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Original Article

Association between collagen IX tryptophan polymorphisms and risk of lumbar disc degeneration: a meta-analysis

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Abstract: Purpose: The aim of this study was to examine the association between collagen IX tryptophan (COL9A2/Trp2, COL9A3/Trp3) polymorphisms and risk of lumbar disc degeneration (LDD). Methods: Data were collected from several electronic bibliographical databases, including PubMed, EMBASE, the Cochrane Library, and Web of Science, with the most recent report published on June 20, 2018. Odds ratios (OR) and 95% confidence intervals (CI) were used to assess the strength of association between collagen IX tryptophan (COL9A2/Trp2, COL9A3/Trp3) polymorphisms and LDD risk. Statistical analysis was performed using STATA 12.0 software. Results: A total of 1,509 LDD cases and 1646 controls from 9 studies were included, comprising Asian and Caucasian populations. For the determination of associations of collagen IX Trp2 allele and Trp3 allele polymorphisms, six and eight studies, respectively, were included in the final meta-analysis. There was no evidence that Trp2 polymorphism in COL9A2 had a significant association with LDD risk. However, Trp3 polymorphism had a significant association with LDD risk (allele model: OR=2.11, 95% CI=1.52-2.93, P<0.001; dominant model: OR=2.13, 95% CI=1.51-3.01, P<0.001; heterozygote model: OR=2.31, 95% CI=1.44-2.89, P<0.001; additive model: OR=0.50, 95% CI=0.35-0.70, P<0.001). Subgroup analysis, stratified by Caucasian populations, confirmed the above results. Furthermore, no significant publication bias was observed in this study. Conclusion: Overall, this meta-analysis suggests that the Trp3 allele polymorphism in COL9A3 may be associated with an increased risk of LDD. However, the Trp2 allele polymorphism is nota major risk factor for LDD. Further studies with a larger and more homogeneous sampling of individuals with LDD are required to confirm these results.

Keywords: Lumbar disc degeneration, polymorphism, COL9A3, COL9A2, tryptophan, meta-analysis

Introduction

Lumbar disc degeneration (LDD) is the most common spinal condition in adults, typically developing after the first decade of life [1]. In LDD, the dynamic equilibrium between the buildup and breakdown of tissue within the disc is disturbed, leading to an alteration of biomechanical properties [1]. Furthermore, a degenerated disc is more prone to herniation, which has been associated with severe low back pain and unilateral leg pain upon exposure to biomechanical forces [2]. Therefore, LDD is believed to be a significant factor contributing to the pathogenesis of lumbar disc herniation. Studies have shown that 20% of patients with lumbar disc herniation have required surgical treatment during the follow-up period, due to aggravated or prolonged leg pain [2]. Thus, LDD is an important health issue that affects both individuals and society at large.

The most common concerns associated with LDD are the effects of reduplicative mechanical forces on the intervertebral disc material, observed to play a lesser role in the disease than genetic influences [3]. Genetic factors found to be associated with LDD in subsequent studies include aggrecan [4-13], interleukins [11, 12, 14-23], vitamin-D receptor [24-26], the matrix metalloproteinase [11, 12, 27-33], and-type I, IX, and XI collagen mutations [34-37].

Intervertebral discs contain an abundant extracellular matrix composed of collagens and proteoglycans. Collagen IX has been considered to serve as a bridging material between collagenous and non-collagenous tissues [40]. Recently, association of collagen IX tryptophan

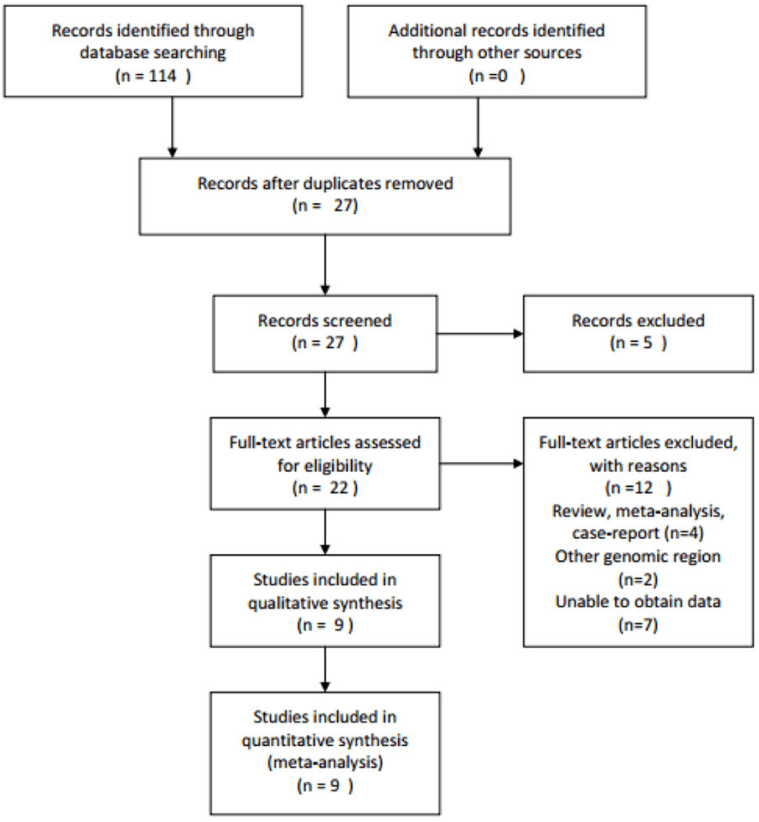

Figure 1. Flowchart for the meta-analysis.

(COL9A2/Trp2, COL9A3/Trp3) polymorphisms with LDD has been reported. However, conflicting results regarding the association of these polymorphisms with LDD susceptibility limit the usefulness of the pathogenetic studies of LDD [38]. The present study conducted a meta-analysis of studies on the genetic association of collagen IX tryptophan (COL9A2/Trp2, COL9A3/Trp3) polymorphisms and LDD. Present results may provide a more accurate estimate of the relevance of these polymorphisms to LDD.

Materials and methods

Literature search strategy

To acquire studies concerning the association between COL9A2/Trp2 and COL9A3/Trp3 polymorphisms and predisposition to LDD, systematic and comprehensive searches of several electronic bibliographical databases were conducted, including PubMed, EMBASE, the Cochrane Library, and Web of Science, for all relevant research articles published on or before June 20, 2018. The search strategy used to identify all possible relevant articles included the use of the following keywords: ("Collagen IX" or "COL9A2" or "COL9A3") or ("polymorphism" or "single nucleotide polymorphism" or "SNP" or "variation") and ("disc degeneration" or "LDD" or "lumbar disc disease").

Inclusion and exclusion criteria

To be included in this meta-analysis, an article had to satisfy the following inclusion criteria: (1) A case-control or cohort study; (2) Involved research on human subjects; (3) Focused on the association of COL9A2/Trp2 and COL9A3/Trp3 polymorphisms with LDD; (4) Provided sufficient data for the calculation of an odds ratio (OR) with a 95% confidence interval (CI); and (5) Published in English. Moreover, the following exclusion criteria were used: (1) Case report or review rather than a case-control study; (2) Duplicate of a publication already included; (3) Did not include sufficient data to estimate the OR and 95% CI; (4) Not relevant to LDD; (5) Involved research only on animal subjects; (6) Published in a language other than English; and (7) Did not use the Hardy-Weinberg equilibrium (HWE) as a control measure. Two authors (Y. Z. and X. Y.) independently assessed these studies for compliance with inclusion and exclusion criteria, as described above. If these 2 investigators could not reach an agreement, a third investigator (Y. L.) was consulted to resolve the dispute.

Data extraction

The following information was extracted from each qualified study: (1) First author's name; (2) Year of publication; (3) Country of origin; (4) Ethnicity, gender, and age of enrolled subjects; (5) Number of LDD cases and controls; (6) Disease and diagnostic criteria; (7) Detection methods used; and (8) Genotypes and allelic distributions for both cases and controls.

Table 1. Characteristics of case-control studies included in the meta-analysis

Author	Year	Country	Ethnicity	Gender	Age (years)	Number (cases/ controls)	Disease	Diagnostic criteria	Method
Rathod et al. [46]	2012	India	Asian	Both	15 to 60	100/100	LDD	MRI	RT-PCR
Noponen-Hietala et al. [50]	2003	Finland	Caucasian	Both	22 to 75	29/56	LDD	MRI	PCR-Seq
Bagheri et al. [42]	2016	Iran	Caucasian	Both	20 to 66	108/57	LDD	MRI	PCR
Toktas et al. [43]	2015	Turkey	Caucasian	Male	35 to 45	75/25	LDD	MRI	PCR
Lim et al. [47]	2011	Singaporean	Asian	Male	Mean age 27.05	34/20	LDD	MRI	PCR
Seki et al. [2]	2006	Japan	Asian	NA	13 to 86	470/554	LDD	MRI	PCR
Kales et al. [49]	2004	USA	Caucasian	Both	Less than 60	100/102	LDD	MRI	PCR
Solovieva et al. [48]	2006	Finland	Caucasian	Male	NA	77/55	LDD	MRI	PCR
Paassilta et al. [44]	2001	Finland	Caucasian	NA	19 to 78	170/319	LDD	MRI	PCR

NA: not available; PCR: polymerase chain reaction; RT-PCR: reverse-transcription polymerase chain reaction; PCR-Seq: polymerase chain reaction and pyrosequencing.

Table 2. Distribution of the genotypes and alleles of all study samples, with *P* values for HWE analyses of the controls

Study	Year	Cases (n)					Controls (n)					HWE (P) of controls
		MM	MN	NN	M	N	MM	MN	NN	M	N	
COL9A2												
Rathod et al. [46]	2012	15	42	43	72	128	0	17	83	17	183	0.35
Noponen-Hietala et al. [50]	2003	0	1	28	1	57	0	0	56	0	112	1.00
Bagheri et al. [42]	2016	0	34	74	34	182	0	13	44	13	101	0.94
Toktas et al. [43]	2015	0	3	72	3	147	0	0	25	0	50	1.00
Lim et al. [47]	2011	1	3	30	5	63	0	3	17	3	37	0.72
Seki et al. [2]	2006	9	91	370	109	831	14	136	504	164	1144	0.19
COL9A3												
Rathod et al. [46]	2013	0	5	95	5	195	0	7	93	7	193	0.72
Noponen-Hietala et al. [50]	2003	1	3	25	5	53	0	0	56	0	112	1.00
Bagheri et al. [42]	2016	0	29	79	29	187	0	10	47	10	104	0.47
Kales et al. [49]	2004	0	9	91	9	191	0	5	97	5	199	0.80
Solovieva et al. [48]	2006	1	14	62	16	138	0	8	47	8	102	0.56
Toktas et al. [43]	2015	0	5	70	5	145	0	0	25	0	50	1.00
Lim et al. [47]	2011	0	0	34	0	68	0	0	20	0	40	1.00
Paassilta et al. [44]	2001	2	38	130	42	298	0	30	289	30	608	0.38

M and N indicate Trp2+ and Trp2-, respectively, for COL9A2/Trp2 and Trp3+ and Trp3-, respectively, for COL9A3/Trp3. MM, MN, and NN indicate Trp2+/Trp2+, Trp2+/Trp2-, and Trp2-/Trp2-, respectively, for COL9A2/Trp2 and Trp3+/Trp3+, Trp3+/Trp3-, and Trp3-/Trp3-, respectively, for COL9A3/Trp3.

Statistical analysis

PRISMA checklists and flow diagrams were closely followed during the entire process of this study. The HWE for control subjects in each study was calculated using the χ^2 test, prior to statistical analysis, and an HWE with $P<0.05$ indicates significant disequilib-rium. Associationbetween COL9A2/Trp2 and COL9A3/Trp3 polymorphisms and LDD was evaluated and analyzed using the following genetic models: allele model (M vs. N), dominant model (MM+MN vs. NN), recessive model (MM vs. MN+NN), homozygous model (MM vs. NN), heterozygous model (MN vs. NN), and additive model (MM+NN vs. MN). M and N indicate Trp2+ and Trp2-, respectively, for COL9A2/Trp2 and Trp3+ and Trp3-, respectively, for COL9A3/Trp3. MM, MN, and NN indicate Trp2+/Trp2+, Trp2+/Trp2-, and Trp2-/Trp2-, respectively, for COL9A2/Trp2 and Trp3+/Trp3+, Trp3+/Trp3-, and Trp3-/Trp3-, respectively, for COL9A3/Trp3. Odds ratios (OR) and 95% confidence intervals (95% CI) were used to assess the strength of association. Subgroup analysis based on racial classifications was also con-

Table 3. Meta-analysis of the association of COL9A2/Trp2 and COL9A3/Trp3 polymorphisms with LDD risk

Genetic model	Analysis model	Test of association		Test for heterogeneity		Egger's test	Begg's test
		OR (95 % CI)	*P*	I^2	*P*	*P*	*P*
COL9A2							
Caucasian population							
M vs. N	FEM	1.58 (0.82, 3.03)	0.17	0.00	0.68	NA	NA
MM vs. NN	NA	NA	NA	NA	NA	NA	NA
MN vs. NN	FEM	1.70 (0.84, 3.43)	0.14	0.00	0.71	NA	NA
MM+MN vs. NN	FEM	1.70 (0.84, 3.43)	0.14	0.00	0.71	NA	NA
MM vs. MN+NN	NA	NA	NA	NA	NA	NA	NA
MM+NN vs. MN	FEM	1.00 (0.71, 1.41)	1.00	0.00	1.00	NA	NA
Asian population							
M vs. N	REM	1.83 (0.42, 7.89)	0.42	0.94	<0.001	NA	NA
MM vs. NN	REM	3.87 (0.20, 76.35)	0.37	0.80	0.01	NA	NA
MN vs. NN	REM	1.49 (0.40, 5.52)	0.55	0.90	<0.001	NA	NA
MM+MN vs. NN	REM	1.74 (0.38, 7.92)	0.47	0.93	<0.001	NA	NA
MM vs. MN+NN	REM	3.26 (0.24, 45.05)	0.38	0.75	0.02	NA	NA
MM+NN vs. MN	FEM	1.04 (0.87, 1.23)	0.69	0.00	0.54	NA	NA
Population-based study							
M vs. N	REM	1.92 (0.76, 4.86)	0.17	0.86	<0.001	0.41	0.45
MM vs. NN	REM	3.87 (0.20, 76.35)	0.37	0.80	0.01	0.45	1.00
MN vs. NN	REM	1.70 (0.75, 3.86)	0.20	0.77	<0.001	0.41	0.71
MM+MN vs. NN	REM	1.91 (0.75, 4.91)	0.18	0.84	<0.001	0.40	0.71
MM vs. MN+NN	REM	3.26 (0.24, 45.05)	0.38	0.75	0.02	0.44	1.00
MM+NN vs. MN	FEM	1.03 (0.88, 1.20)	0.73	0.00	0.94	0.51	0.26
COL9A3							
Caucasian population							
M vs. N	FEM	2.34 (1.52, 2.93)	<0.001	0.04	0.39	NA	NA
MM vs. NN	FEM	5.74 (0.94, 35.09)	0.06	0.00	0.79	NA	NA
MN vs. NN	FEM	2.27 (1.57, 3.22)	<0.001	0.00	0.53	NA	NA
MM+MN vs. NN	FEM	2.38 (1.65, 3.43)	<0.001	0.00	0.45	NA	NA
MM vs. MN+NN	FEM	5.19 (0.85, 31.68)	0.07	0.00	0.80	NA	NA
MM+NN vs. MN	FEM	0.45 (0.31, 0.64)	<0.001	0.00	0.54	NA	NA
Asian population							
M vs. N	NA	0.71 (0.22, 2.27)	0.56	NA	NA	NA	NA
MM vs. NN	NA	NA	NA	NA	NA	NA	NA
MN vs. NN	NA	0.70 (0.21, 2.28)	0.55	NA	NA	NA	NA
MM+MN vs. NN	NA	0.70 (0.21, 2.28)	0.55	NA	NA	NA	NA
MM vs. MN+NN	NA	NA	NA	NA	NA	NA	NA
MM+NN vs. MN	NA	1.43 (0.44, 4.67)	0.55	NA	NA	NA	NA
Population-based study							
M vs. N	FEM	2.11 (1.52, 2.93)	<0.001	0.32	0.19	1.00	1.00
MM vs. NN	FEM	5.74 (0.94, 35.09)	0.06	0.00	0.79	0.48	1.00
MN vs. NN	FEM	2.04 (1.44, 2.89)	<0.001	0.20	0.27	0.95	1.00
MM+MN vs. NN	FEM	2.13 (1.51, 3.01)	<0.001	0.28	0.21	0.96	1.00
MM vs. MN+NN	FEM	5.19 (0.85, 31.67)	0.07	0.00	0.80	0.49	1.00
MM+NN vs. MN	FEM	0.50 (0.35, 0.70)	<0.001	0.19	0.29	0.99	1.00

NA: not available; OR: odds ratio; CI: confidence interval; FEM: fixed-effect model; REM: random-effects model.

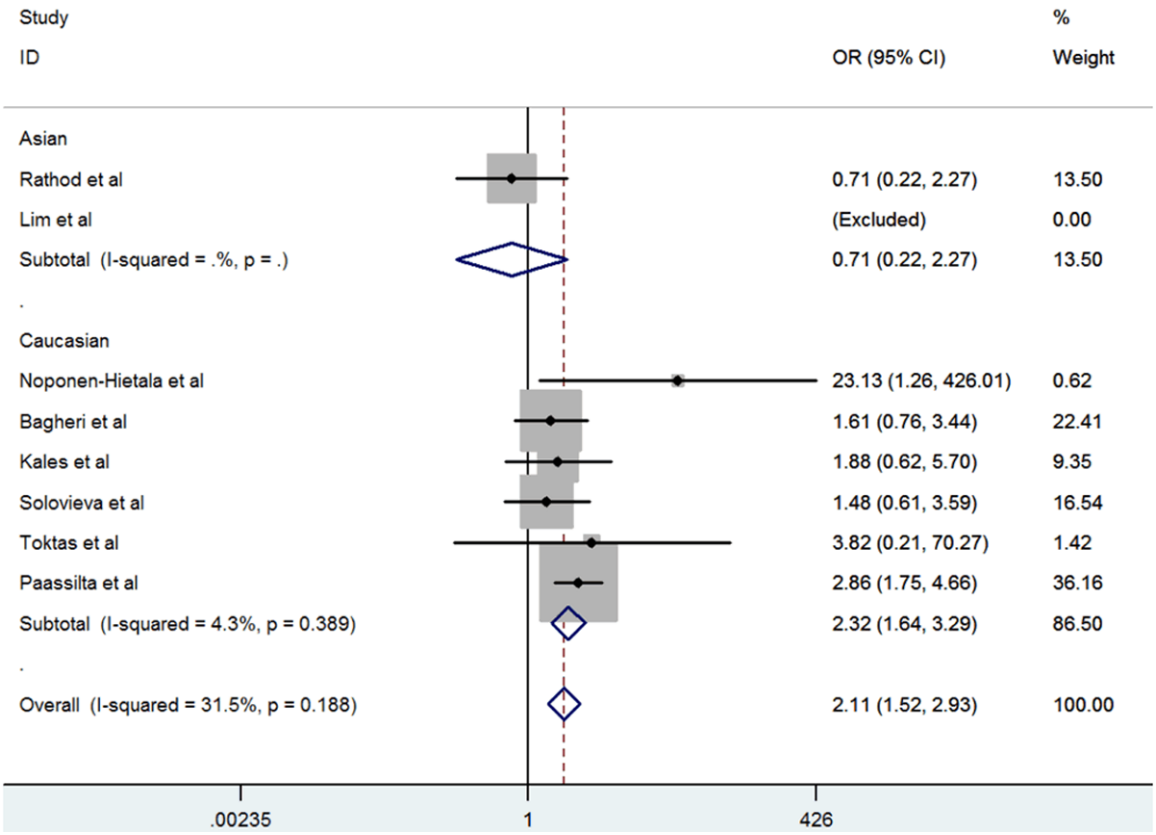

Figure 2. Forest plot of pooled ORs with 95% CIs for subgroup analysis of association between the Trp3 polymorphism of the COL9A3 gene and LDD predisposition, stratified by ethnicity under the allele model (M vs. N).

ducted. The degree of heterogeneity was assessed using I^2 statistics in combination with corresponding *P* values. A fixed-effects model was employed to assess the OR and 95% CI when heterogeneity was low ($P>0.10$ or $I^2<50\%$), while a random-effects model was used when heterogeneity was high ($P<0.10$ or $I^2>50\%$). Sensitivity analyses were performed by removing one study during each iteration to determine the reliability of results. Publication bias was evaluated using Begg's test and Egger's test, with $P<0.05$ indicating statistical significance. All statistical analyses were conducted using STATA 12.0 (Stata, College Station, TX). All *P* values were two-sided.

Results

Characteristics of included studies

A flowchart for this meta-analysis is presented in **Figure 1**. The initial literature search identified 114 potentially relevant articles. Of these, 40 articles were excluded because of duplication and 47 articles were excluded because their title or abstract made it clear that they were not relevant. Full-texts of the 27 remaining articles were carefully examined. Four articles were excluded because they were not a case-control or cohort study, 2 articles were excluded because they examined other single nucleotide polymorphisms (SNPs), and 7 articles were excluded due to a lack of usable data. In the end, 9 studies [2, 35, 36, 39-44] were included in the quantitative synthesis. In total, 1,509 LDD cases and 1,646 controls from 9 studies were included in this meta-analysis, comprising Asian and Caucasian populations. Magnetic resonance imaging (MRI) was used for diagnosis for each patient. Characteristics of research subjects included in the 9 studies are listed in **Table 1**. Genotypes and allelic distributions, as well as *P* values for HWE determinations of the controls, are shown in **Table 2**.

Quantitative data synthesis

Association of COL9A3/Trp3 and LDD risk: As shown in **Table 3**, no significant heterogeneity

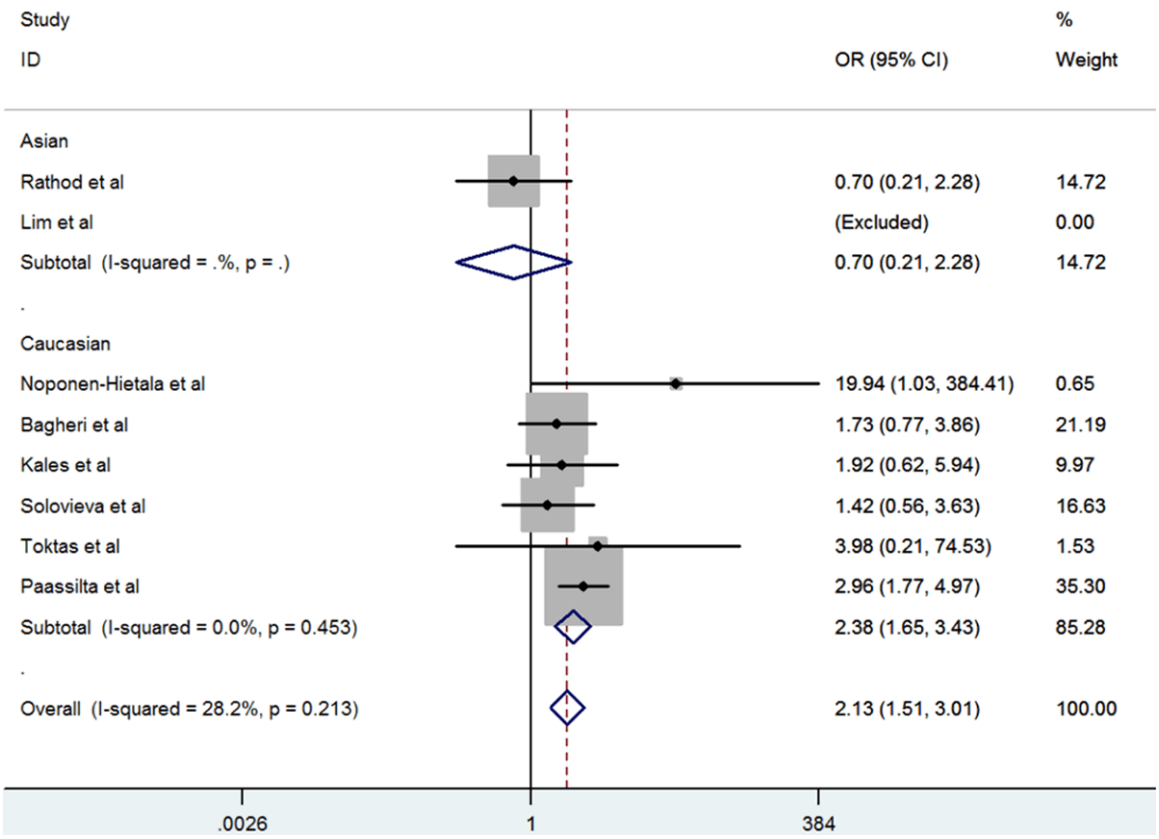

Figure 3. Forest plot of pooled ORs with 95% CIs for subgroup analysis of association between the Trp3 polymorphism of the COL9A3 gene and LDD predisposition, stratified by ethnicity under the dominant model (MM+MN vs. NN).

among 8 studies was observed (heterogeneity test: P>0.10 and I^2<50% for all genetic models). A fixed-effects model was employed to evaluate the association between COL9A3/Trp3 and LDD. It was found that polymorphism of Trp3 in COL9A3 had a significant association with LDD risk (allele model: OR=2.11, 95% CI=1.52-2.93, P<0.001; dominant model: OR=2.13, 95% CI=1.51-3.01, P<0.001; heterozygote model: OR=2.31, 95% CI=1.44-2.89, P<0.001; additive model: OR=0.50, 95% CI=0.35-0.70, P<0.001). Subgroup analysis stratified by Caucasian subjects confirms the above results (allele model: OR=2.33, 95% CI=1.52-2.93, P<0.001; dominant model: OR=2.38, 95% CI=1.653.43, P<0.001; heterozygote model: OR=2.27, 95% CI=1.57-3.23, P<0.001; additive model: OR=0.45, 95% CI=0.31-0.64, P<0.001) (**Figures 2**-**5**).

Association of COL9A2/Trp2 and LDD risk

As shown in **Table 3**, significant heterogeneity among 6 studies was observed (heterogeneity test: P<0.10 and I^2>50% for all genetic models). A random-effects model was employed to evaluate the association between COL 9A2/Trp2 and LDD. It was found that polymorphism of Trp2 in COL9A2 had no significant association with LDD risk in all genetic models (P>0.05). Subgroup analysis stratified by Caucasian and Asian populations confirmed this conclusion (P>0.05).

Sensitivity analysis

Sensitivity analysis was conducted to assess the influence of heterogeneity. No significant differences existed in overall OR values, regardless of which study was excluded, suggesting the high level of reliability of this meta-analysis.

Publication bias

Publication bias was evaluated using Begg's funnel plot and Egger's test. No evidence of publication bias was observed, as shown in **Table 3**, with all P>0.05.

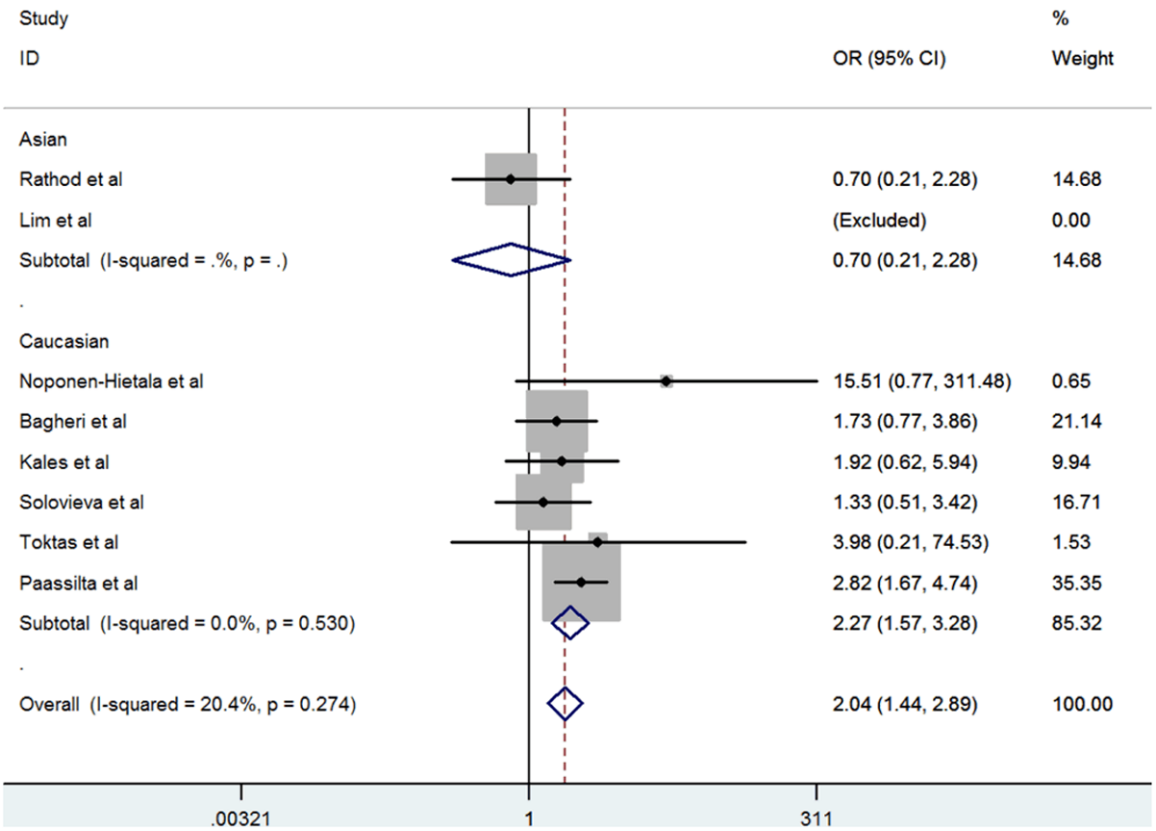

Figure 4. Forest plot of pooled ORs with 95% CIs for subgroup analysis of association between the Trp3 polymorphism of the COL9A3 gene and LDD predisposition, stratified by ethnicity under the heterozygous model (MN vs. NN).

Discussion

LDD has been identified as a multifactorial disease influenced by both environmental and genetic factors. Although various environmental factors, such as gender, age, smoking, and mechanical load, can increase susceptibility to LDD, studies conducted over the past two decades have shown that genetic factors comprise approximately 75% of underlying causes contributing to LDD etiology [45]. In recent years, many genetic polymorphisms have been confirmed to be associated with incidence of LDD [46]. However, the genetic mechanisms underlying the development of LDD remain unclear. Recent studies have suggested the significance of genetic factors, particularly those involving collagen type IX, which plays an important role in maintaining the stability of intervertebral discs [40].

Collagen IX is a heterotrimeric protein composed of three unique polypeptides, α1 (IX), α2 (IX), and α3 (IX), which are encoded separately by the COL9A1, COL9A2, and COL9A3 genes, respectively. The COL9A2 tryptophan polymorphism (Trp2) results from the substitution of tryptophan for glutamine at codon 326, which consists of two variants altogether [47]. In one variant of the COL9A2 tryptophan polymorphism (Trp2), rs7533552 (location chr1: 40545736, at the second base within the codon), the G allele changes glutamine (Gln) to arginine (Arg). In the other variant, rs12077871 (location chr1: 40545737, at the first base within the codon), the T allele changes arginine (Arg) to tryptophan (Trp), as presented in **Figure 6**. A similar variant at codon 103 that substitutes the codon encoding arginine with that encoding tryptophan has recently been discovered in the COL9A3 gene, which encodes the α3 subunit of type IX collagen (Trp3) [48]. However, results concerning the relationship between LDD and tryptophan polymorphism have been inconsistent, limiting efforts to clarify factors contributing to the pathogenesis of LDD in the current study.

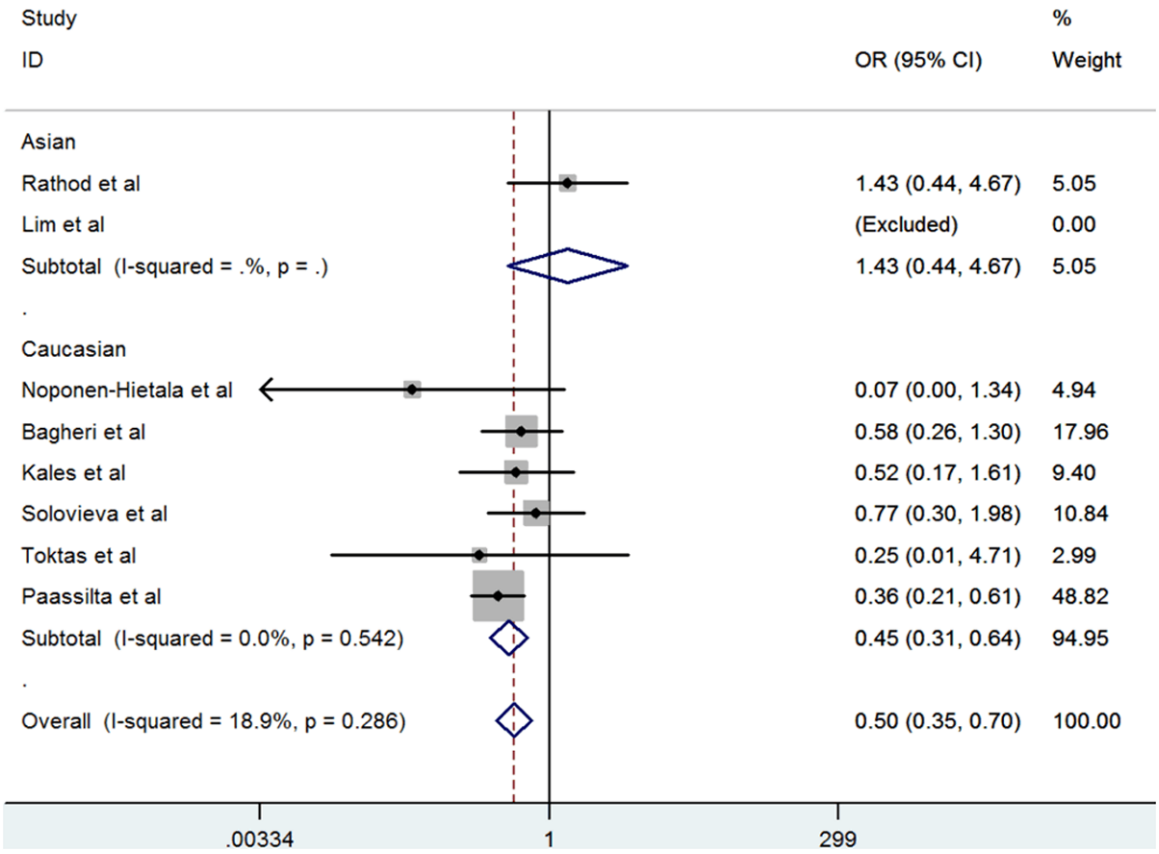

Figure 5. Forest plot of pooled ORs with 95% CIs for subgroup analysis of association between the Trp3 polymorphism of the COL9A3 gene and LDD predisposition, stratified by ethnicity under the additive model (MM+NN vs. MN).

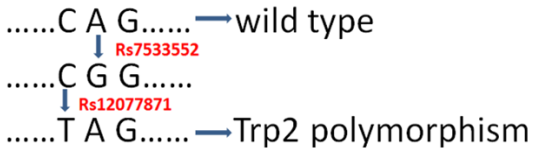

Figure 6. Single nucleotide polymorphisms in the COL9A2 gene at the amino acid position Gln^{326}.

Allelic polymorphisms within the collagen IX genes, including COL9A2/Trp2, may constitute genetic risk factors for LDD. They block the formation of crosslinking between type IX and XI collagen, resulting in the reduced stability of intervertebral discs [39]. Association of the Trp2 polymorphism with LDD has been affirmed in several population studies [2, 39]. However, other studies have been unable to corroborate this finding [35, 36, 40, 43]. Similar contradictory results have also been found regarding the association between Trp3 polymorphism and LDD. Four studies reported a significant association [35, 36, 41, 44], whereas four other studies found no association [39, 40, 42, 43]. Therefore, to systematically evaluate the association between COL9A2/Trp2 and COL9A3/Trp3 polymorphisms and LDD risk, the present meta-analysis was conducted of the genetic studies of Trp2 and Trp3, including 1,509 LDD cases and 1,646 controls from 9 published studies. Present analysis found no evidence that the Trp2 polymorphism in COL9A2 had significant association with LDD risk. However, the Trp3 polymorphism was shown to have a significant association with LDD risk in the allele model, dominant model, heterozygote model, and additive model. Therefore, the Trp3 allele was demonstrated to be a risk factor for LDD, especially for Caucasian populations.

In 2018, Wu reported a meta-analysis of the association between Trp3 polymorphism and risk of LDD. It was determined that the Trp3 polymorphism was not significantly associated with risk of LDD [49]. This meta-analysis, which included only 4 studies, may have fail-

ed to include data from the most comprehensive studies. The authors also indicated that their results needed to be verified by future studies because of the limited number of publications included. The previous meta-analysis of the association between the COL9A2 gene polymorphisms and risk of LDD was based separately on rs7533552 and rs12077871. It may have failed to include all the information available about Trp2 polymorphisms [49, 50]. The present analysis of tryptophan polymorphisms included a greater number of studies and evaluated more risk factors by subgroup, allowing more accurate and reliable results.

There were some limitations to the present meta-analysis. First, the small sample size restricted the statistical power of observed correlations. Second, this study was unable to make precise adjustments to OR values that accounted for gender and age. Third, stratification analysis could not be conducted in terms of obesity, smoking status, or physical load.

Conclusion

The current meta-analysis demonstrated that the Trp3 polymorphism in COL9A3 was significantly associated with a predisposition toward development of LDD, especially for Caucasian populations. The Trp2 polymorphism was not found to be significantly associated with risk of LDD. However, due to the limitations of this study described above, association between the Trp2 polymorphism and a predisposition toward LDD cannot be excluded.

Disclosure of conflict of interest

None.

Abbreviations

LDD, Lumbar Disc Degeneration; COL9A2, Collagen IX alpha 2 chain; COL9A3, Collagen IX alpha 3 chain; SNP, Single Nucleotide Polymorphism; Trp, Tryptophan; Gln, Glutamine; Arg, Arginine; HWE, Hardy-Weinberg Equilibrium; OR, Odds Ratio; CI, Confidence Interval; MRI, Magnetic Resonance Images.

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