions should be taken into consideration to investigate this correlation.

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