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ORIGINAL ARTICLE

Vitamin D receptor gene polymorphisms and lumbar disc degeneration: a systematic review and meta-analysis

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Abstract
Purpose To examine the association between Vitamin D receptor (VDR) gene polymorphisms and lumbar disc degeneration (LDD) predisposition.
Methods A comprehensive literature search was conducted to identify all the relevant studies. The allele/genotype frequencies were extracted from each study. We calculated the pooled odds ratios (ORs) and 95 % confidence intervals (CI) to assess the strength of the association between the VDR gene polymorphisms and LDD risk. Statistical analysis was performed using RevMan 5.31 software.
Results A total of 23 case–control studies (1835 cases and 1923 controls) were included in this systematic review. For the TaqI (rs731236), FokI (rs2228570) and ApaI (rs7975232) polymorphisms of VDR gene, nine studies, seven studies, and five studies, were eventually included in the meta-analysis, respectively. There was no evidence that the VDR gene polymorphisms (TaqI, FokI, ApaI) had significant associations with LDD risk.(for TaqI allelic comparison, OR = 1.07, 95 % CI 0.81–1.40, $p = 0.64$; for FokI allelic comparison, OR = 1.23, 95 % CI 0.83–1.82, $p = 0.31$; for ApaI allelic comparison, OR = 0.79, 95 % CI 0.55–1.14, $p = 0.20$). For stratified analyses by ethnicity and study design, no significant associations were found in Caucasian population and Asian population, as well as the population-based studies and hospital-based studies under all genetic models.
Conclusions TaqI, FokI, and ApaI polymorphisms of VDR gene were not significantly associated with the predisposition of LDD. Large-scale and well-designed international studies are needed to further analyze this field.

Keywords Lumbar disc degeneration · Meta-analysis · Polymorphisms · Systematic review · Vitamin D receptor

Introduction

Low back pain is a common musculoskeletal disorder leading to work disability. It is estimated that 50-80 % of adults experience at least one episode of back pain during their lifetime [1]. Lumbar disc degeneration (LDD) is regarded as a major cause of low back pain [2, 3], which is a multifaceted chronic process that alters the structure and function of lumbar intervertebral discs [4]. Many environmental and constitutional risk factors were reported to have accelerated disc degeneration [5]. However, the exact etiology of LDD remains unknown. Recently, researchers found that genetic factors play a crucial role in the occurrence and development of LDD [6, 7].

Vitamin D receptor (VDR) gene is one of the most studied candidate genes associated with LDD, which is located on human chromosome 12, with a length of 100 kb, and transcribed and translated into VDR. VDR is an endocrine member of the nuclear receptor superfamily for steroid hormones and binds the biologically most active vitamin D metabolite, 1α, 25-dihydroxyvitamin D_3 (1α, 25$(OH)_2D_3$), and is known to have an important role in normal bone mineralization and remodeling [8]. Given the functional importance of the VDR, mutations in the VDR gene and

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adjacent regulatory regions are plausible susceptibility candidates for LDD predisposition [9]. To date, several groups have reported the association between the VDR gene polymorphisms including TaqI (rs731236), FokI (rs2228570) and ApaI (rs7975232) and the risk of LDD [10–22]. Unfortunately, these published studies have yielded contradictory results rather than conclusive evidence. For example, the case–control studies suggested an association with TaqI and FokI polymorphisms in Chinese, Brazilian and Turkish populations [11, 12, 20, 23]. However, these associations were not confirmed in Finnish, Japanese and Danish populations [14, 15, 17, 19]. A single study may be underpowered to detect slight effects of these SNPs on LDD due to the relatively small sample size. Under the circumstances, systematic review and meta-analysis could provide more credible information by improving the statistical power of the association analysis [24]. A previous meta-analysis suggested that VDR gene polymorphisms (TaqI, FokI, ApaI) were not significantly associated with the risk of LDD [25]. In the past several years, many studies addressing this topic have been published in different ethnic populations [10, 13, 20, 22, 26–28]. Therefore, it is necessary to update the meta-analysis, which might provide more solid evidence and minimize potential bias caused by limited publications in the past. In this study, we performed a systematic review and meta-analysis to provide a formal assessment and synthesis of the currently available evidence concerning the VDR gene polymorphisms and susceptibility to LDD.

Materials and methods

Literature and search strategy

PubMed, EMBASE, and ISI Web of Science databases were searched from inception using the following key words: ''disc degeneration'' and ("vitamin D receptor" or "VDR") or ("polymorphism'' or "SNP") or ("TaqI" or "rs731236") or ("FokI" or "rs2228570") or ("ApaI" or "rs7975232"). The reference lists of included studies, review articles and meta-analysis were also inspected for additional relevant studies. If more than one article were published using the same case series, only the study with largest sample size was selected. No language or publication date restrictions were applied. The last electronic search was performed on June 1, 2016.

Inclusion criteria

Search results were screened independently by two reviewers. Any further disagreements between reviewers were resolved by consensus, and if necessary, a third reviewer was consulted. The criteria for inclusion of a study were: (1) Case–control or cohort design; (2) LDD diagnosed on the basis of clinical and/or radiological examination; (3) Investigated and reported association between VDR (TaqI, FokI, or ApaI) polymorphisms and LDD; (4) Providing sufficient data for calculation of odds ratio (OR) with the corresponding 95 % confidence interval (95 % CI).

Data extraction

A standard data extraction table was constructed based on a discussion of the literature. Two investigators extracted data independently and crosschecked mutually. The following information was extracted from the included studies: (1) authors; (2) publication year; (3) country of origin; (4) subject characteristics (i.e., number of cases and controls, age, gender, and ethnic composition); (5) case and control selection criteria; (6) genotyping method; (7) allele/genotype frequencies.

Statistical analysis

Meta-analysis was performed using Review Manager 5.31 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). Odds ratios (ORs) with 95 % confidence intervals (CIs) were used to assess the strength of association between VDR gene polymorphisms and LDD risk. The pooled OR was calculated by a fixed-effect model or a random-effect model according to the heterogeneity. Heterogeneity was checked by a χ^2-based Q statistic, and $p < 0.10$ was considered statistically significant. A p value ≥ 0.10 for the Q test indicated the lack of heterogeneity among the studies, and so, the summary OR estimate of each study was calculated by the fixed-effect mode. Otherwise, the random-effect model was used. Summary ORs were estimated for the allelic comparison and genotypic comparisons of codominant, dominant, and recessive genetic models. A pooled OR was determined by Z test and a p value of 0.05 was used as the level. Hardy–Weinberg equilibrium (HWE) was checked in study controls using the χ^2 goodness-of-fit test as a quantitative assessment for potential selection bias and confounding. Sensitivity analysis was performed to check the robustness of meta-analysis findings by assessing the influence of individual studies and any HWE-deviated studies for both the overall analysis and subgroup analysis. Funnel plots were undertaken to assess the potential publication bias.

Results

Study inclusion and characteristics

As shown in Fig. 1, the initial search identified 134 articles from the selected electronic databases. Of these, 103 articles were excluded after reading the titles and abstracts. 26 potential articles were subsequently included for full-text view. Three articles were excluded for repeating or overlapping. [9, 29, 30] According to the inclusion criteria, 23 case–control studies were included in systematic review [10–23, 27, 28, 31–36]. Of those, nine studies were excluded from meta-analysis due to lack of usable data for pooling [23, 26, 27, 31–36]. For the TaqI, FokI and ApaI polymorphisms of VDR gene, nine studies [10–12, 14, 15, 17, 19, 21, 28], seven studies [10, 13, 14, 16–18, 20], and five studies [11, 15, 21, 22, 28] were eventually included in the meta-analysis, respectively. The characteristics of each case–control study are listed in Table 1. Magnetic resonance images (MRI) or/and computed tomography (CT) were used for the detection of disc degeneration in the majority of studies, while plain radiography was used in four studies [31, 33–35]. Seventeen studies were conducted in Caucasian populations [10, 13, 14, 16–18, 20, 22, 23, 26–28, 31–34], and six studies in Asian population [11, 12, 15, 19, 21, 35]. Genotype and allele distributions for each case–control study are shown in Table 2.

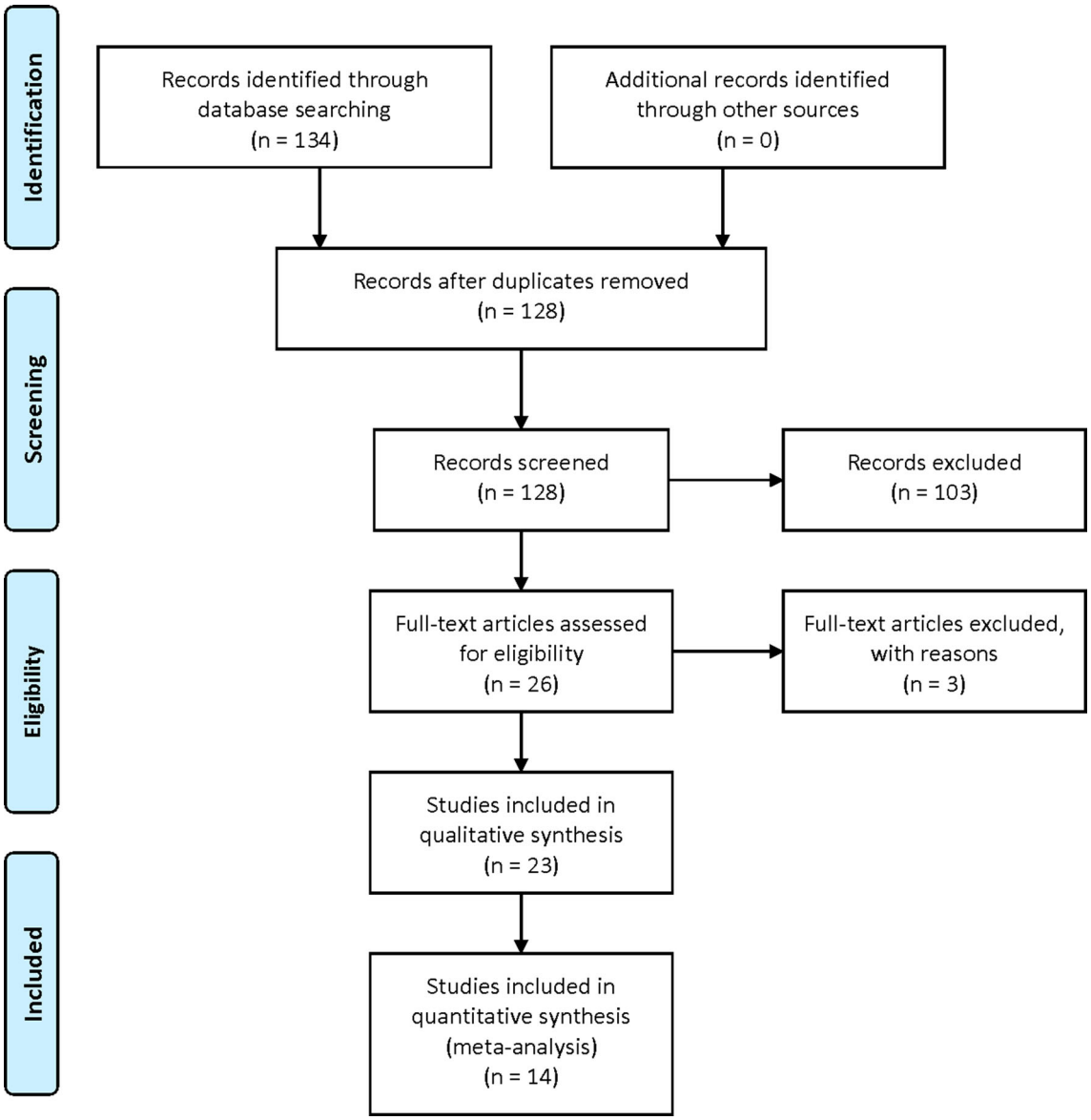

Fig. 1 *Flow diagram* of the selection of eligible studies

Table 1 Characteristics of the case–control studies included in systematic review

First author	Year	Country	Ethnicity	Gender	Age (years)	Study design	Number (cases/controls)	Disease	Diagnostic criteria	Genotyping method
Colombini [28]	2016	Italy	Caucasian	Both	NM	HBS	266/252	LDD	MRI	PCR–RFLP and TaqMan
Toktas [26]	2015	Turkey	Caucasian	Male	35–45	HBS	75/25	LDD	MRI	PCR
Colombini [13]	2014	Italy	Caucasian	Both	Case: 44.19 ± 9.11 Control: 40.08 ± 9.56	HBS	267/220	LDD	MRI	PCR–RFLP
Cervin Serrano [10]	2014	Mexico	Caucasian	Both	Case: 39.22 ± 6.8 Control: 39.13 ± 6.8	HBS	100/100	LDD	MRI	PCR–RFLP
Vieira [20]	2014	Brazil	Caucasian	Both	Case: Male: 46.0 ± 5.4; Female: 45.2 ± 5.9 Control: Male: 33.8 ± 8.2; Female: 33.9 ± 8.1	HBS	121/131	LDD	MRI	PCR–RFLP
Zawilla [22]	2014	Egypt	Caucasian	Both	Case: 44.2 ± 11.28 Control: 43.3 ± 10.57	HBS	84/60	LDD	MRI	PCR–RFLP
Chen [11]	2012	China	Asian	Both	40.3	HBS	81/101	LDD	MRI	PCR–RFLP
Omair [27]	2012	Norway	Caucasian	NA	Case: 53.2 (30–76) Control: 39.3 (24–56)	HBS	146/188	LDD	Plain radiography and either CT or MRI	Sequenom™
Kelempisioti [16]	2011	Finland	Caucasian	Both	40.3	HBS	150/246	LDD	MRI	SNaPshot
Eser [23]	2010	Turkey	Caucasian	NA	20–30	HBS	150/150	LBP	MRI	PCR–RFLP
Eskola [14]	2010	Denmark	Caucasian	Both	13.1	PBS	66/154	LDD	MRI	SNaPshot
Yuan [21]	2010	China	Asian	Both	43.6	HBS	178/284	LDD	CT	PCR–RFLP
Nunes [18]	2007	Brazil	Caucasian	Both	Case: 38 Control: 41	HBS	66/88	LDD	MRI	PCR
Virtanen [36]	2007	Finland	Caucasian	Male	38–56	PBS	150/61	LDD	Clinical assessments	PCR
Cheung [12]	2006	China	Asian	Both	18–55	PBS	388/191	LDD	MRI	PCR
Koshizuka [35]	2006	Japan	Asian	Female	63.7 ± 10.0	PBS	318	LS	Lateral lumbar spine radiograph	PCR–RFLP
Jordan [33]	2005	UK	Caucasian	Both	65.8	PBS	291	LDD	Anteroposterior and lateral thoracolumbar spine radiographs	PCR

Table 1 continued

First author	Year	Country	Ethnicity	Gender	Age (years)	Study design	Number (cases/controls)	Disease	Diagnostic criteria	Genotyping method
Valdes [34]	2005	UK	Caucasian	Female	NM	PBS	700	LDD	Lateral lumbar spine radiograph	TaqMan
Noponen-Hietala [17]	2003	Finland	Caucasian	Both	48.5	PBS	29/56	LSS	CT, MRI	PCR
Oishi [19]	2003	Japan	Asian	Female	73.2	HBS	39/21	LBP	MRI	PCR
Kawaguchi [15]	2002	Japan	Asian	Both	22	HBS	116/89	LBP	MRI	PCR–RFLP
Videman [32]	2001	Finland	Caucasian	Man	48.9 ± 8.1	PBS	142	LDD	MRI	PCR
Jones [31]	1998	Australia	Caucasian	Both	69.5	PBS	282	LDD	Lateral lumbar spine radiograph	PCR

LDD lumbar disc degeneration, *LBP* low back pain, *LS* lumbar spondylosis, *LSS* lumbar spinal stenosis, *HBS* hospital-based study, *PBS* population-based study, *NM* not mentioned, *PCR* polymerase chain reaction, *RFLP-PCR* polymerase chain reaction–restriction fragment length polymorphism

Quantitative data synthesis

All studies

As shown in Table 3, the pooled results suggested no significant association between TaqI polymorphism of VDR gene and LDD predisposition in allelic contrast model. (t vs. T: OR = 1.07, 95 % CI 0.81–1.40) (Fig. 2). Furthermore, we did not detect the obvious association between TaqI polymorphism and the risks of LDD when examining under the codominant model (tt vs. TT, tT vs. TT), dominant model (tT+TT vs. tt) and recessive model (tt+tT vs. TT), respectively. Similar to TaqI polymorphism, no significant associations were found between VDR (FokI and ApaI) polymorphisms and LDD risk using odds ratio estimation based on all genetic models (Figs. 3, 4).

Subgroup analysis

Subgroup analysis by ethnicity and study design was performed. For TaqI polymorphism, subgroup analysis was stratified into two ethnic groups: Caucasian (573 cases and 692 controls) and Asian (690 cases and 556 controls). The data suggested that TaqI polymorphism of VDR gene was not associated with LDD risk under dominant model in individual population groups (for Caucasian, OR = 0.95, 95 % CI 0.69–1.32, $p = 0.77$; for Asian, OR = 0.98, 95 % CI 0.46–2.06, $p = 0.95$) (Table 4).

In addition, the subgroup analysis was also divided into population-based study (417 cases and 247 controls) and hospital-based study (846 cases and 1001 controls). The results further confirmed the null association between TaqI polymorphism of VDR gene and LDD predisposition under dominant model (for population-based study, OR = 1.75, 95 % CI 0.97–3.14, $p = 0.06$; for hospital-based study, OR = 0.98, 95 % CI 0.73–1.33, $p = 0.91$) (Table 4). Similarly, no significant association was found between ApaI polymorphism and LDD risk in Asian population (for allelic comparison: OR = 0.91, 95 % CI 0.65–1.29, $p = 0.61$) (Table 4).

Sensitivity analysis

A sensitivity analysis was conducted to explore the source of this heterogeneity. In our study, we performed sensitivity analysis to assess the influence of each study on the TaqI polymorphism of VDR gene under allelic contrast model (t vs. T), codominant model (tt vs. TT, tT vs. TT), and recessive model (tt+tT vs. TT). In addition, we also undertook sensitivity analysis for all comparison genetic models of FokI and ApaI VDR gene polymorphism. By the sequential omission of individual studies in these models,

Table 2 Distribution of TaqI, FokI and ApaI polymorphism of VDR gene genotype and allele among LDD cases and controls

Study		Cases (*n*)[a]			Controls (*n*)[a]			Cases (*n*)		Controls (*n*)		HWE[b] for control *p*
Author	Year	11	12	22	11	12	22	1	2	1	2	
TaqI (rs731236)												
Colombini [28]	2016	35	117	114	37	109	106	187	345	183	321	0.30
Cervin Serrano [10]	2014	4	27	69	3	35	62	35	165	41	159	0.4606
Chen [11]	2012	0	2	79	1	14	86	2	160	16	186	0.6172
Eskola [14]	2010	9	28	29	23	74	57	46	86	120	188	0.8985
Yuan [21]	2010	0	22	156	0	28	256	22	334	28	540	0.3822
Cheung [12]	2006	1	33	354	0	8	183	35	741	8	374	0.7675
Noponen-Hietala [17]	2003	6	11	12	11	19	26	23	35	41	71	0.0441
Oishi [19]	2003	0	8	31	0	5	16	8	70	5	37	0.5357
Kawaguchi [15]	2002	0	37	79	0	17	72	37	195	17	161	0.3192
FokI (rs2228570)												
Colombini [13]	2014	30	120	117	34	99	89	180	354	167	277	0.4582
Cervin Serrano [10]	2014	20	65	15	32	51	17	105	95	115	85	0.6637
Vieira [20]	2014	17	50	54	10	46	75	84	158	66	196	0.4341
Kelempisioti [16]	2011	12	57	81	16	119	111	81	219	151	341	0.0361
Eskola [14]	2010	9	28	29	23	74	57	46	86	120	188	0.8985
Nunes [18]	2007	3	54	9	0	27	61	60	72	27	149	0.0892
Noponen-Hietala [17]	2003	6	12	11	5	26	25	24	34	36	76	0.6302
ApaI (rs7975232)												
Colombini [28]	2016	84	141	41	82	108	52	309	223	272	212	0.05
Zawilla [22]	2014	17	48	19	34	22	4	82	86	90	30	0.8633
Chen [11]	2012	44	28	9	43	46	12	116	46	132	70	0.9549
Yuan [21]	2010	58	100	20	128	129	27	216	140	385	183	0.5004
Kawaguchi [15]	2002	51	48	17	41	39	9	150	82	121	57	0.9509

[a] 11,12,22 represent tt, Tt, TT for TaqI(rs731236), ff, Ff, FF for FokI (rs2228570), and aa, Aa, AA for ApaI (rs7975232), respectively

[b] HWE, Hardy–Weinberg equilibrium

we found that none of the individual studies significantly affected the pooled ORs, and that the association between VDR gene polymorphism (TaqI, FokI and ApaI) and LDD did not change, suggesting the high stability of the meta-analysis.

Publication bias

We assessed publication bias by Begg's funnel plot. The shape of funnel plots did not suggest any evidence of obvious asymmetry in all comparison models (Fig. 5).

Discussion

The etiology of disc degeneration is multifactorial including environmental and genetic determinants. A range of environmental factors may be associated with disc degeneration, such as age, obesity, mechanical loading, injury, vibration, and smoking status [5, 37]. Accumulating evidence highlights that genetic factors play critical role in etiology and pathogenesis of disc degeneration [38]. Moreover, gene factors have an influence on adjacent-segment disc degeneration in patients treated with lumbar fusion [39]. In recent years, many gene polymorphisms have been reported to be associated with the occurrence of LDD. The most known and studied polymorphism sites have been identified in the VDR gene sequence including TaqI (rs731236), FokI (rs2228570) and ApaI (rs7975232). The Finnish Twin Cohort study was the first genetic association investigation to report a statistically significant association between the VDR gene polymorphisms (TaqI and FokI) and risk of disc degeneration [9]. The association of the TaqI polymorphism to LDD was subsequently confirmed in several population studies [12, 15, 23]. However, other studies were unable to replicate this initial finding [14, 17, 19]. Similar contradictory results have also been reported in the association between FokI and ApaI polymorphisms and LDD. For FokI polymorphisms, four studies showed a significant association [13, 18, 20, 23],

Table 3 Meta-analysis of the TaqI, FokI and ApaI polymorphisms of VDR gene on LDD

Genetic model	Analysis model	Test of association		Test for heterogeneity	
		OR (95 % CI)	*p*	I^2	*p*
TaqI (rs731236)					
Allelic					
1 vs. 2	REM	1.07 (0.81, 1.40)	0.64	50	0.04
Codominant model					
11 vs. 22	FEM	0.94 (0.64, 1.38)	0.75	41	0.13
12 vs. 22	REM	1.06 (0.74, 1.52)	0.75	51	0.04
Dominant model					
12+22 vs. 11	FEM	0.98 (0.73, 1.32)	0.89	0	0.99
Recessive model					
11+12 vs. 22	REM	1.07 (0.75, 1.52)	0.72	53	0.03
FokI (rs2228570)					
Allelic					
1 vs. 2	REM	1.23 (0.83, 1.82)	0.31	86	<0.0001
Codominant model					
11 vs. 22	FEM	1.05 (0.76, 1.45)	0.76	59	0.02
12 vs. 22	REM	1.16 (0.95, 1.43)	0.14	87	<0.0001
Dominant model					
12+22 vs. 11	REM	0.93 (0.58, 1.49)	0.76	53	0.05
Recessive model					
11+12 vs. 22	REM	1.42 (0.78, 2.57)	0.25	87	<0.0001
ApaI (rs7975232)					
Allelic					
1 vs. 2	REM	0.79 (0.55, 1.14)	0.20	81	0.0003
Codominant model					
11 vs. 22	REM	0.65 (0.33, 1.28)	0.21	73	0.006
12 vs. 22	REM	0.60 (0.17, 2.13)	0.43	95	<0.0001
Dominant model					
11+12 vs. 22	REM	0.83 (0.49, 1.38)	0.47	58	0.05
Recessive model					
12+22 vs. 11	REM	1.32 (0.73, 2.37)	0.35	85	<0.0001

OR odds ratio, *CI* confidence interval, *FEM* fixed-effect model, *REM* random-effect model

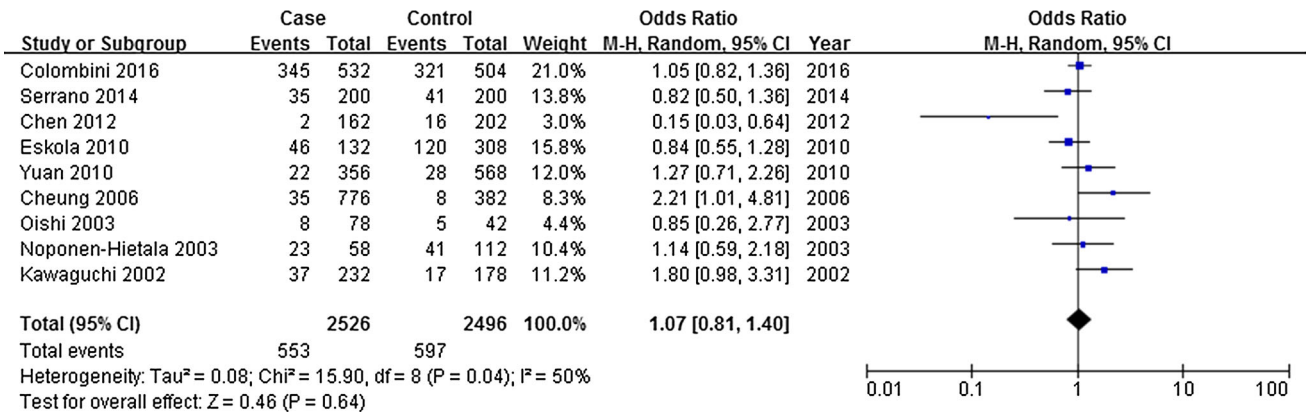

Fig. 2 *Forest plot* of the pooled ORs with 95 % CIs for associations between TaqI polymorphism of VDR gene (rs731236) and lumbar disc degeneration predisposition in overall populations under allelic contrast model (t vs. T); events: the number of t allele

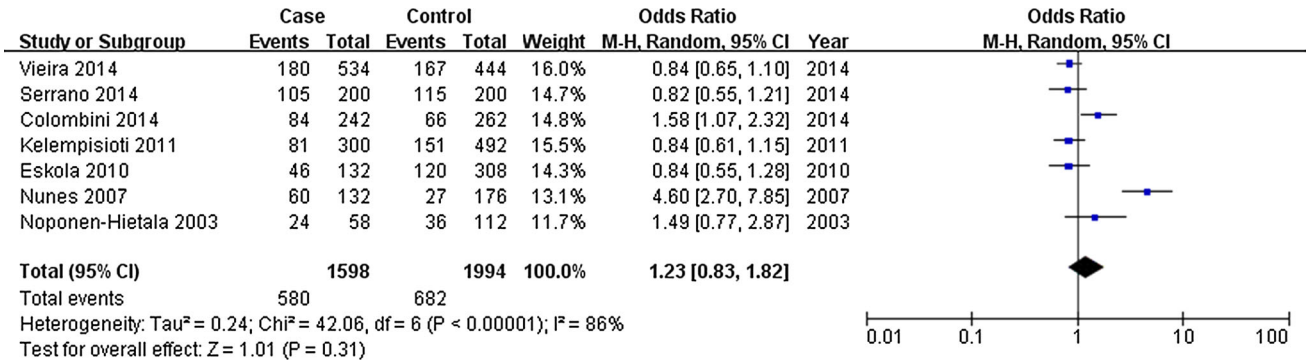

Fig. 3 *Forest plot* of the pooled ORs with 95 % CIs for associations between FokI polymorphism of VDR gene (rs2228570) and lumbar disc degeneration predisposition in overall populations under allelic contrast model (f vs. F); events: the number of f allele

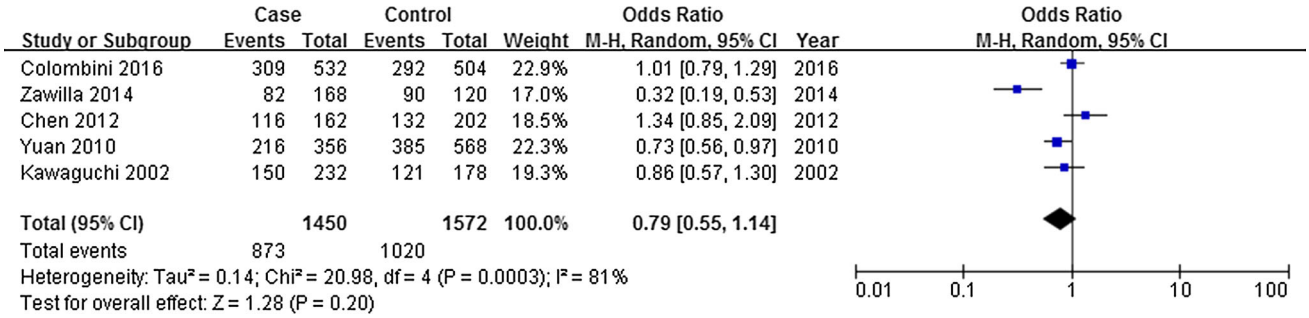

Fig. 4 *Forest plot* of the pooled ORs with 95 % CIs for associations between ApaI polymorphism of VDR gene (rs7975232) and lumbar disc degeneration predisposition in overall populations under allelic contrast model (a vs. A); events: the number of a allele

whereas four demonstrated the null association [10, 14, 16, 17]. A significant association between ApaI polymorphisms and LDD risk was supported by Yuan's and Zawilla's studies [21, 22]. However, the studies by Chen et al. [11], Kawaguchi et al. [15] and Colombini et al. [28] showed no such association. We conducted a systematic review and meta-analysis to examine the associations between the TaqI, FokI, ApaI polymorphisms of the VDR gene and susceptibility of LDD, which included 1835 cases and 1923 controls from 23 published studies (for TaqI polymorphism, 1263 cases and 1248 controls; for FokI polymorphism, 799 cases and 997 controls; for ApaI polymorphism, 725 cases and 786 controls). The main results from our study were that none of these three VDR gene polymorphisms were significantly associated with the LDD predisposition.

In 2012, Xu and colleagues reported a meta-analysis on Aggrecan gene and VDR gene polymorphisms and intervertebral disc degeneration, which suggested that VDR gene polymorphisms were not significantly associated with the risk of disc degeneration [25]. Focusing on this issue, many genetic association studies were published during the past several years [10, 13, 20, 22, 26–28]. The previous meta-analysis may fail to provide the information of the most recent studies. Authors also mentioned that their results needed to be validated in future research as the limited number of included publications and subjects [25]. Meanwhile, Cochrane Back Review Group also recommended that meta-analysis and systematic reviews require timely updates due to upcoming new studies [40]. The present meta-analysis included more studies, and explored more comprehensive potential factors by subgroups, and used sensitivity analysis to find heterogeneity, which made the results more reliable and more accurate.

It is generally recognized that VDR has an important influence on bony and cartilaginous metabolisms, including differentiation, proliferation, and maturation of cartilage cell. VDR is expressed in nucleus pulposus and annulus fibrosus cells, and has marked effect on proteoglycan synthesis. VDR gene variants have been supposed to be involved in the pathophysiology of the degenerated disc through the generation of an altered VDR expression. Until now, several studies have reported that VDR gene polymorphisms were related to LDD predisposition in different ethnic population groups [38]. However, our study did not find any significant association between the three VDR gene polymorphisms including TaqI (rs731236), FokI (rs2228570), and ApaI (rs7975232), and the susceptibility of LDD, which was partly in accordance with previous meta-analysis study [25]. Heterogeneity is a potential problem when interpreting the results of meta-analysis. We minimized the

Table 4 Subgroup meta-analysis of the TaqI and ApaI polymorphism of VDR gene on LDD

Genetic model	Analysis model	Test of association		Test for heterogeneity	
		OR (95 % CI)	*p*	I^2	*p*
TaqI (rs731236)					
Caucasian population					
1 vs. 2	FEM	0.98 (0.81, 1.18)	0.80	0	0.69
11 vs. 22	FEM	0.88 (0.59, 1.30)	0.52	8	0.35
12 vs. 22	FEM	0.90 (0.65, 1.23)	0.50	0	0.53
12+22 vs. 11	FEM	0.95 (0.69, 1.32)	0.77	0	0.95
11+12 vs. 22	FEM	1.05 (0.78, 1.42)	0.73	0	0.55
Asian population					
1 vs. 2	REM	1.14 (0.60, 2.16)	0.69	66	0.22
12 vs. 22	REM	1.17 (0.61, 2.24)	0.63	64	0.03
12+22 vs. 11	REM	0.98 (0.46, 2.06)	0.95	73	0.005
11+12 vs. 22	FEM	1.14 (0.52, 2.46)	0.75	0	0.85
Population-based study					
1 vs. 2	FEM	1.54 (0.95, 2.51)	0.08	40	0.20
11 vs. 22	FEM	1.79 (0.60, 5.33)	0.30	52	0.15
12 vs. 22	FEM	1.78 (0.96, 3.28)	0.07	0	0.42
12+22 vs. 11	FEM	1.75 (0.97, 3.14)	0.06	0	0.34
11+12 vs. 22	FEM	0.90 (0.32, 2.57)	0.85	0	0.85
Hospital-based study					
1 vs. 2	FEM	1.02 (0.75, 1.40)	0.88	48	0.08
11 vs. 22	FEM	0.92 (0.60, 1.42)	0.71	43	0.15
12 vs. 22	FEM	1.02 (0.67, 1.55)	0.93	51	0.05
12+22 vs. 11	FEM	0.98 (0.73, 1.33)	0.91	0	0.97
11+12 vs. 22	REM	0.93 (0.61, 1.41)	0.72	54	0.04
ApaI (rs7975232)					
Asian population					
1 vs. 2	REM	0.91 (0.65, 1.29)	0.61	60	0.08
11 vs. 22	FEM	0.76 (0.48, 1.20)	0.24	0	0.38
12 vs. 22	REM	0.33 (0.06, 1.91)	0.21	90	0.001
12+22 vs. 11	REM	1.08 (0.60, 1.94)	0.79	75	0.02
11+12 vs. 22	FEM	0.83 (0.54, 1.28)	0.39	0	0.74

OR odds ratio, *CI* confidence interval, *FEM* fixed-effect model, *REM* random-effect model

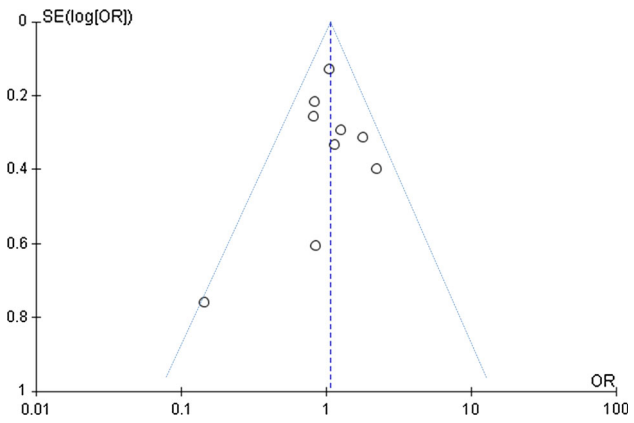

Fig. 5 *Funnel plot* analysis for publication bias; VDR gene TaqI polymorphism (rs731236) under allelic contrast model

likelihood of this problem by using explicit criteria for study inclusion, precise data extraction, and strict data analysis. However, significant heterogeneity between studies existed in some comparisons. There are several possible explanations for the presence of heterogeneity, including study design, genetic background and environment factors. Thus, the subgroup analysis was stratified by ethnicity (Caucasian and Asian) and study design (population-based study and hospital-based study). After subgroups were analyzed by ethnicity and study design, heterogeneity had effectively decreased in the meta-analysis of Caucasian descent and population-based study group. The results of subgroup analysis also confirmed that there was no association between TaqI and ApaI polymorphisms of VDR gene and risk of LDD.

Some limitations of this study should be acknowledged. First, our results were based on unadjusted estimates. If the original data were available, we could perform stratification analysis by age, gender, smoking status, obesity, and physical load. Second, heterogeneity limited the statistical power, which may result from different phenotype selection and diagnostic criteria of LDD [41]. There is an obvious discrepancy in disc degeneration-related clinical phenotypes (signal intensity, disc height and disc herniation) and diagnostic criteria by imaging techniques (plain radiography, CT and MRI) among the included studies. Thus, the case–control genetic studies with highly specific LDD-related phenotypes seem warranted.

Conclusions

The current systematic review and meta-analysis showed that the TaqI, FokI, and ApaI polymorphisms of VDR gene were not significantly associated with the predisposition of LDD. Due to limitations showed above in this analysis, the associations between VDR gene polymorphisms and the risks of LDD could not be entirely excluded. Thus, it is critical that more large-scale and well-designed international studies are performed to clarify the possible role of the TaqI, FokI, and ApaI polymorphisms of VDR gene in LDD.

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Compliance with ethical standards

Conflict of interest None.

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