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A Single Nucleotide Polymorphism in the GDF5 Gene (rs143383) may contribute to the Increased Risk of Osteoarthritis and Lumbar Disc Degeneration: an Updated Meta-Analysis

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Abstract

Background: Although previous studies have investigated the association between GDF5 polymorphism rs143383 and osteoarthritis (OA) or lumbar disc degeneration (LDD), the results were inconsistent. Given the availability of more recent data, we performed a meta-analysis to access the association between GDF5 polymorphism rs143383 and OA or LDD as well as whether the association vary by ethnicity, sex, study design and disease sites.

Method: Published literature from PubMed, Embase, SCOPUS, Google Scholar, and China National Knowledge Infrastructure (CNKI) databases were retrieved. ORs and 95%CIs were calculated to estimate the strength of the association between the GDF5 polymorphism rs143383 and the risk of OA or LDD.

Results: A total of 15 articles containing 33 studies were enrolled in this meta-analysis. Overall, a statistically association was found between the GDF5 rs143383 polymorphism and the risk of OA or LDD in the allele model(OR=0.86, 95%CI=0.81-0.91) and dominant model(OR=0.86, 95%CI=0.79-0.91). In the subgroup analyses by ethnicity, sex, study design and disease site, we observed a significant association in Caucasian subgroup (allele model, OR=0.91,95%CI=0.87-0.95, dominant model, OR=0.89, 95%CI=0.82-0.96), Asian subgroup (allele model, OR=0.72, 95%CI=0.61-0.84, dominant model, OR=0.69, 95%CI=0.56-0.85), case-control study subgroup (allele model, OR=0.80, 95%CI=0.73-0.88, dominant model, OR=0.80, 95%CI=0.70-0.91), cohort study subgroup (allele model, OR=0.91, 95%CI=0.86-0.97, dominant model, OR=0.87,95%CI=0.79-0.96), males and females subgroup(allele model, OR=0.86, 95%CI=0.81-0.92, dominant model, OR=0.84, 95%CI=0.77-0.92), and weight-bearing joints subgroup(allele model, OR=0.83,95%CI=0.78-0.89, dominant model, OR=0.80, 95%CI=0.73-0.88).

Conclusion: Our study demonstrated significant associations between the rs143383 polymorphism and the susceptibility to OA and LDD.

Keywords: Osteoarthritis; Lumbar disc degeneration; Polymorphism

Background

Osteoarthritis (OA), a major cause of pain and disability among the elderly, is the most common type of articular cartilage degeneration around the world [1,2]. According to published studies on the prevalence of OA, out of 100 people aged 60 years and over, approximately 10 people have clinical problems that might be attributable to OA [3]. The health care cost and financial burden of OA is increasing commensurate with the obesity prevalence and longevity [4]. OA definitely include diverse clinical types, such as knee, hip, hand, and temporomandibular joint OA [5]. Although the high prevalence and substantial public health concerns, the etiology of OA is still not well understood. Growing evidence have implicated that genetic predisposition, aging, obesity, occupation, smoking, physical activities, and traumatic injury may predispose to OA development [6-8].

Lumbar Disc Degeneration (LDD) is a kind of age-related skeletal disease, which is a common cause of disability and loss of productivity [9,10]. Epidemiologic evidence suggested that approximately 20% of patients with LDD required a surgical treatment owing to prolonged or aggravated leg pain [11,12]. OA is a multifactorial disease characterized by the degeneration of articulating synovial joints, while LDD is common in fibrocartilage and known to be a cause of low back pain. Although they are different type of cartilage, both of them can be viewed as sharing similar etiological routes including multiple abnormalities of joint and dysfunctions in bones and appendicular skeleton [13,14].

Growth differentiation factor 5(GDF5), an extracellular signaling molecule, is a member of the transforming growth factor-β(TGF-β) superfamily. It participates in the development, maintenance and repair of articular cartilage and synovial joint [15,16]. The GDF5 gene is located on chromosome 20q11.2 and spans 21.43 kb [17]. The mutations of the GDF5 gene may result in a series of skeletal disorders such as brachydactyly and chondrodysplasia [18-20]. Rs143383 is one of the most common studied polymorphisms in the 5'-UTR of GDF5, which has been proved to be a risk factor of OA and LDD [21]. T to C substitution of rs143383 may have an effect on transcriptional activity and the expression of GDF5 production, with lower GDF5 expression of the OA-associated risk allele [22,23].Several animal models have further confirmed the evidence supporting a crucial role of GDF5 in the development of OA [24-27]. The above evidence implies that the GDF5 polymorphism may play an essential role in the aetiology and pathogenesis of OA or LDD.A variety of previous studies have focused on the functions of the GDF5 polymorphism in the development of

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OA and/or LDD [28-43]. Most studies reported a positive association between rs143383 polymorphism and the risk of OA and LDD [28,29,31-38,40-43], while few studies generated negative results[30,39]. Two previous meta-analyses have reported that the rs143383 polymorphism was important in the progression of knee OA [44,45]. Zhang et al. performed an updated meta-analysis to explore the association between the genetic variant and OA in common affected sites [46]. However, they did not conduct subgroup analysis between case-control and cohort studies. Also, Williams et al. conducted the association of GDF5 with LDD risk in 3 cohorts from Northern Europe and indicated that a variant in the GDF5 gene may increase the risk of LDD in women. In view of the shared genetic risk and epidemiological characteristics between OA and LDD [13], it is necessary to perform a meta-analysis to explore a real association between this gene variation and these diseases. Most importantly, the associations between the rs143383 polymorphism and susceptibility to OA and LDD lack a quantitatively assessment. Therefore, we conducted this study to explore whether the associations vary by ethnicity, sex, study design, and disease sites.

Methods

Data sources

To identify those pertinent papers that explored the correlations of GDF5 rs143383 polymorphism with the susceptibility to OA and LDD, we comprehensively searched PubMed, Embase, SCOPUS, Google Scholar, and China National Knowledge Infrastructure (CNKI) databases (last updated search in March 30,2017). We utilized the following keywords regarding the GDF5 gene, OA, and LDD ("Growth Differentiation Factor 5" or "GDF5" or "rs143383" or "Cartilage-derived Morphogenetic Protein 1" or "CDMP1") for the exposure factors, and ("osteoarthritis" or "OA") and ("lumbar disc degeneration" or "LDD") for the outcome factors. No restriction was set on the language of the article. We also further scrutinized the bibliographies of relevant articles manually to identify all possible studies. When the enrolled papers supplied unclear data about their original publications, we would contact the first author and asked for clarifications.

Selection criteria

We searched for all human case-control studies and cohort studies providing genotypic data for GDF5 genetic polymorphisms, including subjects with OA and LDD. The enrolled studies reported sufficient information to estimate the odds ratio (OR) and 95% confidence intervals (CIs). We only selected studies that supplied the sample number and sufficient information about GDF5 genetic variants. Those studies with incomplete information would be excluded. OA and LDD were diagnosed based on clinical and/or radiographic evaluation, or ascertained by total joint replacement [44,45]. We merely enrolled the most recent and complete publications when multiple studies were published by the same authors on the same study population [46]. Studies based on family or sibling pairs were excluded because of linkage considerations [47,48].

Data extraction

In order to reduce bias and enhance credibility, two investigators independently extracted information from all included papers and arrived at a consensus on all the items through discussion and reexamination. The following relevant data were extracted from eligible studies: first author, year of publication, ethnicity and country of origin, primary reported disease, study design, source of controls, sample size, age, sex, genotyping method, BMI, OA definition criteria, available genotype, genotype and mutation frequencies, HWE evidence in controls. All authors approved the final determination of these studies.

Statistical analysis

We assessed Hardy-Weinberg equilibrium (HWE) separately in the control group in different studies. Deviation from HWE was considered statistically significant when $P < 0.05$. To calculate the effect size for each study, the summary ORs with 95% CIs were used the allele model(mutant allele C versus wild allele T), dominant model (TC+CC versus TT), and recessive model (CC versus TC+TT) with the utilization of Z test. In order to supply quantitative evidence of all included studies and minimized the variance of the summary ORs with 95% CIs, we conducted the current statistical meta-analysis by employing a random-effect model or a fixed-effect model. The subgroup meta-analysis was also conducted by ethnicity, disease site, sex, and study design to explore potential effect modification, and heterogeneity was evaluated by the Cochran's Q-statistic ($P<0.05$ was regarded as statistically significant) [49]. As a result of the low statistical power of the Cochran's Q-statistic, the I2 test (0%, no heterogeneity; 100%, maximal heterogeneity) was also conducted to reflect the possibility of heterogeneity [50]. The sensitivity analysis was performed by omitting each study in our meta-analysis to reflect the influence of the individual data set on the pooled ORs. The funnel plot was constructed to assess publication bias, which might affect the validity of the estimates. The symmetry of the funnel plot was further evaluated by Egger's linear regression test [51]. P value of <0.05 was regarded as statistically significant. All statistical analyses were performed with STATA 14.0 software (Stata Corporation, College Station, TX).

Results

Characteristics of studies

The flow chart of screening displayed the detailed process of the study selection (Figure 1). A total of 97 papers were obtained after an initial literature search from these electronic database through screening the title and abstract. We then excluded duplicates (n=14), letters (n=2), reviews or meta-analysis (n=8), non-human studies (n=16), and studies not associated with our research topics (n=19). The remaining studies (n=38) were reviewed and additional 22 studies were excluded for not being case-control or cohort studies (n=6), not relevant to the GDF5 gene (n=3), not related to OA or LDD (n=7), or unavailable genotyping data (n=6). In the final analysis, there were 15 articles that were combined to perform an association analysis of rs143383 with OA and/or LDD [28-33,35-43].The characteristics of these included articles were presented in Table 1. All the studies conformed to HWE in the control group. Among these available articles, there were 9 case-control studies and 6 cohort studies including 18732 patients and 24335 controls. Seven studies Table 2 were conducted in Asian populations, while eight studies were based on Caucasians. Two studies only covered females, whereas other studies contained males and females. The weight-bearing joints involved knee and hip sites, while non-weight-bearing joints affected hand and temporomandibular joints. The definition of OA or LDD contained radiographic criteria (Kellgren-Lawrence grade ≥ II), clinical criteria (the American College of Rheumatology), and total joint replacement.

Overall population

Our meta-analysis had a total of 33 separate studies to explore the association between the rs143383 polymorphism and OA and/or LDD. As shown in Table 3, the results of overall comparison showed that significant associations were observed under the allele model (OR=0.86, 95%CI=0.81-0.91) and dominant model (OR=0.86, 95%CI=0.79-0.91).

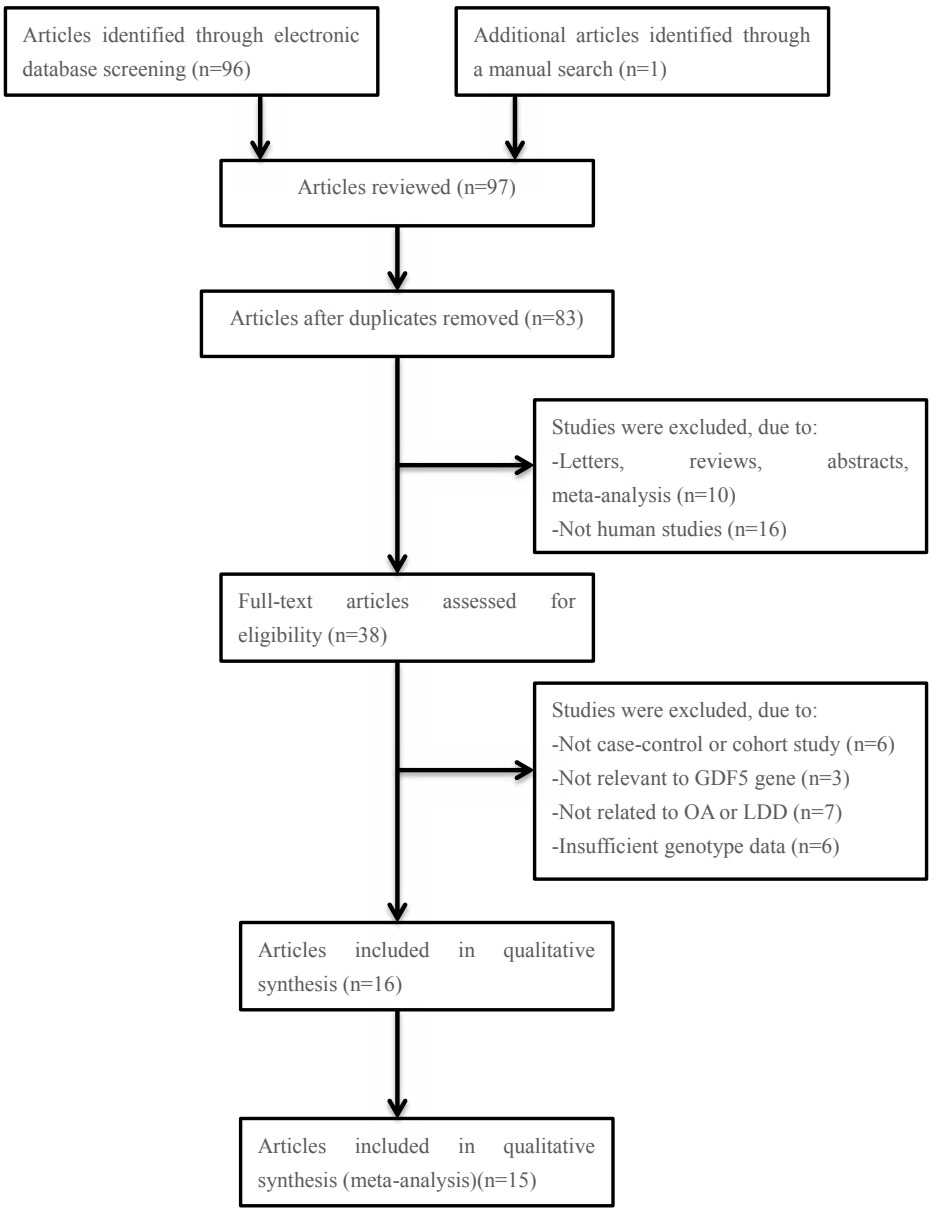


Figure 1: Flow chart of literature search and study selection.

Subgroup analyses by ethnicity

In the subgroup analyses based on ethnicity (Figure 2), studies were divided into Asian and Caucasian. Rs143383 polymorphism was positively related to the risk of OA and LDD in Asian (allele model: OR=0.72, 95%CI=0.61-0.84; dominant model: OR=0.69,95%CI=0.56-0.85). A similar correlation was also observed in Caucasian (allele model: OR=0.91,95%CI=0.87-0.95; dominant model: OR=0.89,95%CI=0.82-0.96).

Subgroup analyses by study design

After stratified by study design (Figure 3), the T allele of GDF5 was found to be significantly associated with OA and LDD in case-control study(allele model: OR=0.80, 95%CI=0.73-0.88; dominant model: OR=0.80, 95%CI=0.70-0.91) and cohort study(allele model: OR=0.91, 95%CI=0.86-0.97; dominant model: OR=0.87, 95%CI=0.79-0.96).

Subgroup analyses by sex

The significant association between rs143383 polymorphism and the risk of OA and/or LDD was only observed in the males and females subgroup under the allele model (OR=0.86, 95%CI=0.81-0.92) and dominant model (OR=0.84, 95%CI=0.77-0.92). However, the statistically significant association was not seen only for women under the allele model (OR=0.85, 95%CI=0.71-1.02) and dominant model (OR=0.81, 95%CI=0.64-1.02).

Subgroup analyses by disease sites

Further subgroup analyses based on disease sites implied that

First author	Year of publication	Ethnicity	Primary report	Study design	Source of controls	Mean age		BMI(kb/m²)		Genotyping method	OA definition
						Cases	Controls	Cases	Controls		
Southam [28]	2007	Caucasian	OA(knee,hip,hand)	Case-control	HB	65.0	69.0	NA	NA	PCR-RFLP, Taqman	Radiographic*, TKR
Miyamoto [29]	2007	Asian	OA(knee,hip)	Case-control	HB	58.8	56.8	24.9	23.6	Taqman,Invader,DNA fragment analysis, direct sequence	Radiographic
Tsezou [30]	2007	Caucasian	Knee OA	Case-control	HB	67.9	65.2	29.5	25.0	Direct sequence	Radiographic
Yao [31]	2008	Asian	Knee OA	Case-control	PB	58.8	56.8	24.8	23.6	Real-time PCR	Radiographic, clinic#l+
Chapman [32]	2008	Caucasian	OA(knee, hip, hand)	Cohort study	PB	60.4	59.4	NA	NA	Mass spectrometry	Radiographic
Vaes [33]	2009	Caucasian	OA(knee, hip, hand)	Cohort study	PB	>55.0	>55.0	25.5	25.6	Taqman	Radiographic
Evangelo [34]	2009	Caucasian	Knee OA	Cohort study	PB	74.8	74.8	NA	NA	Centaurus platform	Radiographic, TKR
Valdes [35]	2009	Caucasian	OA(knee, hip)	Cohort study	PB	68.5	66.9	26.8	25.2	Allele-specific PCR	Radiographic
Cao [36]	2010	Asian	Knee OA	Case-control	PB	63.0	44.0	NA	NA	PCR-RFLP	TKR
Valdes [37]	2011	Caucasian	Knee OA	Cohort study	PB	65.5	65.5	27.7	24.1	Allele-specific PCR	Radiographic
Tawonsawatruk [38]	2011	Asian	Knee OA	Case-control	HB	68.5	59.3	26.6	24.5	PCR-RFLP	TKR
Shin [39]	2012	Asian	Knee OA	Cohort study	PB	67.4	62.7	25.3	24.1	High resolution melting analysis	Radiographic
Mishra [40]	2013	Asian	Knee OA	Case-control	HB	54.0	55.2	25.5	23.7	PCR-RFLP	Radiographic, clinical
Bijsterbosch [41]	2013	Caucasian	Hand OA	Case-control	PB	60.0	61.0	27.2	26.2	Mass spectrometry	Radiographic
Williams [42]	2011	Caucasian	LDD	Cohort study	PB	65.7	62.9	26.3	25.0	Illumina paltform	Radiographic
Xiao [43]	2015	Asian	TMJOA	Case-control	HB	47.8	41.2	NA	NA	Direct sequence	Radiographic

NA data not available, HB hospital-based, PB population-based, LDD lumbar disc degeneration, TMJOA temporomandibular joint osteoarthritis, TKR total knee replacement, BMI body mass index.
*Radiographic criteria (Kellgren-Lawrence grade≥Ⅱ)
+Clinical criteria are based on the American College of Rheumatology

Table 1: Principle characteristics of all studies for GDF5 rs143383 polymorphism included in the meta-analysis

Author	Year	Country	Disease	Study participants(females)		Genotypes distribution										P_{HWE} [a]
						Cases					Controls					
						TT	TC	CC	T	C	TT	TC	CC	T	C	
Southam	2007	Spain	Knee OA	274(178)	1196(614)	102	136	36	340	208	439	563	194	1441	951	0.550
Southam	2007	Spain	Hip OA	304(197)	1196(614)	102	157	45	361	247	439	563	194	1441	951	0.550
Southam	2007	Spain	Hand OA	240(156)	1196(614)	98	105	37	301	179	439	563	194	1441	951	0.550
Southam	2007	UK	Knee OA	509(331)	822(422)	219	238	52	676	342	324	372	126	1020	624	0.262
Southam	2007	UK	Hip OA	1290(839)	822(422)	519	607	164	1645	935	324	372	126	1020	624	0.262
Southam	2007	UK	Hand OA	515(335)	822(422)	233	226	56	692	338	324	372	126	1020	624	0.262
Miyamoto	2007	China	Knee OA	313(205)	485(316)	197	97	19	491	135	244	193	48	681	289	0.283
Miyamoto	2007	Japan	Knee OA	718(664)	861(405)	444	243	31	1131	305	473	330	58	1276	446	0.966
Miyamoto	2007	Japan	Hip OA	998(923)	983(462)	701	266	31	1668	328	542	371	70	1455	511	0.552
Tsezou	2007	Greece	Knee OA	251(205)	268(169)	95	126	30	316	186	99	125	44	323	213	0.669
Yao	2008	China	Knee OA	298(207)	452(316)	189	93	16	471	125	232	182	38	646	258	0.785
Chapman	2008	Netherland	Knee OA	142(NA)	724(NA)	54	72	16	180	104	289	331	104	909	539	0.558
Chapman	2008	Netherland	Hip OA	106(NA)	724(NA)	43	50	13	136	76	289	331	104	909	539	0.558
Chapman	2008	Netherland	Hand OA	200(NA)	724(NA)	64	111	25	239	161	289	331	104	909	539	0.558
Vaes	2009	Netherland	Knee OA	667(306)	2097(1007)	276	298	93	850	484	752	1014	331	2518	1676	0.724
Vaes	2009	Netherland	Hip OA	287(NA)	2757(NA)	111	131	45	353	221	1040	1298	419	3378	2136	0.672
Vaes	2009	Netherland	Hand OA	870(395)	2080(1036)	367	391	112	1125	615	790	1041	249	2621	1539	0.080
Evangelou	2009	UK	Knee OA	1003(NA)	647(NA)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-
Evangelou	2009	Iceland	Knee OA	1071(NA)	1169(NA)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-
Evangelou	2009	UK	Hip OA	790(NA)	921(NA)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-
Evangelou	2009	Iceland	Hip OA	1724(NA)	1160(NA)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-
Evangelou	2009	Iceland	Hand OA	2510(NA)	1169(NA)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	-
Valdes	2009	UK1	Knee OA	259(259)	509(509)	126	98	35	350	168	181	244	84	606	412	0.908
Valdes	2009	UK2	Knee OA	735(631)	646(309)	337	313	85	987	483	238	329	79	805	487	0.320
Valdes	2009	UK1	Hip OA	77(NA)	509(NA)	32	27	18	91	63	181	244	84	606	412	0.908
Valdes	2009	UK2	Hip OA	787(NA)	646(NA)	345	339	103	1029	545	238	329	79	805	487	0.320
Cao	2010	Korea	Knee OA	276(226)	298(135)	150	115	11	415	137	159	113	26	431	165	0.361
Valdes	2011	Estonia	Knee OA	65(45)	427(295)	32	24	9	88	42	168	179	80	515	339	0.056
Valdes	2011	Netherland	Knee OA	867(417)	758(521)	413	361	93	1187	547	294	354	110	942	574	0.837
Valdes	2011	UK	Knee OA	1141(560)	536(371)	467	511	163	1445	837	219	237	80	675	397	0.229
Tawonsawatruk	2011	Thailand	Knee OA	90(79)	103(93)	38	41	11	117	63	33	47	23	113	93	0.425
Shin	2012	Korea	Knee OA	725(554)	1737(855)	382	305	38	1069	381	942	689	106	2573	901	0.176
Mishra	2013	India	Knee OA	300(196)	300(177)	124	130	46	378	222	84	160	56	328	272	0.188
Bijsterbosch	2013	Netherland	Hand OA	248(201)	725(587)	86	131	31	303	193	290	330	105	910	540	0.480
Williams	2011	Netherland1	LDD	519(519)	944(944)	194	247	78	635	403	340	443	161	1123	765	0.418
Williams	2011	Netherland2	LDD	124(124)	448(448)	48	51	25	147	101	160	215	73	535	361	0.957
Williams	2011	London	LDD	189(189)	569(569)	73	85	31	231	147	225	250	94	700	438	0.086
Xiao	2015	China	TMJOA	114(114)	126(126)	62	47	5	171	57	53	54	19	160	92	0.397

NA data not available, LDD lumbar disc degeneration, TMJOA temporomandibular joint osteoarthritis.
[a]*P* value for Hardy-Weinberg equilibrium test in controls

Table 2: Genotypes distribution of GDF5 rs143383 polymorphism among cases and controls.

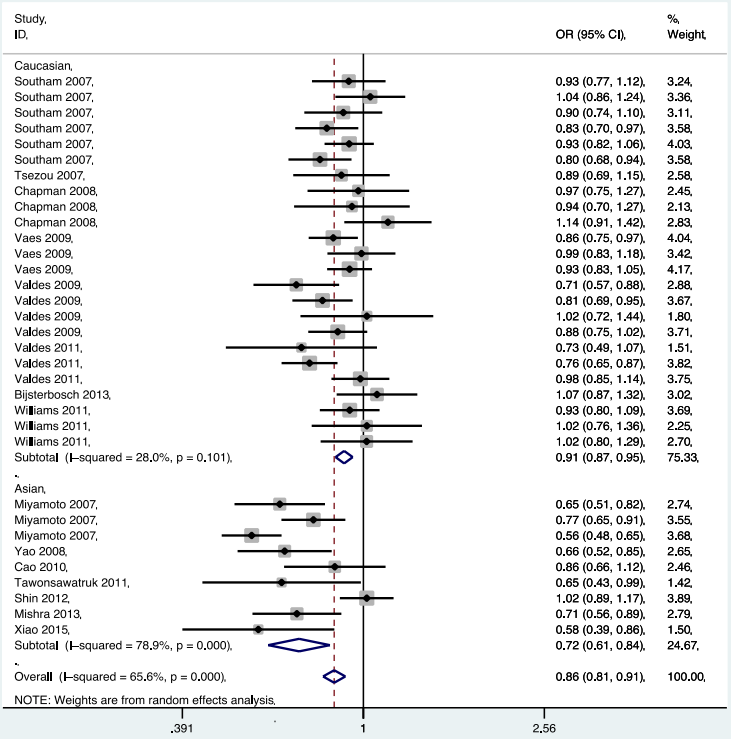
Subgroup	Genetic model	No. of studies	Type of model	Test of heterogeneity		Test of association	
				I^2 (%)	*P*-value	OR	95% CI
Overall	C vs. T	33	Random	65.6	0.000	0.86	0.81-0.91
	CC vs. TT	33	Random	42.9	0.005	0.75	0.68-0.83
	CT vs. TT	33	Random	67.8	0.000	0.86	0.79-0.94
	CC+CT vs. TT(Dominant model)	33	Random	68.5	0.000	0.83	0.77-0.91
	CC vs. CT+TT(Recessive model)	33	Random	35.1	0.026	0.82	0.75-0.89
Ethnicity							
Caucasian	C vs. T	24	Fixed	28.0	0.101	0.91	0.87-0.95
	CC vs. TT	24	Fixed	0	0.500	0.83	0.77-0.89
	CT vs. TT	24	Random	57.9	0.000	0.90	0.83-0.99
	CC+CT vs. TT(Dominant model)	24	Random	51.2	0.002	0.88	0.82-0.96
	CC vs. CT+TT(Recessive model)	24	Fixed	1.3	0.444	0.88	0.82-0.95
Asian	C vs. T	9	Random	78.9	0.000	0.72	0.61-0.84
	CC vs. TT	9	Fixed	41.8	0.088	0.51	0.40-0.65
	CT vs. TT	9	Random	77.8	0.000	0.74	0.60-0.91
	CC+CT vs. TT(Dominant model)	9	Random	88.0	0.000	0.69	0.56-0.85
	CC vs. CT+TT(Recessive model)	9	Fixed	28.5	0.191	0.59	0.48-0.73
Study design							
Case-control	C vs. T	16	Random	72.9	0.000	0.80	0.73-0.88
	CC vs. TT	16	Random	49.5	0.013	0.63	0.54-0.75
	CT vs. TT	16	Random	73.2	0.000	0.85	0.74-0.98
	CC+CT vs. TT(Dominant model)	16	Random	74.7	0.000	0.80	0.70-0.91
	CC vs. CT+TT(Recessive model)	16	Fixed	23.5	0.188	0.69	0.61-0.79
Cohort study	C vs. T	17	Random	39.2	0.049	0.91	0.86-0.97
	CC vs. TT	17	Fixed	0	0.530	0.85	0.78-0.94
	CT vs. TT	17	Random	63.0	0.000	0.87	0.78-0.97
	CC+CT vs. TT(Dominant model)	17	Random	59.1	0.001	0.87	0.79-0.96
	CC vs. CT+TT(Recessive model)	17	Fixed	0	0.624	0.93	0.85-1.02
Sex							
Males and females	C vs. T	28	Random	67.1	0.000	0.86	0.81-0.92
	CC vs. TT	28	Random	41.4	0.012	0.75	0.68-0.83
	CT vs. TT	28	Random	70.4	0.000	0.87	0.79-0.95
	CC+CT vs. TT(Dominant model)	28	Random	70.6	0.000	0.84	0.77-0.92
	CC vs. CT+TT(Recessive model)	28	Random	33.4	0.046	0.81	0.74-0.89
Only females	C vs. T	5	Random	63.6	0.027	0.85	0.71-1.02
	CC vs. TT	5	Random	59.2	0.044	0.77	0.54-1.10
	CT vs. TT	5	Fixed	52.3	0.079	0.82	0.65-1.04

	CC+CT vs. TT(Dominant model)	5	Random	58.7	0.046	0.81	0.64-1.02	
	CC vs. CT+TT(Recessive model)	5	Fixed	52.2	0.079	0.86	0.64-1.17	
Disease site								
Weight-bearing joints	C vs. T	24	Random	67.7	0.000	0.83	0.78-0.89	
	CC vs. TT	24	Random	39.8	0.024	0.72	0.64-0.80	
	CT vs. TT	24	Random	70.0	0.000	0.83	0.75-0.92	
	CC+CT vs. TT(Dominant model)	24	Random	70.6	0.000	0.80	0.73-0.88	
	CC vs. CT+TT(Recessive model)	24	Fixed	30.5	0.079	0.79	0.72-0.87	
Nonweight-bearing joints	C vs. T	6	Random	63.3	0.018	0.91	0.80-1.04	
	CC vs. TT	6	Random	56.6	0.042	0.82	0.62-1.07	
	CT vs. TT	6	Random	70.9	0.004	0.97	0.78-1.21	
	CC+CT vs. TT(Dominant model)	6	Random	69.4	0.006	0.93	0.76-1.14	
	CC vs. CT+TT(Recessive model)	6	Random	55.2	0.048	0.83	0.65-1.06	
LDD	C vs. T	3	Fixed	0	0.772	1.04	0.92-1.17	
	CC vs. TT	3	Fixed	0	0.622	1.07	0.84-1.36	
	CT vs. TT	3	Fixed	0	0.612	1.04	0.87-1.25	
	CC+CT vs. TT(Dominant model)	3	Fixed	0	0.815	1.05	0.88-1.24	
	CC vs. CT+TT(Recessive model)	3	Fixed	0	0.383	0.96	0.77-1.20	

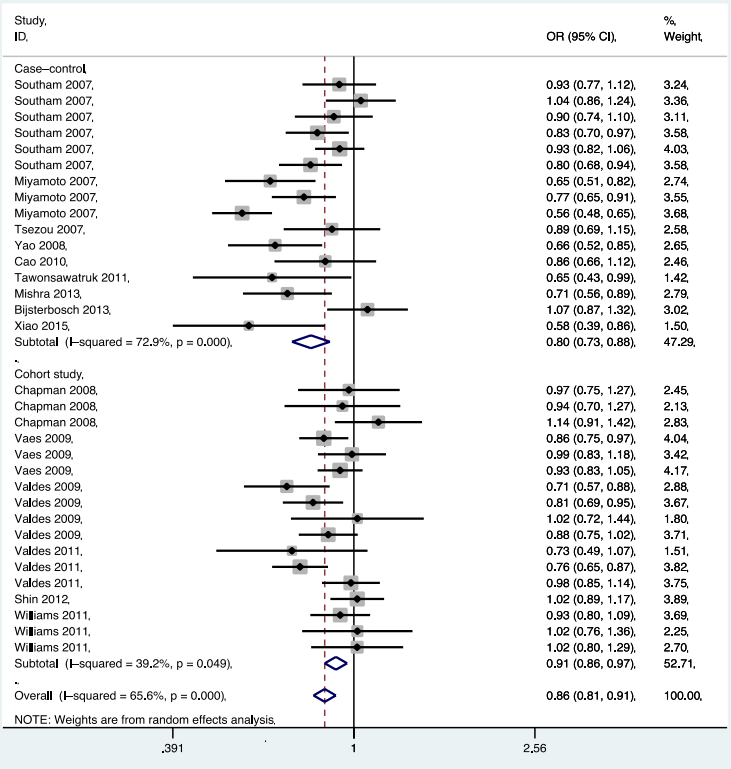
OR odds ratio, CI confidence interval, LDD lumbar disc degeneration.

Table 3: Summary ORs and 95%CIs of the association between GDF5 rs143383 polymorphism and OA susceptibility

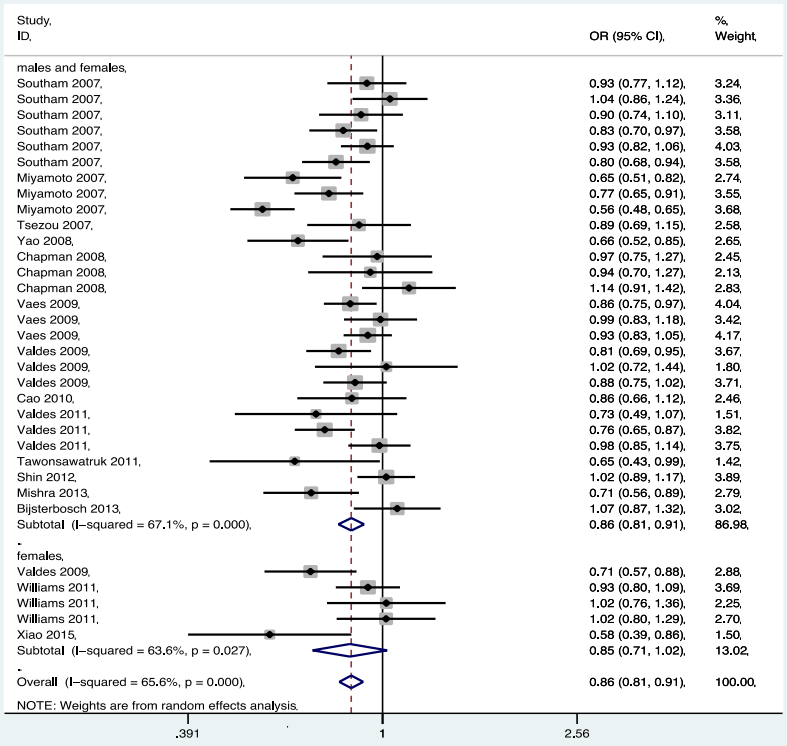
Ethnicity: allele model



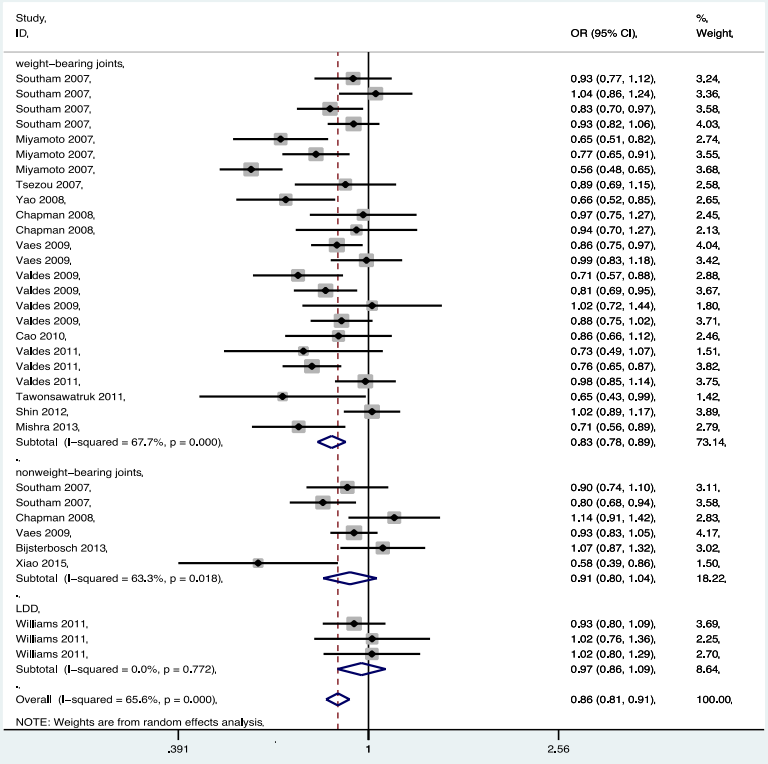
Study design: allele model



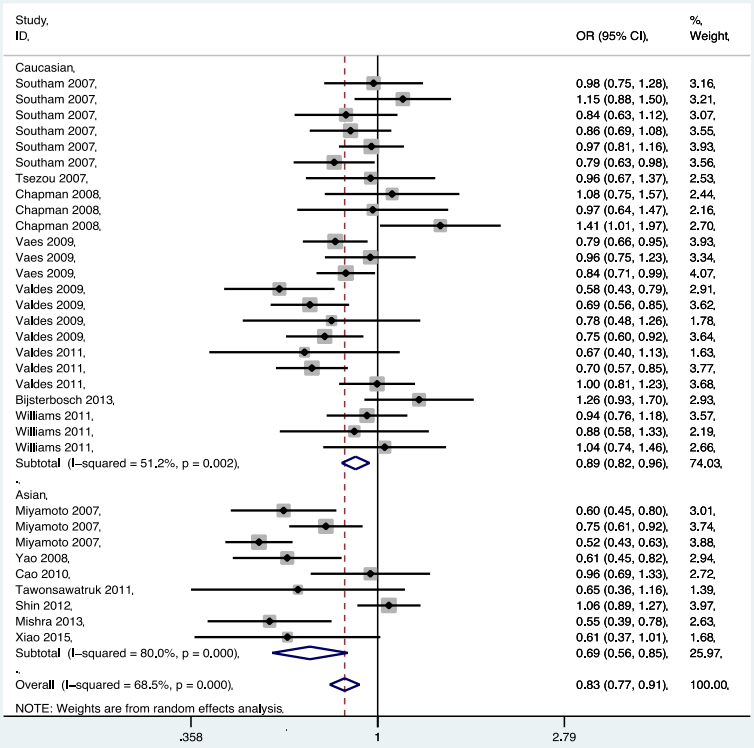
Sex: allele model



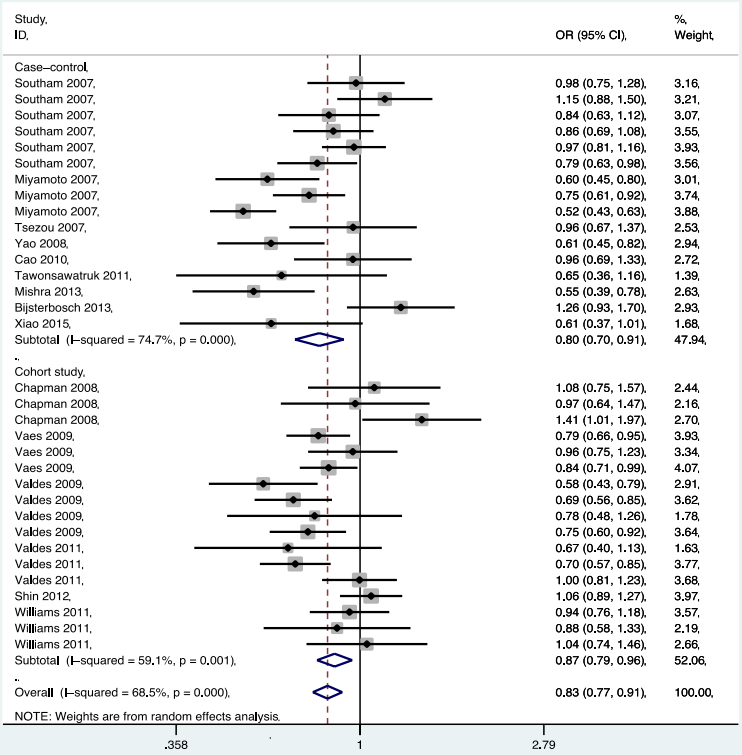
Disease site: allele model

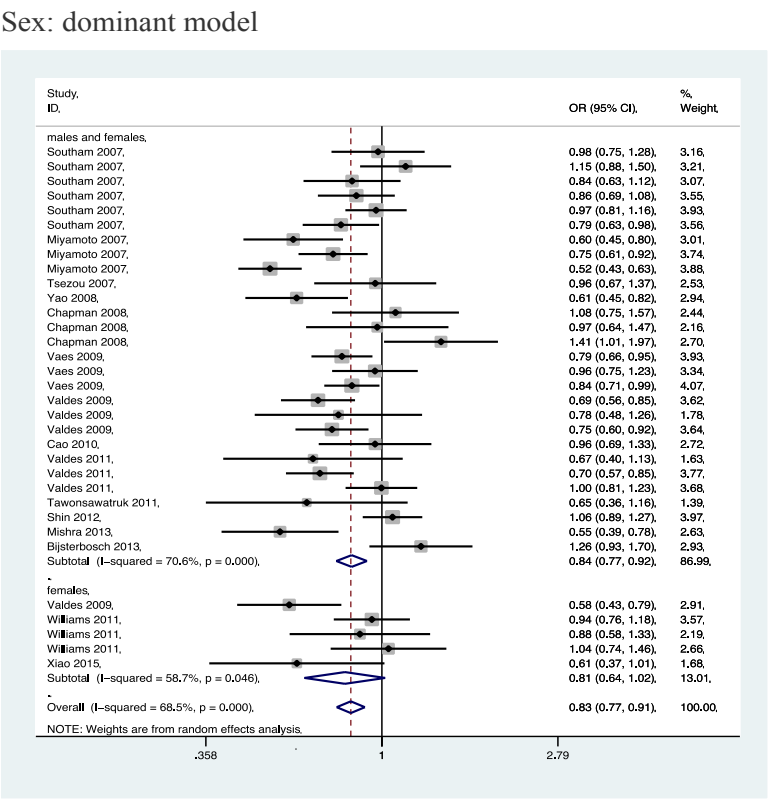


Ethnicity: dominant model



Study design: dominant model





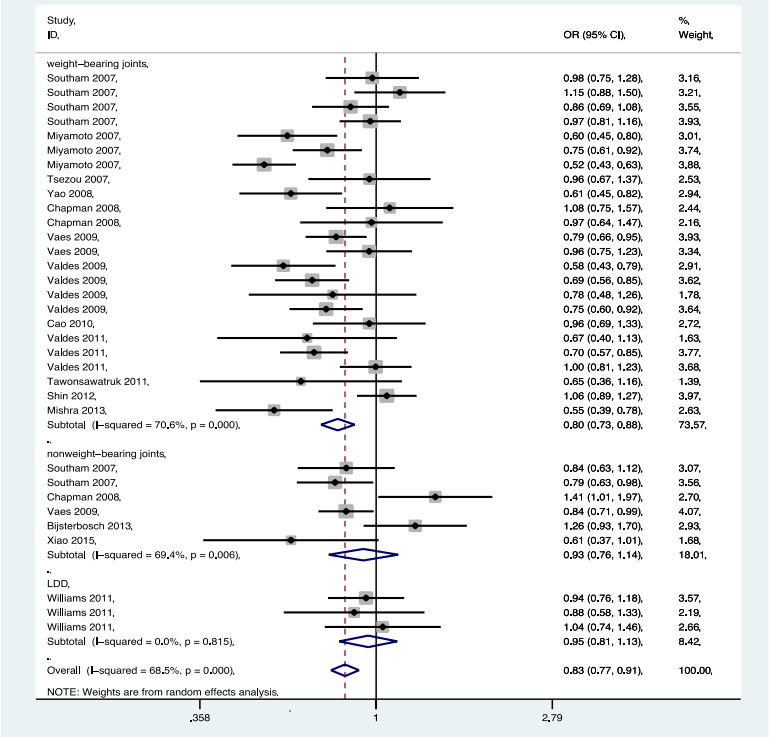


Figure 2: Subgroup analysis for the correlations of rs143383 between the risks of OA and LDD (A) Ethnicity: allele model; (B) Study design: allele model; (C) Sex: allele model; (D) Disease site: allele model; (E) Ethnicity: dominant model; (F) Study design: dominant model; (G) Sex: dominant model; (H) Disease site: dominant model.

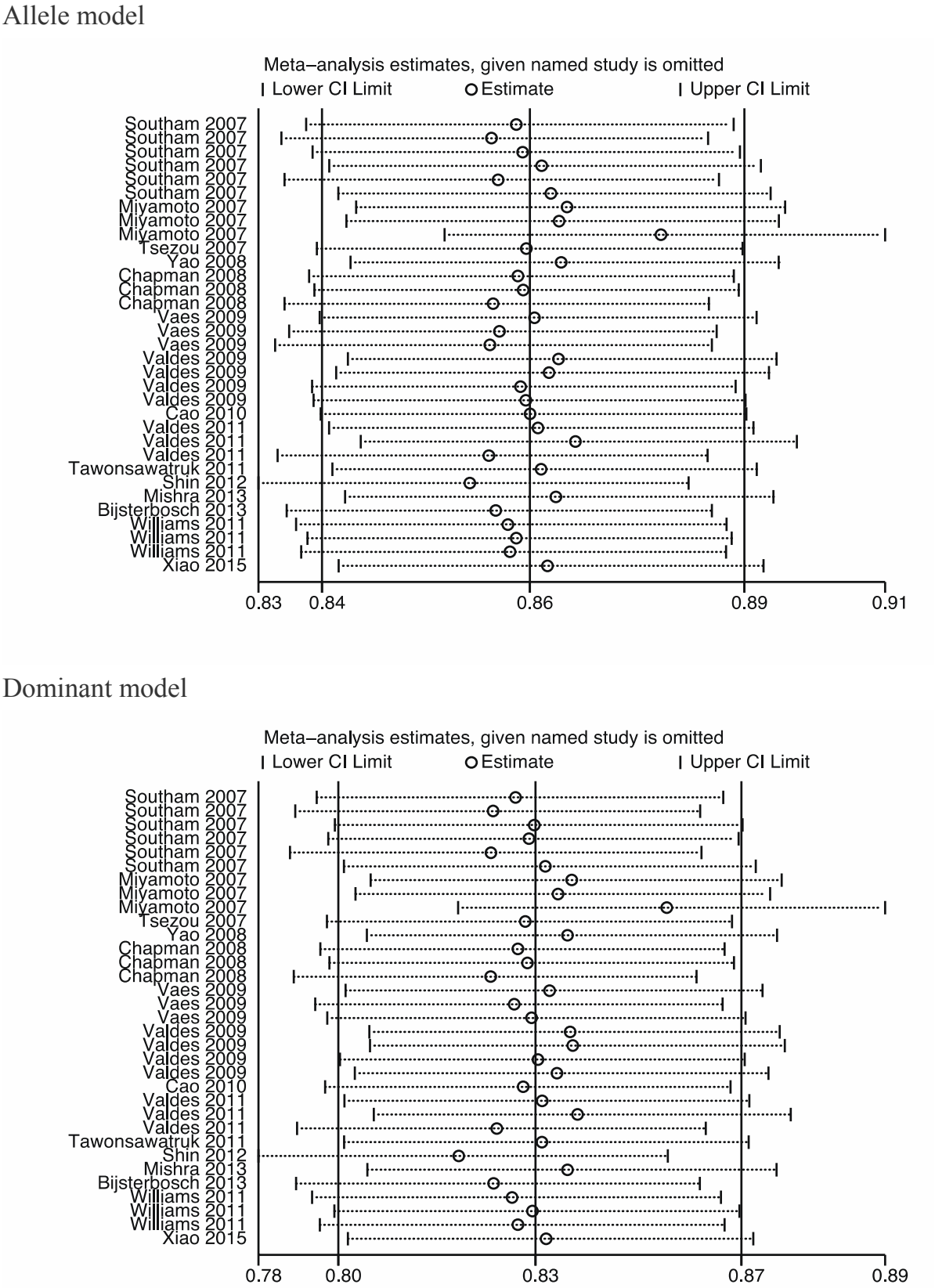


Figure 3: Sensitivity analysis of the summary ORs in the allele model and dominant model (A) Allele model; (B) Dominant model.

rs143383 polymorphism was positively related to the occurrence of weight-bearing joints under both allele model (OR=0.83, 95%CI=0.78-0.89) and dominant model (OR=0.80, 95%CI=0.73-0.88). Whereas, the association of rs143383 with the occurrence of non-weight-bearing joints and LDD was not observed under the allele model (non-weight-bearing joints: OR=0.91, 95%CI=0.80-1.04; LDD: OR=0.93, 95%CI=0.76-1.14) and dominant model (non-weight-bearing joints: OR=1.04, 95%CI=0.92-1.17; LDD: OR=1.05, 95%CI=0.88-1.24).

Sensitivity analysis

We also performed a sensitivity analysis to evaluate the stability of the overall results. When each individual study was omitted, the pooled ORs of the allele model and dominant model were not substantially changed (Figure 5). This indicated that results were statistically robust.

Publication bias

The funnel plots for ORs of the allele model and dominant model were presented in Figure 4. Shape of the funnel plot did not reveal any evidence of obvious asymmetry. Subsequently, results of Egger's test did not suggest any evidence of publication bias (allele model: OR=0.49, 95%CI=-2.72-1.33; dominant model: OR=0.89, 95%CI=-1.94-2.22).

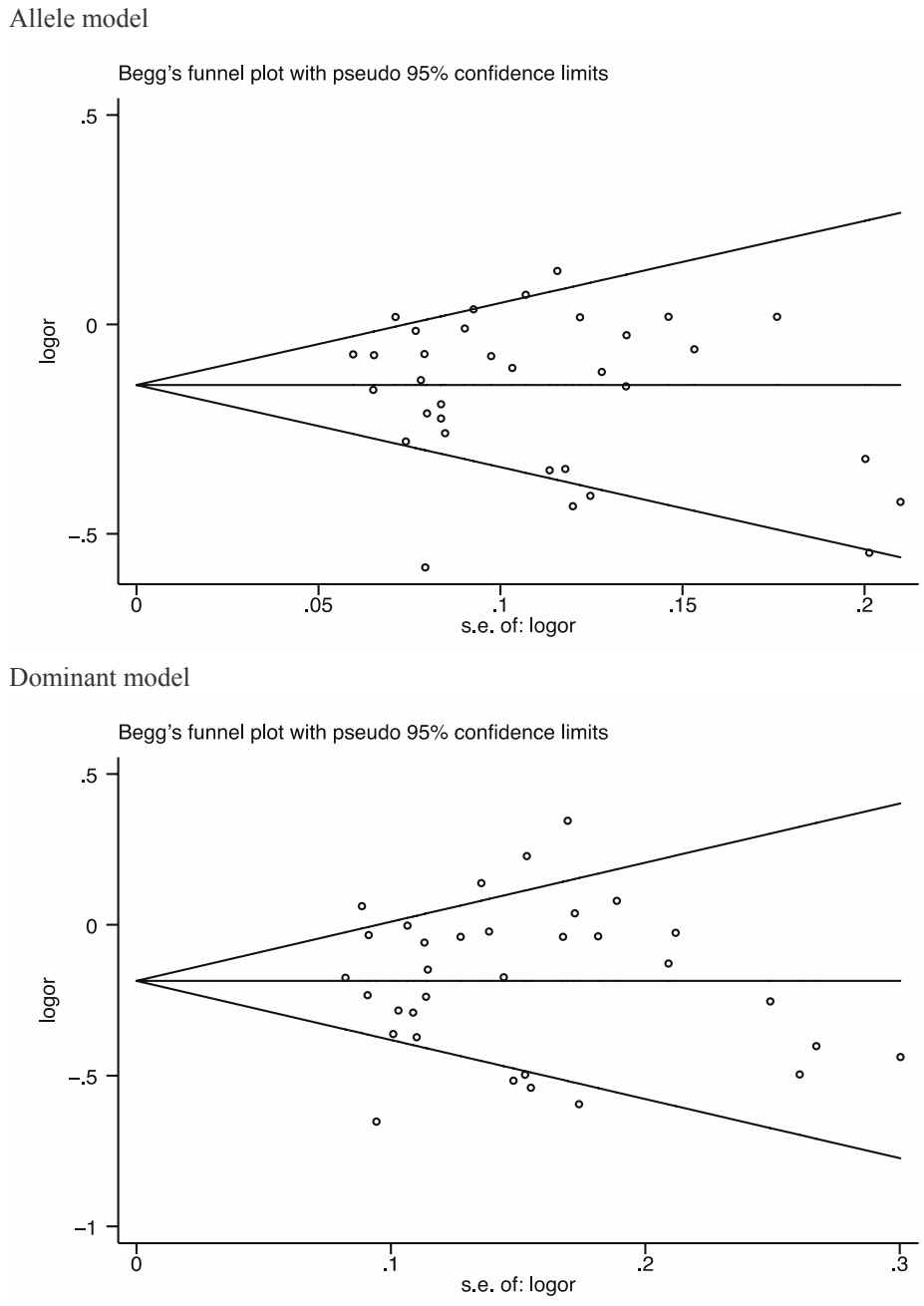


Figure 4: Begg's funnel plot of GDF5 rs143383 polymorphism and OA/LDD under the allele model and dominant model (A) Allele model (B) Dominant model.

Discussion

Several studies have revealed the facts that GDF5 participated in controlling bone formation and resorption of OA and LDD [52-54]. In consideration of similar etiological routes and a shared genetic risk between OA and LDD, we also examined the relationship between GDF5 polymorphism and LDD susceptibility. To the best of our knowledge, this is the first meta-analysis which comprehensively assessed the association between rs143383 polymorphism and the risk of OA and LDD. The results indicated that GDF5 rs143383 polymorphism was highly related to the development of OA with protective associations for the C allele, which has been demonstrated in different populations. Also, the study indicated that the SNP in the GDF5 gene exerted its influence on LDD risk, including direct effects on the disc or indirect effects on spinal ligaments. Recently, we have noticed that three meta-analyses have been conducted to explore the association between GDF5 polymorphism and knee OA based on case-control studies, illustrating that the T allele might increase susceptibility to knee OA in Asian and Caucasian populations [55,56]. With the update of data, the latest comprehensive meta-analysis was performed to explore the association between genetic variants of GDF5 and OA of knee, hip and hand using all published case-control and cohort studies [52]. The results demonstrated that GDF5 polymorphism was significantly correlated with OA risk in knee and hip sites among different ethnicities. However, the findings did not distinguish the bias of observational studies, that of case-control study is recall bias and that of cohort study is withdraw bias, which may distort the results of the meta-analysis. In our study, significant heterogeneity was observed in our overall effect. The diversity in ethnicity, study design, sex, and OA sites would further complicate the heterogeneity. Moreover, OA cases were defined with different criteria in different studies, which might be one of sources of observed heterogeneity. Some studies defined their patients using the K/L classification and/or ACR criteria [29-35,37,39-43], while other studies defined their patients using the TKR [28,36,38]. This discrepancy on those key characteristics of the participants such as age and BMI, might also lead to the heterogeneity [34]. In order to further clarify the source of heterogeneity and attenuate the heterogeneity, we performed subgroup analyses. When being stratified by ethnicity, study design, sex, and disease sites, the results further strengthened our conclusion that GDF5 polymorphism rs143383 was related to the susceptibility to OA/LDD. Additionally, we also performed a sensitivity analysis omitting each study, which indicated that the overall results should be relatively stable. Although the primary results of this meta-analysis were suggestive, several potential limitations should be acknowledged. First of all, we explored only one SNP(rs143383) in the GDF5 locus. The evidence may be relatively weak due to one genetic marker. And, we have not addressed the interactions of gene-gene and gene-environment owing to the lack of relevant information. What's more, the number of studies in non-weight-bearing joints was definitely insufficient, indicating that this study may not have enough power on exploring the association between GDF5 rs143383 and OA, especially for LDD. Last but not the least, body mass index, age, and other potential confounding factors were definitely recognized as important risk factors of OA. A more precise analysis based on adjusted estimates could be conducted if these data were available. In conclusion, this meta-analysis demonstrated a significant association between the rs143383 polymorphism and the susceptibility to OA and LDD. C allele of rs143383, located in the 5'-UTR of GDF5, is a protective factor and can confer susceptibility to OA and LDD in these subjects. Given the fact that the genetic factors may vary with different gender and populations, further research should be conducted in large and more diverse populations.

Ethics approval and consent to participate: Not applicable

Consent to Publish: Not applicable

Availability of Data and Materials

All of the data for this study are contained in the manuscript, the additional files, or the individuals included in this systematic review.

Competing Interests

The authors are fully responsible for all content and editorial decisions, and they have declared that no conflicts of the interests exist.

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Authors' Contributions

Liying Jiang drafted the protocol and wrote the final manuscript. Aidong Liu contributed to the research design and made critical revisions. Yidan Wang and Xiaoyue Zhu were responsible for the statistical design of trial and wrote portions of the statistical methods, data handing and monitoring sections. All authors have read and approved the final manuscript.

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