Association of GDF-5 rs143383 polymorphism with radiographic defined knee osteoarthritis: A systematic review and meta-analysis

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ABSTRACT

Objective: To assess the association of GDF-5 rs143383 polymorphism with radiographic defined knee osteoarthritis (OA), a systematic review and meta-analysis was conducted.

Methods: A total of 17 relevant case-control studies with 7424 cases and 11,310 controls was collected from several electronic databases up to June 2018.

Results: The pooled results showed that GDF-5 rs143383 polymorphism was significantly associated with radiographic defined knee OA in overall and stratified analysis by ethnicity, source of controls and genotyping techniques.

Conclusions: The GDF-5 rs143383 polymorphism might be used as a relevant risk estimate for radiographic defined Knee OA.

1. Introduction

Osteoarthritis (OA), a severe joint disease, is one of the main leading causes of restricted activity and disability worldwide.^{1–3} In addition, persistent pain due to knee OA can be lead to a loss of function, reduced quality of life and increasingly heavy economic burden on social welfare and health care systems.^{4,5} Knee OA is a disease caused by multiple interrelated factors (biomedical and biomechanical) that contribute to a cascade leading to joint degeneration. Knee OA is a multi-factorial disease.⁶ Female sex, age, obesity, Knee Injury, heavy physical activity and occupational load are important risk factors for the incidence of knee OA.⁷

Several sets of diagnostic criteria have been proposed for knee OA. They usually rest upon radiographic findings, physical findings, clinical findings, or a combination of these.⁸ For example, to best define the presence of knee OA, the American College of Rheumatology (ACR) criteria combine outcomes from radiographs and physical examination.⁹ Radiographic assessments have long been considered as the primary method for imaging in the diagnosis and severity assessment of knee OA.¹⁰ The advantages of radiography are cost-effectiveness,

safety, and excellent availability. However, it is rather insensitive at detecting early signs of knee OA. Moreover, there are several radiological classification systems for assessing the severity of knee OA, including those by Ahlbäck (1968), Nagaosa (2000), and Kellgren and Lawrence (K&L) (1957).¹¹ For the classification of the structural changes associated with knee OA, K&L composed criteria for a 5-point grading scale using radiographic features. These K&L grades range from 0 (no OA) to 4 (severe OA), with grades ≥ 2 defined as definite knee OA.¹²

Increasing evidence has suggested that pain is poorly correlated with symptoms of radiologic knee OA and most risk factors for radiologic knee OA are not strong predictors of knee pain.¹³ A systematic review revealed that in 15–81% of patients the radiological knee OA has been associated with pain symptoms.¹⁴ Moreover, the radiographic severity of knee OA has been reported to have weak or no significant association with disability in knee OA patients. There is a large body of evidence demonstrating the role of genetic as a risk factor for knee OA. Though a number of genetic epidemiological studies have been conducted to explore the association of different single nucleotide polymorphisms with knee OA, there is no study evaluated the association of

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Fig. 1. Studies identification, inclusion and exclusion.

genetic polymorphisms with radiologic defined knee OA. Therefore, we have performed a meta-analysis to elucidate the association of growth and differentiation factor 5 (GDF-5) rs143383 polymorphism with radiographic knee OA.

2. Materials and methods

2.1. Search strategy

To identify all articles that examined the association of GDF-5 rs143383 polymorphism with radiographic knee OA and TKR, we conducted an electronic search in the PubMed, EMBASE, CNKI (China National Knowledge Infrastructure) and Chinese Biomedicine databases up to June 2018 using the combination of following MeSH terms and keywords ("knee osteoarthritis" OR "radiographic knee osteoarthritis" OR "RKO") AND ("Growth differentiation factor 5" OR "GDF-5" OR "BMP-14" OR "rs143383" OR "+104 T > C") AND ("SNPs" OR "polymorphism" OR "genotype" OR "allele" OR "variation"). In addition, we also reviewed the references list of relevant reviews and eligible publications to find other potentially sources. The search was

limited to human studies and English language published studies.

2.2. Inclusion criteria

All of the included original studies were selected according to the following selection criteria. Inclusion criteria: (1) case-control, family based study, linkage study, or cohort studies; (2) studies evaluating the association of GDF-5 rs143383 polymorphism with radiologic defined knee OA; (3) studies with sufficient data of genotype or allele frequency for examining an Odds Ratios (ORs) with 95% Confidence Intervals (CIs). Accordingly, the following exclusion criteria were also utilized: (1) not a case-control study or a cohort study; (2) case only and/or no controls; (3) no sufficient data reported; (4) abstracts, comments, case reports, letters, reviews, meta-analysis, and (5) duplicates of previous publications. If more than one article was published by the same authors using the same case series, the studies with the largest sample size or the most recently published case-control study was selected. In addition, in this meta-analysis different case-control groups in one publication were considered as independent case-control studies.

Table 1

Characteristics of studies included in the meta-analysis.

SOC: source of control; PB: Population based; HB: Hospital based; NS: Not Stated; PCR: Polymerase chain reaction; AS-PCR: Allele-specific PCR; RFLP: restriction fragment length polymorphism; MS: Mass spectrometry; DS: Direct sequencing; RT: Real-time PCR; HRMA: High Resolution Melt (HRM) analysis; HWE: Hardy–Weinberg equilibrium.

First Author	Country (Ethnicity)	SOC	Genotyping Technique	Case/Control	Cases					Controls					HWE
					Genotypes			Allele		Genotypes			Allele		
					TT	TC	CC	T	C	TT	TC	CC	T	C	
Miyamoto 2007 ¹⁹	Japan(Asian)	HB	TaqMan	313/485	197	97	19	491	135	473	330	58	681	289	0.965
Miyamoto 2007 ¹⁹	China(Asian)	HB	TaqMan	718/861	444	243	31	1131	305	244	193	48	1276	446	0.040
Tsezou 2007 ²⁰	Greece(Caucasian)	HB	DS	251/267	95	126	30	316	186	99	125	44	323	213	0.668
Yao 2008 ²⁵	China(Asian)	PB	RT	298/452	189	93	16	471	125	232	182	38	646	258	0.344
Chapman 2008 ²⁶	Netherland(Caucasian)	PB	MS	142/724	54	72	16	180	104	289	331	104	909	539	0.558
Vaes 2009 ²⁷	Netherland(Caucasian)	PB	TaqMan	667/2097	276	298	93	850	484	752	1014	331	2518	1676	0.723
Valdes 2009 ²⁸	UK(Caucasian)	PB	AS-PCR	259/509	126	98	35	350	168	181	244	84	606	412	0.907
Takahashi 2010 ²⁹	Japan(Asian)	NS	TaqMan	933/1225	566	313	54	1445	421	684	461	80	1829	621	0.844
Valdes 2011 ³⁰	Estonia(Caucasian)	PB	AS-PCR	65/427	32	24	9	88	42	168	179	80	515	339	0.010
Valdes 2011 ²⁷	Netherland(Caucasian)	HB	AS-PCR	867/758	413	361	93	1187	547	294	354	110	942	574	0.836
Valdes 2011 ²⁷	UK(Caucasian)	PB	AS-PCR	1141/536	467	511	163	1445	837	219	237	80	675	397	0.229
Tawonsawatruk 2011 ³¹	Thailand(Asian)	HB	PCR-RFLP	103/103	35	41	11	117	63	33	47	23	113	93	0.424
Shin 2012 ³²	Korea(Asian)	PB	HRMA	725/1737	382	305	38	1059	381	942	689	105	2573	901	0.154
Mishra 2013 ²¹	India(Asian)	HB	PCR-RFLP	300/300	124	130	46	378	222	54	160	56	328	272	0.002
Sabah-Ozcan 2017 ²²	Turkey(Caucasian)	HB	PCR-RFLP	94/279	37	43	14	117	71	74	153	52	301	257	0.083
Mishra 2017 ²³	India(Asian)	NS	PCR-RFLP	500/500	199	226	75	624	376	131	272	97	534	466	0.037
Elazeem 2017 ²⁴	Egypt(African)	PB	TaqMan	50/50	20	14	16	56	44	12	13	25	49	51	0.001

2.3. Data extraction

Two authors independently and carefully extracted data from all eligible studies according to the inclusion criteria listed above. Disagreements were resolved by discussion between the two investigators. If the two authors could not reach a consensus, then a third author was consulted to resolve the disagreements and a final decision was made. For each included study, the following information was collected: first author, year of publication, country, ethnicity, number of cases and controls, genotyping techniques, and p-value for Hardy–Weinberg equilibrium (HWE).

2.4. Statistical analysis

The strength of the association of GDF-5 rs143383 polymorphism with radiographic knee OA were estimated using ORs, with the corresponding 95% CIs. The significance of pooled ORs was tested by Z-test, in which $P < 0.05$ was considered significant. The risks (ORs) of knee OA and TKR associated with the GDF-5 rs143383 polymorphism were estimated for each study under five genetic models including allele model (C vs. G), homozygous model (CC vs. GG), heterozygous model (CC vs. GC), dominant model (CC + GC vs. GG), and recessive model (CC vs. GG + GC). The Q-statistic and the I^2 statistic were used to assess between study heterogeneity in the meta-analysis. In addition, we used the I^2 statistics to quantify the between study heterogeneity, which ranges from 0 to 100% and represents the proportion of between-study variability attributable to heterogeneity rather than chance. I^2 values of 25%, 50%, and 75% were nominally considered low, moderate, and high estimates, respectively.^{15,16} A p-value of less than 0.05 for the Q-statistic indicated presence of between study heterogeneity, so that the pooled OR estimate of each study was calculated by the random-effects model (the DerSimonian and Laird method). Otherwise, the fixed-effects model (the Mantel–Haenszel method) was used. For each study, we examined whether the genotype distribution in control groups was in agreement with Hardy–Weinberg Equilibrium (HWE) using the χ^2 test. One-way sensitivity analysis, by which a single study in the meta-analysis was omitted each time to reflect the influence of the individual data set for the pooled OR, was carried out to assess the stability of the results. Moreover, sensitivity analysis was performed by deletion those studies did not in agreement with HWE. To detect the presence of

potential publication bias, visual inspection of Begg's funnel plot symmetry was used in which an asymmetric plot suggests a possible publication bias. In addition, Egger's linear regression test which measures funnel plot asymmetry using a natural logarithm scale of OR was also used to evaluate the publication biases statistically.^{17,18} When publication bias existed, the Duval and Tweedie non-parametric “trim and fill” method was used to adjust for it. All statistical tests were performed using Comprehensive Meta-Analysis (CMA) software version 2.0 (Bio-stat, USA). All P values in the meta-analysis were 2-sided, and P values less than 0.05 were considered significant, except for tests of between study heterogeneity where a level of 0.10 was used.

3. Results

3.1. Characteristics of studies

The literature search and study selection procedures are shown in Fig. 1. There were 170 studies retrieved through electronic database and hand search on the basis of the above criteria. Of those, 73 publication were excluded after title and abstract review. Of the remaining 97 studies, we further removed 80 articles due to reviews articles, case reports, case-only design, and insufficient data to calculate ORs. Finally, 17 case-control studies in 14 publications^{19–32} with 7424 cases and 11,310 controls were included in the meta-analysis. The detailed characteristics of the included studies were summarized in Table 1. All studies were case-control studies, the sample sizes of radiographic knee OA cases ranged from 50 to 933, and publication dates ranged 2007 to 2017. Among the 17 case-control studies, there were eight studies of Caucasians, eight studies of Asians, and one study of Africans. There were seven hospital-based studies, eight population based studies and two studies not stated. Different genotyping techniques were used, including TaqMan, allele-specific PCR (AS-PCR), restriction fragment length polymorphism (RFLP-PCR), mass spectrometry, direct sequencing, real-time PCR, and high resolution melt (HRM) analysis. The distributions of genotype and allele frequency in the cases and controls are presented in Table 1. The distribution of the genotypes in the control group was consistent with Hardy–Weinberg equilibrium (HWE), except for four case-control studies.

Table 2

Results of the association of the GDF-5 rs143383 polymorphism with radiographic defined Knee OA.

Subgroup	Genetic Model	Type of Model	Heterogeneity		Odds Ratio		Publication Bias			
			I ² (%)	P _H	OR	95% CI	Z _{test}	P _{OR}	P _{Begg}	P _{Egger}
Overall	C vs. T	Random	58.36	0.001	0.792	0.732–0.857	–5.828	≤0.001	0.174	0.048
	CC vs. TT	Random	44.45	0.025	0.634	0.544–0.739	–5.824	≤0.001	0.127	0.065
	CT vs. TT	Fixed	0.00	0.809	1.144	1.029–1.272	2.489	0.013	0.149	0.090
	CC + CT vs. TT	Random	91.80	0.00	0.682	0.541–0.860	–3.237	0.001	0.266	0.114
	CC vs. CT + TT	Fixed	0.00	0.759	0.772	0.999–0.853	–5.064	≤0.001	0.004	0.002
By Ethnicity Caucasians	C vs. T	Fixed	39.69	0.114	0.835	0.760–0.917	–3.761	≤0.001	0.901	0.548
	CC vs. TT	Fixed	0.00	0.504	0.727	0.630–0.839	–4.369	≤0.001	0.710	0.355
	CT vs. TT	Fixed	0.00	0.906	1.122	0.974–1.292	1.598	0.110	0.386	0.338
	CC + CT vs. TT	Random	57.25	0.022	0.787	0.673–0.920	–3.004	0.003	1.000	0.716
	CC vs. CT + TT	Fixed	0.00	0.895	0.810	0.709–0.925	–3.107	0.002	0.386	0.200
Asian	C vs. T	Random	72.36	0.001	0.749	0.656–0.856	–4.266	≤0.001	0.009	0.012
	CC vs. TT	Random	60.75	0.013	0.568	0.432–0.745	–4.072	≤0.001	0.710	0.318
	CT vs. TT	Fixed	7.36	0.373	1.161	0.987–1.366	1.807	0.071	0.536	0.337
	CC + CT vs. TT	Random	96.05	≤0.001	0.612	0.390–0.960	–2.140	0.032	0.265	0.123
	CC vs. CT + TT	Fixed	0.00	0.469	0.737	0.632–0.860	–3.867	≤0.001	0.063	0.018
By Technique PCR-RFLP	C vs. T	Fixed	0.00	0.979	0.538	0.448–0.646	–6.638	≤0.001	0.734	0.555
	CC vs. TT	Fixed	0.00	0.669	0.682	0.602–0.772	–6.057	≤0.001	0.734	0.384
	CT vs. TT	Fixed	0.00	0.696	0.459	0.353–0.598	–5.791	≤0.001	0.734	0.853
	CC + CT vs. TT	Fixed	0.00	0.644	1.094	0.856–1.398	0.719	0.472	0.734	0.352
	CC vs. CT + TT	Fixed	0.00	0.546	0.716	0.568–0.903	–2.826	0.005	0.734	0.357
AS-PCR	C vs. T	Random	66.68	0.029	0.803	0.674–0.956	–2.468	0.014	1.000	0.596
	CC vs. TT	Fixed	43.24	0.152	0.701	0.533–0.923	–2.535	0.011	1.000	0.613
	CT vs. TT	Fixed	0.00	0.861	1.101	0.908–1.335	0.983	0.326	1.000	0.889
	CC + CT vs. TT	Random	71.13	0.016	0.738	0.571–0.954	–2.320	0.020	1.000	0.603
	CC vs. CT + TT	Fixed	0.00	0.545	0.809	0.675–0.969	–2.307	0.021	0.734	0.683
TaqMan	C vs. T	Fixed	30.77	0.228	0.792	0.723–0.868	–4.986	≤0.001	0.734	0.431
	CC vs. TT	Random	67.45	0.027	0.569	0.367–0.882	–2.520	0.012	0.734	0.415
	CT vs. TT	Fixed	51.95	0.100	1.173	0.951–1.447	1.494	0.135	0.734	0.546
	CC + CT vs. TT	Random	97.98	≤0.001	0.550	0.207–1.462	–1.198	0.231	0.734	0.578
	CC vs. CT + TT	Fixed	42.98	0.154	0.753	0.619–0.917	–2.821	0.005	0.308	0.116
By Source of Control HB	C vs. T	Fixed	3.68	0.398	0.739	0.682–0.802	–7.284	≤0.001	0.367	0.256
	CC vs. TT	Fixed	33.36	0.173	0.532	0.441–0.641	–6.616	≤0.001	0.763	0.732
	CT vs. TT	Fixed	14.44	0.320	1.253	1.043–1.506	2.408	0.016	1.000	0.733
	CC + CT vs. TT	Random	96.15	≤0.001	0.587	0.323–1.064	–1.756	0.079	0.763	0.369
	CC vs. CT + TT	Fixed	0.00	0.660	0.682	0.573–0.812	–4.314	≤0.001	0.229	0.245
PB	C vs. T	Random	59.15	0.017	0.855	0.760–0.962	–2.605	0.009	0.536	0.207
	CC vs. TT	Fixed	9.29	0.358	0.767	0.659–0.892	–3.439	0.001	0.063	0.060
	CT vs. TT	Fixed	0.00	0.939	1.112	0.956–1.293	1.376	0.169	0.173	0.054
	CC + CT vs. TT	Random	71.21	0.001	0.804	0.666–0.970	–2.272	0.023	0.265	0.199
	CC vs. CT + TT	Fixed	0.00	0.765	0.829	0.720–0.956	–2.585	0.010	0.004	0.005

3.2. Quantitative data synthesis

3.2.1. Overall estimations

The results of meta-analysis of GDF-5 rs143383 polymorphism was listed in Table 2. When all the eligible studies were pooled into the meta-analysis of GDF-5 rs143383 polymorphism, a significant association was found with radiographic knee OA in overall population under all five genetic models, i.e., allele (C vs. T: OR = 0.792, 95% CI 0.732–0.857, $p \leq 0.001$), homozygote (CC vs. TT: OR = 0.634, 95% CI 0.544–0.739, $p \leq 0.001$, Fig. 2A), heterozygote (CT vs. TT: OR = 1.144, 95% CI 1.029–1.272, $p = 0.013$, Fig. 2B), dominant (CC + CT vs. TT: OR = 0.682, 95% CI 0.541–0.860, $p = 0.001$) and recessive (CC vs. CT + TT: OR = 0.772, 95% CI 0.999–0.853, $p \leq 0.001$).

3.2.2. Subgroup analyses

Table 2 lists the subgroup analyses results of this meta-analysis. Eight case-control studies with 3486 cases and 5597 controls were used to investigate the association of GDF-5 rs143383 polymorphism with radiographic knee OA in Caucasians. The results showed that the GDF-5 rs143383 polymorphism was associated with radiographic knee OA in Caucasians under four genetic models, i.e., allele (C vs. T: OR = 0.835, 95% CI 0.760–0.917, $p \leq 0.001$), homozygote (CC vs. TT: OR = 0.727,

95% CI 0.630–0.839, $p \leq 0.001$), dominant (CC + CT vs. TT: OR = 0.787, 95% CI 0.673–0.920, $p = 0.003$) and recessive (CC vs. CT + TT: OR = 0.810, 95% CI 0.709–0.925, $p = 0.002$). Similarly, a total of eight case-control studies with 3890 cases and 5663 controls were used to investigate the association of GDF-5 rs143383 polymorphism with radiographic knee OA in Asians. The results showed that the GDF-5 rs143383 polymorphism was associated with radiographic knee OA in Asians under four genetic models, i.e., allele (C vs. T: OR = 0.835, 95% CI 0.656–0.856, $p \leq 0.001$), homozygote (CC vs. TT: OR = 0.727, 95% CI 0.432–0.745, $p \leq 0.001$), dominant (CC + CT vs. TT: OR = 0.612, 95% CI 0.390–0.960, $p \leq 0.001$) and recessive (CC vs. CT + TT: OR = 0.737, 95% CI 0.632–0.860, $p \leq 0.001$).

The studies were further stratified on the basis of genotyping technique and source of control subjects. In the PCR-RFLP, AS-PCR and TaqMan group, a significant association between GDF-5 rs143383 polymorphism and radiographic knee OA were found (Table 2). Moreover, subgroup analysis based on the source of controls showed that there was a significant association between GDF-5 rs143383 polymorphism and radiographic knee OA in population based and hospital based studies (Table 2).

A **B**

Fig. 2. Forest plots for the GDF-5 rs143383 polymorphism with radiographic knee OA. A: the homozygote model (CC vs. TT); B: the heterozygote model (CT vs. TT).

3.3. Heterogeneity and sensitivity analysis

There was obvious between study heterogeneity under three genetic models, i.e., allele ($I^2 = 58.36\%$, $P_{het} = 0.001$), homozygote ($I^2 = 44.45\%$, $P_{het} = 0.025$), and recessive ($I^2 = 91.80\%$, $P_{het} \leq 0.001$). Thus, a subgroup analysis by ethnicity, genotyping method and source of controls was conducted to assess the source of heterogeneity. Heterogeneity dramatically decreased or disappeared when stratification analyses for Caucasians, PCR-RFLP and hospital based studies was conducted (Table 2). Moreover, we performed sensitivity analyses to assess the stability of our results, namely, a single study in the meta-analysis was omitted each time to reflect the

influence of the individual study to the pooled OR. The sensitivity analysis indicated that no single study influenced the pooled OR and also between studies heterogeneity, suggesting that the results of this meta-analysis are stable. In addition, we excluded those HWE-violating studies for sensitivity analyses. However, the pooled ORs in overall was not statistically altered, indicating that the results was stable (data not shown).

3.4. Publication bias

The Begg's funnel plot and Egger's test were performed to examine the publication bias in this meta-analysis. There was evidence of

Fig. 3. Begg's funnel plot for publication bias (blue) and the Duval and Tweedie nonparametric "trim and fill" method's funnel plot (red) for the meta-analysis of GDF-5 rs143383 polymorphism with radiographic knee OA under the allele genetic model (C vs. T).

significant publication bias two genetic models allele ($P_{\text{Begg's}} = 0.174$ and $P_{\text{Egger's}} = 0.048$, Fig. 3) and recessive ($P_{\text{Begg's}} = 0.004$ and $P_{\text{Egger's}} = 0.002$). This might be due to that the present meta-analysis was limited to radiographic knee OA published studies. Therefore, we have performed the Duval and Tweedie non-parametric "trim and fill" method to adjust the publication bias test results for the allele and recessive models. However, the results did not change GDF-5 rs143383 polymorphism with radiographic knee OA (data not shown), indicating that our results were statistically robust (Fig. 3).

4. Discussion

Human GDF-5 gene (also called BMP-14), a well-characterized member of the transforming growth factor beta (TGF- β) signaling pathway, is promotes chondrogenesis and chondrocyte proliferation. Mutations in TGF- β superfamily members can lead to developmental disorders. GDF-5 is essential for joint formation during digit development and proper formation of adult nuclei pulposi.³³ It has been demonstrated that the common polymorphisms in the GDF-5 gene contribute to variation in human height.³¹ Moreover, mutations in the GDF-5 gene result in severe chondrodysplasia and skeletal dysplasia such as brachydactyly type C and proximal symphalangism,³⁴ while a milder variant that influences GDF-5 expression levels, results in a slightly elevated risk for OA.³⁰ In 1996, the human GDF-5 gene is mapped to chromosome 20q11.2, contains two coding exons and spans approximately 4878 bp.³⁵ The rs144383 (+104 T > C) C to T SNP located in the 5'UTR of GDF-5 gene, has been studied intensively.^{24,30}

Previously published studies have indicated a significant association between GDF-5 rs143383 polymorphism and OA risk. However, the conclusions are still inconsistent. Furthermore, no meta-analysis has been evaluated the association of GDF-5 rs143383 polymorphism with radiographic defined knee OA. Therefore, our meta-analysis represents the first meta-analysis investigating the association of GDF-5 rs143383 polymorphism with radiographic knee OA. In the current meta-analysis, a total of 17 eligible case-control studies with 7424 radiographic defined knee OA cases and 11,310 controls were selected. In the total population, the pooled results of our meta-analysis indicated that there was an obviously significant association between the GDF-5 rs143383 polymorphism with radiographic knee OA under all five genetic models. In addition, subgroup analyses showed that the GDF-5 rs143383 polymorphism was significantly associated with radiographic defined knee OA among Caucasian and Asian populations.

Between studies heterogeneity is a potential issue in a meta-analysis of genetic association studies.^{36,37} Ethnicity, sample size, study design, gender distribution, genotyping techniques, and so on, might be contribute to the between study heterogeneity.^{38–40} To explore the source of heterogeneity, subgroup analyses according to ethnicity, genotyping method and source of controls were conducted. The results showed the heterogeneity dramatically decreased or disappeared by

subgroup analyses, suggesting that those studies on Caucasians, PCR-RFLP and hospital based was the major source of heterogeneity in the present meta-analysis. In addition, the problem of publication bias, which may influence the results of a meta-analysis, should also be explained. In this meta-analysis also there was a significant publication bias under two genetic models. It seems the limitation of search to the radiographic knee OA and English language published studies could bring bias in this meta-analysis. However, the results of "trim and fill" method did not adjust pooled ORs, indicating that our results were statistically reliable and robust.

The most important advantage of this meta-analysis is that this is the first meta-analysis to evaluate the association of GDF-5 rs143383 polymorphism with radiographic defined knee OA. Previous studies were all single case-control studies, which had limited statistical power due to the limited sample size. Meta-analysis is a very powerful tool for analyzing cumulative data of studies where the individual sample sizes are small and the statistical power is low. Therefore, the results of this meta-analysis were more robust and precise than that of previous individual case-control studies. However, several limitations may be considered for the interpretation of results. First, we performed a comprehensive search to obtain relevant studies through electronic databases, leading to a potential bias caused by missing of unpublished studies and the exclusion of one study which could not be included due to a lack of data. Second, predominantly studies on Caucasians and Asians were included in the present meta-analysis. Data on other ethnicities such as Africans and Latinos must be performed to evaluate the potential effects of ethnic variation on radiographic knee OA. Third, in the present meta-analysis a moderate to high heterogeneity was detected, which could influence the conclusions. However, when subgroup analysis was performed the heterogeneity obviously reduced or disappeared, suggesting that heterogeneity might be caused due to the differences in ethnicity background, genotyping method and source of controls. Fourth, Fourthly, in this meta-analysis publication bias existed because only published studies in English on radiographic knee OA were selected. Those studies not selected or published in other, which might contain other eligible studies and thus cause publication bias. Fifth, our analysis was based on ORs estimated without adjustment for several important confounding factors, such as age, gender, obesity, mechanical injury, severity of pain, and other factors owing to insufficient data in the primary reports, which are known to have significant effects on the development of knee OA. Thus, a more rigorous analysis should be assessed by stratifying other risk factors if data was available. Finally, a single gene polymorphism has only a moderate effect on knee OA development; hence, the GDF-5 rs143383 polymorphism may influence susceptibility of knee OA along with other polymorphisms in the GDF-5 gene, polymorphisms in the other genes, and environmental factors. However, enough data for further analysis is not available.

5. Conclusion

This systematic review and meta-analysis for the first time provided an overview on the association of GDF-5 rs143383 polymorphism with radiographic defined knee OA. Our meta-analysis showed that the GDF-5 rs143383 polymorphism is associated with radiographic defined knee OA in overall population and by ethnicity. Further studies with large sample size are needed to establish a more definitive conclusion. In addition, more studies should be performed in other ethnic groups such as African and Latinos populations are warranted to confirm this finding.

Conflicts of interest

The authors declare that they have no conflict of interest.

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