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SYSTEMATIC REVIEW

REVISED The role of single nucleotide polymorphisms of *IL-1A* -889C>T (rs1800587), *TNF-A* -238G>A (rs361525), and *VDR TaqI* (rs731236) on susceptibility to herniated nucleus pulposus: a systematic review and meta-analysis [version 3; peer review: 2 approved]

Previous title: The role of single nucleotide polymorphisms of *IL-1A* -889C>T (rs1800587), *TNF-A* -238G>A (rs361525), and *VDR TaqI* (rs731236) on susceptibility to herniated nucleus pulposus

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Abstract

Background: The pathogenesis of herniated nucleus pulposus (HNP) is complex and may involve the wide variety of gene polymorphism. However, the reports from the existing studies are inconclusive. The objective of this study was to determine the role of single nucleotide polymorphisms (SNPs) in interleukin 1 alpha (*IL-1A*), tumor necrosis factor-alpha (*TNF-A*), and vitamin D receptor (*VDR*) genes on the

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version 2	?	

susceptibility to herniated nucleus pulposus (HNP).
Methods: Four databases (PubMed, Embase, Cochrane, and Web of Science) were searched as of April 1 st, 2021. Authors, publication year, targeted genes, genotype and allele frequency in each case and control groups were collected. Newcastle-Ottawa scale was used to evaluate the publication quality. The pooled estimates of association of *IL-1A* -889C>T (rs1800587), *TNF-A* -238G>A (rs361525), and *VDR TaqI* (rs731236) and susceptibility to HNP were assessed using Z test.
Results: We screened 3,067 unique studies for eligibility and three, two and nine case-control studies on *IL-1A* -889C>T, *TNF-A* -238G>A, and *VDR TaqI* were included, respectively, in our meta-analysis. The studies consisting 369 HNP cases and 433 controls for *IL-1A* -889C>T, 252 cases and 259 controls for *TNF-A* -238G>A and 1130 cases and 2096 controls for *VDR TaqI.* Our pooled estimates indicated that there was no significant association of those SNPs with the susceptibility to HNP in any genotype, dominant model, recessive model, or allele comparations.
Conclusion: Although individual studies suggested the important role of gene expression dysregulation associated with SNPs in *IL-1A*, *TNF-A*, and *VDR*, our data indicated that *IL-1A* -889C>T, *TNF-A* -238G>A, and *VDR TaqI* had weak association with HNP susceptibility in both genotypes and allele distributions. However, since heterogeneity was identified among studies included in this meta-analysis, further meta-analysis with a larger population and subgroup analysis on specific population are warranted to support this finding.

Keywords
Spinal disc herniation, SNP, IL-1A, TNF-A, VDR

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REVISED **Amendments from Version 2**

We have added additional discussion about compression of our finding with previous studies based on recommendation of the reviewer. We added: The role of gene polymorphism of IL-1A (rs1800587) was rarely reported. Studies found that IL-1A (rs1800587) has no association with rheumatoid arthritis and systemic sclerosis.[52,53] Another study also found no association between TNF-A gene variants and the risk of bone-joint and spinal tuberculosis.[54] Furthermore, a study assessing the role of VDR gene polymorphism in the case of osteoarthritis also failed to show the potential contribution of VDR gene variant in the development of osteoarthritis.[55] These evidences suggested that, while theoretically the gene variants of IL-A, TNF-A, and VDR may contribute to the development of bone diseases, the evidence reveals otherwise.

Any further responses from the reviewers can be found at the end of the article

Introduction

Herniated nucleus pulposus (HNP) or disc herniation is the most common spinal degenerative disease associated with lower back pain and radicular pain of the lower extremities due to nerve compression.[1] HNP is also the most common cause of persistent sciatic pain due to displacement of the nucleus pulposus beyond the intravertebral disc space.[2] The most prevalent HNP locations are between the L4 and L5 vertebrae and between the L5 and S1 vertebrae[3] whilst the highest incidence is observed amongst people aged 30-50 years old.[4] Diabetes,[5] smoking,[5,6] obesity,[5-7] type of occupation,[8] age,[7] and gender[4,9] have all been associated with a high risk of developing disc degenerative diseases. However, it has been suggested that genetic factors also play a vital role in susceptibility to disc degenerative diseases. A study showed that individuals aged younger than 30 years who have a family history of disc herniation have a 14.5 times higher risk of developing disc protrusion than individuals who have no family history.[8] Family history is also attributed to a 5.1 times higher risk of disc herniation in people aged between 30-50 years old.[8] The Twin Spine Study found that heredity substantially influences disc degeneration by 43-77%.[10,11]

The intervertebral disc (IVD) consists of two different components: the nucleus pulposus (NP) and the annulus fibrosus (AF),[12] where proteoglycans (mostly found in NP) acts as an internal semi-fluid mass and collagen (mostly found in AF) acts as a laminar fibrous container.[13] Genes encoding components of IVD such as collagens I,[14] collagens IX,[15] collagens XI,[16] aggrecan,[17] cartilage intermediate layer protein (CILP),[18] and vitamin D receptor (VDR)[19] have previously been studied to determine susceptibility to lumbar disc diseases. Other factors such as increased production of extracellular matrix-degrading enzymes (encoded by matrix metalloproteinase 3 gene (*MMP*-3) and *MMP-9*[20] and increased expression of inflammatory cytokines such as interleukin-1 alpha (IL-1A), IL-18,[21] IL-6, and tumor necrosis factor-alpha (TNF-α)[22]) are commonly found in disc degeneration. Excessive synthesis, secretion, and biological activity of these inflammatory mediators are associated with tissue destruction and are therefore commonly found in inflammatory disorders including disc degeneration.[23]

One of the mechanisms that alters the production of protein mediators in the human body are single-nucleotide polymorphisms (SNPs). These genetic variations, single nucleotide changes at specific positions in a gene, may influence gene expression and hence associate to particular disease. A three-fold increase in susceptibility of disc degeneration was observed in individuals with a TT genotype compared to those without the allele (CC genotype) on SNP *IL-1A* -889C>T (rs1800587).[24] People with minor allele of *IL-1A* -889C>T (T allele) also had a 2.4-fold increased risk of disc bulges[24] and a 2.5-fold increased risk of endplate modic change.[25] A study in an Iranian population found that among nine SNPs on pro-inflammatory cytokine genes (*IL-1*, *IL-6* and *TNF-A*), no association to IVD degeneration was found except for two SNPs in the *TNF-A* gene (*TNF-A*−308 G/A and *TNF-A* −238 G/A).[19] TNF-α plays important role in the pathophysiology of HNP such as upregulating the activity and the gene expression of MMP, stimulating other cytokines such as IL-1, IL-6, and IL-8, stimulating cell migration, altering endothelial permeability, and decreasing the synthesis of collagen and proteoglycan.[26] A study reported that G allele and GG genotype of *TNF-A* 238G>A (rs361525) were 2.51 times and 2.98 times, respectively, more prevalent in patients with HNP compared to healthy controls.[19]

Several roles of VDR such as regulating chondrocyte proliferation and differentiation, bone mineralization and remodeling, and matrix production have previously been demonstrated.[27] VDR's role in spinal degenerative disorder has been studied in Italian,[28] Turkish,[29] and Southern European populations.[30] A study in a Chinese population suggested that subjects with the t allele of *VDR TaqI* (rs731236) had a 2.61 times higher risk to have degenerative disc disease.[31] Moreover, individuals aged younger than 40 years who had the t allele were almost six times more likely to develop disc degeneration and 7.17 times more likely to develop disc bulge compared to those without the t allele.[31] However, studies

in Danish[32] and Mexican populations[33] contradict previous results suggesting a role of *VDR TaqI* in disc degenerative disease. This conflicting role of SNPs in*IL-1A, TNF-A* and *VDR* on HNP therefore needs to be further evaluated. This study sought to determine the association of *IL-1A* -889C>T (rs1800587), *TNF-A* 238G>A (rs361525), and *VDR TaqI* (rs731236) in susceptibility to HNP.

Methods

Study design and protocol

A systematic review and meta-analysis were conducted to assess the association of three SNPs, *IL-1A* (rs1800587), *TNF-A* (rs361525), and *VDR* (rs731236), on susceptibility to HNP. The outcome variable of this study was the risk or susceptivity to have HNP while the response variables were the SNPs in three genes: *IL-1A* (rs1800587), *TNF-A* (rs361525), and *VDR* (rs731236). We searched databases for relevant studies, then extracted and analyzed data from those studies to achieve the pooled odds ratios (ORs) and 95% confidence interval (95%CI) using a random or fixed effect model depending on the data. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline.[34,35] The protocol of this study has been registered in PROSPERO (reg. number CRD42021249187).

Literature search strategy

The literature searches were conducted on PubMed, Embase, Cochrane, and Web of Science. The searches were conducted using the keywords:'degenerative disc disease' AND ('IL-1A' OR 'rs1800587' OR '-889C>T') OR ('TNF-A' OR 'rs361525' OR '-238G>A') OR ('VDR' OR 'rs731236' OR 'TaqI') AND 'gene polymorphism', including all results up to April 1st, 2021. The keywords were adapted from Medical Subject Heading (MeSH). Additional studies were also retrieved from the references of relevant papers. If two or more studies with the same study data were identified, the most recent study was used. The processes were conducted by three independent authors (JKF, MI, HAM).

Study eligibility

To be eligible for the meta-analysis, a study had to meet all the inclusion criteria below: (1) the study design should be case-control, cross-sectional, or cohort design; (2) the study should evaluate the association of *IL-1* (rs1800587), *TNF-A* (rs361525), or *VDR* (rs731236) on HNP and have case and control groups; and (3) studies should present genotype frequency or minor allele frequency (MAF). All studies with duplicate records, poor quality or which had deviation from Hardy-Weinberg Equilibrium (HWE) were excluded.[36]

Data extraction

Important information from the studies such as first author name, year of publication, names of targeted gene and the SNP, genotype frequency, or MAF from case and control groups were collected. The allele frequency and MAF were recalculated using Mendel's law. Data extraction processes were conducted by three independent authors (JKF, MI, HAM) and consensus established together with senior authors (AA, HH) if discrepancies were found.

Quality assessment

The quality of the included studies was evaluated using Newcastle-Ottawa Score (NOS)[37] by three independent authors (JKF, MI, HAM). This evaluation was conducted to ensure the quality of three fundamental methodological parameters of the studies: patient selection (four points), comparability of the groups (two points), and ascertainment of exposure (three points); NOS ranged from 0 to 9. Each study was then categorized based on the NOS: (1) good quality (NOS $\geq$ 7); (2) moderate quality (NOS $\geq$ 5); or (3) poor quality (NOS < 5). Consensus was established if discrepancies were found.

Covariates and sub-group analysis

The outcome measure in our study was the incidence of HNP while the predictor covariates were the gene polymorphisms of IL-1A (rs1800587), TNF-A (rs361525), and VDR (rs731236). All genetic models were applied to describe the role of each gene variant in the pathogenesis of HNP. For IL-1A (rs1800587), the allele models were C vs. T and T vs. C; and the genotype models were CC vs. CT + TT, CT vs. CC + TT, and TT vs. CC + CT. For TNF-A (rs361525), the allele models were G vs. A and A vs. G; and the genotype models were GG vs. GA + AA, GA vs. GG + AA, and AA vs. GG + GA. For VDR (rs731236), the allele models were T vs. C and C vs. T; and the genotype models were TT vs. TC + CC, TC vs. TT + CC, and CC vs. TT + TC.

Statistical analysis

To assess the association of *IL-1A* (rs1800587), *TNF-A* (rs361525), and *VDR* (rs731236) on HNP, a Z-test was employed. The Egger test was used to evaluate the publication bias and a $p < 0.05$ indicated the possibility of publication bias in each calculated result. The Q test was used to evaluate the heterogeneity and decide between random and fixed-effect

models for OR calculation. If heterogeneity was indicated (p-value less than 0.10), the random effect model was used; otherwise, the fixed-effect model was used. All analyses were performed using 'meta',[38] ' metafor',[39] and 'dmetar'[40] packages in R version 4.0.4.[41]

Results

Study eligibility results

The literature searches yielded 3,199 articles of which 3,067 references were retained after removing duplicates. Screening of the titles and abstracts excluded 2,965 articles as they did not meet the inclusion criteria. After a further screening of full text, an additional 90 studies were excluded due to lack of relevance (n = 90), incomplete data (n = 5), and HWE deviation (n = 6) (Figure 1). 12 studies were included in the meta-analysis: three studies for *IL-1A* (rs1800587),[19,42,43] two studies for *TNF-A* (rs361525),[19,44] and nine studies for *VDR* (rs731236).[28,42,45-51] The summary of studies included in the meta-analysis is presented in Table 1.

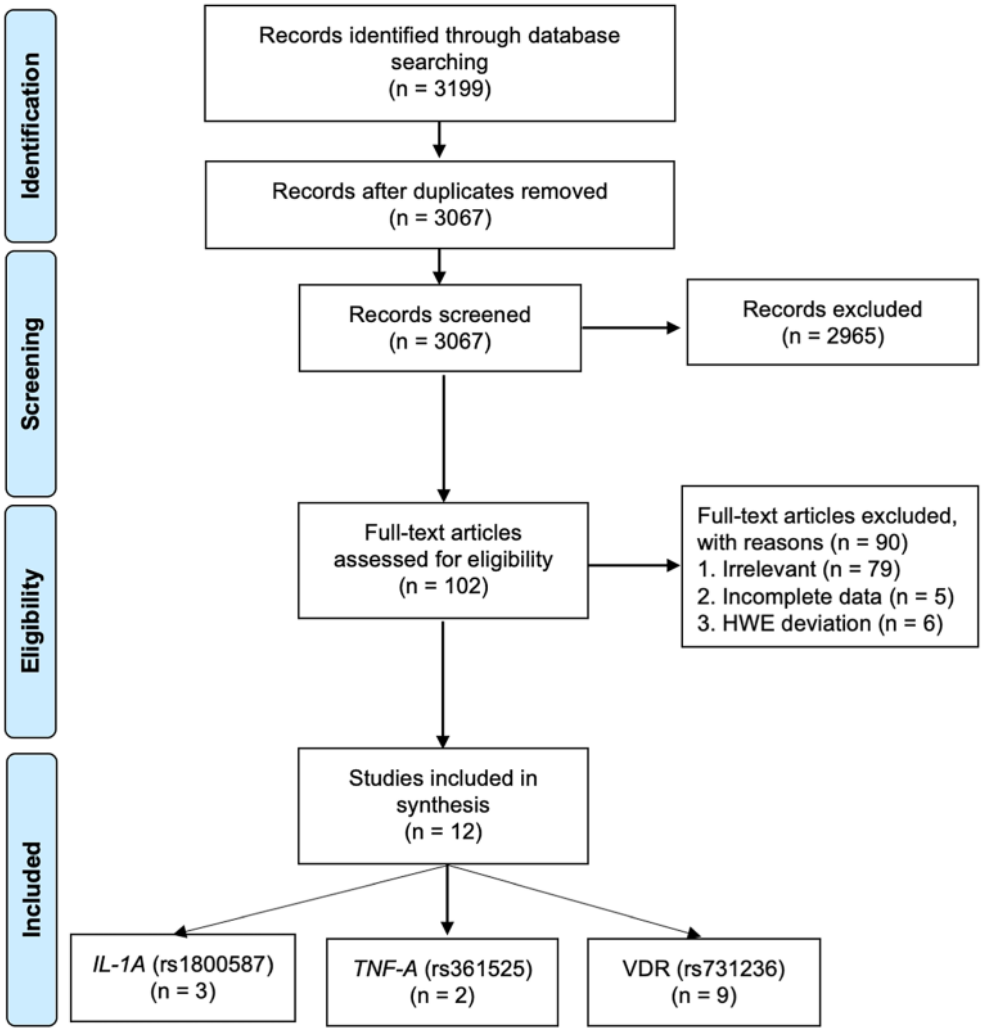

Figure 1. Flowchart of the result of literature searches according to the preferred reporting items of systematic reviews and meta-analyses (PRISMA).

Table 1. Study characteristics of *IL-1A* -889C>T, *TNF-A* 238G>A, and *VDR TaqI* (rs731236) on HNP.

Gene	SNP code	Author	Year	Country	Study design	NOS	Study groups															
							Case								Control							
							Genotype				Allele			HWE	Genotype				Allele			HWE
							AA	AB	BB	*n*	A	B	*n*		AA	AB	BB	*n*	A	B	*n*	
IL1A	-889C>T						CC	CT	TT		C	T			CC	CT	TT		C	T		
		Serrano et al[42]	2014	Mexico	Case-control	8	51	45	4	100	147	53	200	2.41	55	35	10	100	145	55	200	1.49
		Chen et al[43]	2018	China	Case-control	8	87	78	28	193	252	134	386	2.27	102	81	14	197	285	109	394	0.15
		Abdollahzade et al[19]	2018	Iran	Case-control	8	33	33	10	76	99	53	152	0.15	62	62	12	136	186	86	272	0.40
TNF-A	238G>A						GG	GA	AA		G	A		GG	GA	AA		G	A			
		Aparicio et al[44]	2011	Spain	Case-control	7	45	5	0	50	95	5	100	0.14	113	9	0	122	235	9	244	0.18
		Abdollahzade et al[19]	2018	Iran	Case-control	8	61	15	0	76	137	15	152	0.91	79	57	1	137	215	59	274	7.32
VDR	*TaqI*						TT	TC	CC		T	C			TT	TC	CC		T	C		
		Chen et al[45]	2012	China	Case-control	8	79	2	0	81	160	2	162	0.01	86	14	1	101	186	16	202	0.25
		Cheung et al[46]	2012	China	Case-control	9	92	15	1	108	199	17	216	0.19	103	3	0	106	209	3	212	0.02
		Colombini et al[28]	2016	Italy	Case-control	8	114	117	35	266	345	187	532	0.33	106	109	37	252	321	183	504	1.06
		Eser et al[47]	2010	Turkey	Case-control	8	65	67	17	150	198	102	300	0.00	67	66	16	150	201	99	300	0.00
		Li et al[48]	2018	China	Case-control	8	114	6	0	114	234	6	240	0.08	109	11	0	120	229	11	240	0.28
		Oishi et al[49]	2003	Japan	Case-control	8	31	8	0	39	70	8	78	0.51	16	5	0	21	37	5	42	0.38
		Omair et al[50]	2012	Norway	Case-control	9	53	70	23	147	176	116	292	0.00	61	92	35	188	214	163	376	0.00
		Serrano et al[42]	2014	Mexico	Case-control	8	69	27	4	69	165	35	200	0.42	62	35	3	100	159	41	200	0.54
		Yuan et al[51]	2010	China	Case-control	8	156	22	0	156	334	22	356	0.77	256	28	0	284	540	28	568	0.76

'"*/E: Hardy-Weinberg Equilibrium, *IL-1A*: interleukin 1A gene, NOS: New Castle Ottawa Scale, *p-Het*: p-heterogeneity, *TNF-A:* tumor necrosis factor alpha gene, *VDR*: vitamin D receptor gene.

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Table 2. Associations of genotypes and alleles of *IL-1A* -889C>T, *TNF-A* 238G>A, and *VDR TaqI* (rs731236) on HNP.

Gene	Allele/ genotype model	Number of studies	Model	OR (CI 95%)	p-value	p-Het	p-Egger
IL-1A	CC *vs.* CT+TT	3	Fixed	0.82 (0.62, 1.09)	0.170	0.867	0.193
	CT *vs.* CC+TT	3	Fixed	1.07 (0.81, 1.42)	0.637	0.373	0.675
	TT *vs.* CT+CC	3	Random	1.20 (0.13, 11.37)	0.764	0.039	0.177
	C *vs.* T	3	Fixed	0.83 (0.67, 1.02)	0.081	0.369	0.221
	T *vs.* C	3	Fixed	1.21 (0.98, 1.50)	0.081	0.369	0.221
TNF-A	GG *vs.* GA+AA	2	Random	1.60 (0.00,12882.74)	0.628	0.034	0.889
	GA *vs.* GG+AA	2	Random	0.63 (0.00, 4211.31)	0.629	0.038	0.864
	AA *vs.* GG+GA	2	Random	1.34 (0.16, 6712.96)	0.955	0.587	<0.001
	G *vs.* A	2	Random	1.60 (0.00, 12882.74)	0.628	0.034	0.744
	A *vs.* G	2	Random	0.67 (0.00, 1555.67)	0.629	0.056	0.744
VDR	TT *vs.* TC+CC	9	Random	2.65 (0.60, 11.85)	0.172	<0.001	0.986
	TC *vs.* TT+CC	9	Random	1.01 (0.55, 1.85)	0.964	0.041	0.791
	CC *vs.* TC+TT	9	Fixed	0.94 (0.69, 1.28)	0.688	0.970	0.3871
	T *vs.* C	9	Random	1.06 (0.91, 1.22)	0.775	0.023	0.874
	C *vs.* T	9	Random	0.92 (0.50, 1.72)	0.775	0.023	0.874

IL-1A: interleukin 1A gene,*p-Het*:p-heterogeneity, *TNF-A:* tumor necrosis factor alpha gene, *VDR*: vitamin Dreceptor gene.

Distribution of allele and genotype frequency of *IL-1A* -889C>T, *TNF-A* 238G>A and *VDR TaqI*

Our data indicated that the TT genotype of *IL-1A -889C>T* was 1.37 more frequent in HNP patients than in controls, while the distribution of alleles and other genotypes were similar between patients and healthy controls. CT genotype and T allele of *TNF-A* 238G>A were both 1.6 times more frequent in healthy controls than in HNP cases. No difference in the distribution of alleles or genotypes between HNP and controls was observed in *VDR TaqI* (Table 1).

Association between alleles and genotypes of *IL-1A*, *TNF-A*, and *VDR* polymorphism and HNP

Our pooled estimates suggested that no *IL-1A* -889C>T genotypes were associated with the risk of HNPs with CC vs. CT+TT (OR: 0.82, 95%CI: 0.62, 1.09), CT vs. CC+TT (OR: 0.07; 95%CI: 0.81, 1.42), and TT vs. CT+CC (OR: 1.20; 95%CI: 0.13, 11.37) (Table 2 and Figure 2). The pooled data also suggested that allele frequency of *IL-1A* -889C>T had no significant association with the susceptibility to HNP with OR: 0.83; 95%CI: 0.67, 1.02 for C allele compared to T allele.

Pooled estimates for allele and genotype distribution of the *TNF-A* 238G>A also had no significant association with the risk for HNP. No association was observed between genotype models and the risk of HNP: GG *vs.* GA+AA (OR: 1.60; 95%CI: 0.00, 12882.74), GA *vs.* GG+AA (OR: 0.63; 95%CI: 0.00, 4211.31), and AA *vs.* GG+GA (OR: 1.34; 95%CI: 0.16, 6712.96) (Table 2 and Figure 3). Distribution of the allele also had no strong association with HNP susceptibility.

Our estimates for genotypes of *VDR TaqI* (rs731236) suggested that none of the genotypes were associated with susceptibility to degenerative disc disease HNP with OR: 2.65; 95%CI: 0.60, 11.85 for TT *vs.* TC+CC, OR: 1.01; 95%CI: 0.55, 1.85 for TC vs. TT+CC and OR: 0.94; 95%CI: 0.69, 1.28 (Table 2 and Figure 4). None of the alleles of *VDR TaqI* (rs731236) were associated with HNP; people with T allele had OD 1.06 with 95%CI: 0.91, 1.22 for HNP.

Discussion

Our present failed to clarify the role of IL-1A (rs1800587), TNF-A (rs361525), and VDR (rs731236) on the pathogenesis of HNP. To the best of our knowledge, our current study is the first study providing the holistic gene polymorphism in the case of HNP. Therefore, the comprehensive comparison in the context of methodological quality between our study and previous studies was unable to perform. The role of gene polymorphism of IL-1A (rs1800587) was rarely reported. Studies found that IL-1A (rs1800587) has no association with rheumatoid arthritis and systemic sclerosis.[52,53] Another study also found no association between TNF-A gene variants and the risk of bone-joint and spinal tuberculosis.[54] Furthermore, a study assessing the role of VDR gene polymorphism in the case of osteoarthritis also failed to show the potential contribution of VDR gene variant in the development of osteoarthritis.[55] These evidences suggested that, while

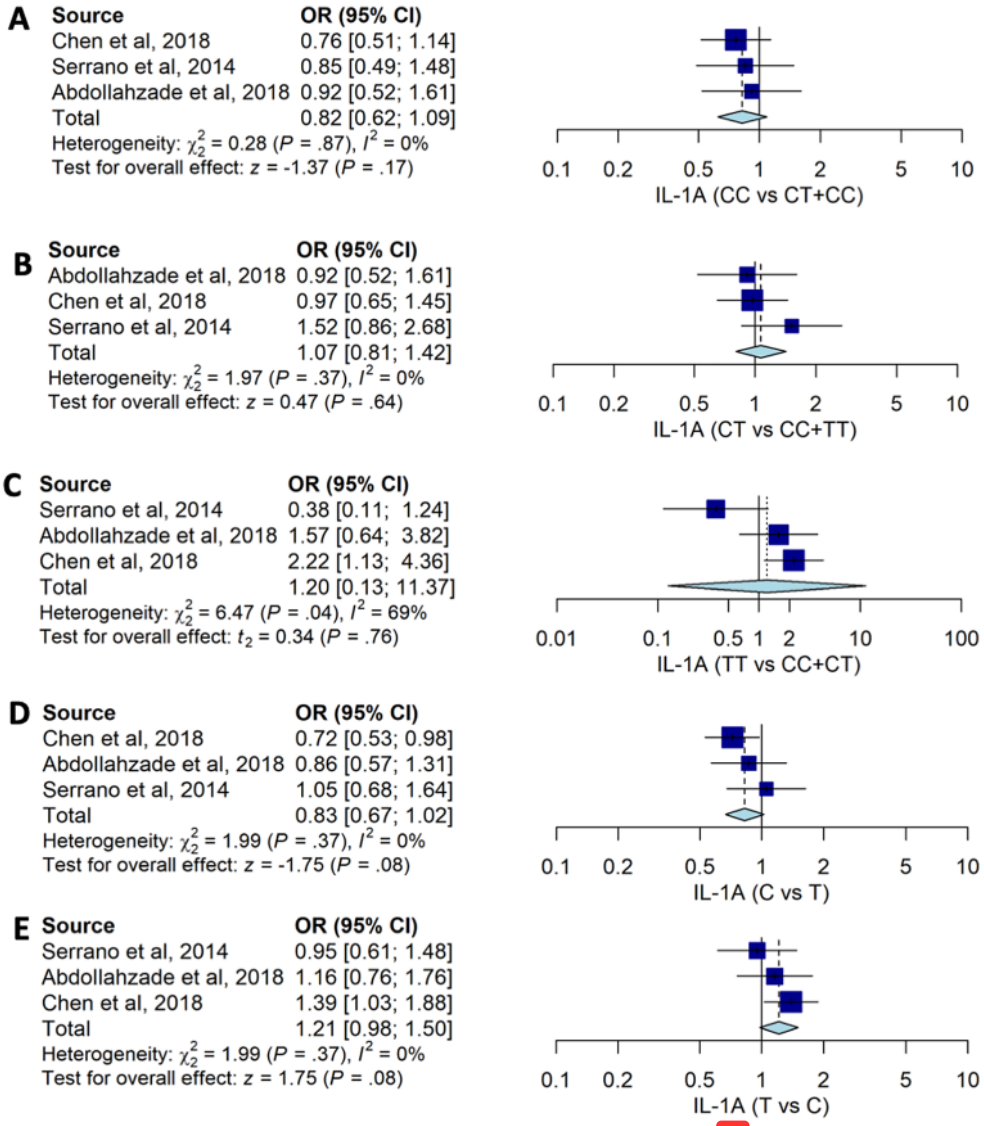

Figure 2. The forest plot of the association of *IL-1A*-889C>T and HNP. (A) CC vs CT+TT (OR: 0.82; 95%CI: 0.62, 1.09); p-value0.170, p-Het 0.867, and p-Egger 0.193, (B) CT vs CC+TT (OR1.07; CI95%: 0.81, 1.42); p-value 0.637; p-Het 0.373; p-Egger 0.675, (C) TT vs CT+CC (OR: 1.20; CI95%: 0.13, 11.37); p-value 0.764, p-Het 0.039, p-Egger 0.177, (D) C vs T (OR0.83; 95%CI: 0.67, 1.02); p-value 0.081; p-Het 0.369; p-Egger 0.221), and (E) T vs C (OR: 1.21; CI95%: 0.98, 1.50); p-value 0.081; p-Het 0.369; p-Egger 0.221.

theoretically the gene variants of IL-A, TNF-A, and VDR may contribute to the development of bone diseases, the evidence reveals otherwise. For the negative findings of our study, several possible reasons might be proposed. First, HNP is a complex disease and is cause by multiple factors. Thus, no single factor such as a single SNP is responsible for the whole pathogenesis. Second, large variations in the number of samples or allele frequencies among studies in our meta-analysis also contribute to the findings. This probably relates to differences in populations where study data were collected. Finally, the small number of samples significantly influenced the results of our meta-analysis. Therefore, studies with larger sample sizes and sub-analyses for different populations such as Asian, Caucasian, and other populations are warranted whenever more data are available.

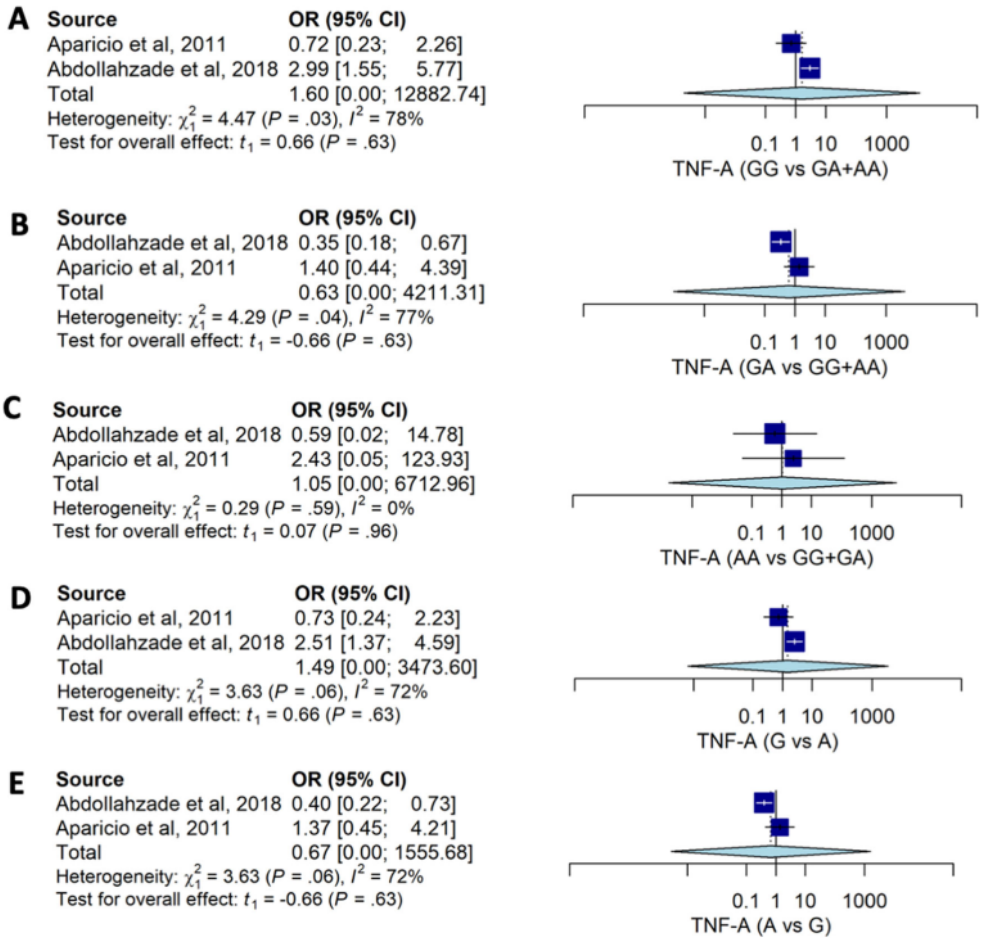

Figure 3. The forest plot of the association of *TNF-A* 238G>A and HNP. (A) GG vs GA+AA (OR1.60; CI95%: 0.00, 12882.74); p-value 0.628, p-Het 0.034, p-Egger 0.889, (B) GA vs GG+AA (OR0.63; CI95%: 0.00, 4211.31); p-value 0.629, p-Het 0.038, p-Egger 0.864, (C) AA vs GG+GA (OR1.05; CI95%: 0.16, 6712.96); p-value 0.955, p-Het 0.587, p-Egger <0.001, (D) G vs A (OR1.49; 95%CI: 0.00, 3473.60); p-value 0.629, p-Het 0.034, p-Egger 0.744, (E) A vs G (OR: 0.67; 95% CI:0.00, 1555.67); p-value 0.629, p-Het 0.056, p-Egger 0.744.

HNP occurs when the central part of the intervertebral disc, the nucleus pulposus, herniates through the surrounding part of the disc, the annulus fibrosus. The damage to the annulus fibrosus resulting in the herniated disc may be associated with factors such as gender, age, certain activities such as lifting of weights and carrying, and being overweight.[56] For example, the degeneration of disc organization could occur during aging as the regulation of the extracellular matrix (ECM), a major component of the disc, is damaged during the aging process.[56] The herniated disc or HNP may occur as a result of several pathological mechanisms. Those mechanisms ultimately cause imbalances in disc composition that are directly linked to the quality of the ECM.[56] Therefore, the balance between the ECM and its degrading enzymes, such as matrix metalloproteases (MMPs), seems to be the key to maintaining normal disc function. Interestingly, of several mechanical pathways, the regulation of the ECM and the MMPs could also be determined by the occurrence of single nucleotide polymorphisms in genes responsible for ECM regulation as explained below.[57]

Two major structural proteins that are important in the matrix structure of the disc are collagen and proteoglycan.[56] The main proteoglycan found in the normal intervertebral disc is aggrecan.[58] Although both annulus fibrosus and nucleus pulposus are mainly composed of water, proteoglycan, and collagen, the level of those contents differ between the structures. The annulus fibrosus consists of 70% water, 15% collagen, and 5% proteoglycan, while the composition in the nucleus pulposus is 77% water, 4% collagen, and 14% proteoglycan.[56] Any event causing disturbances in those ratios

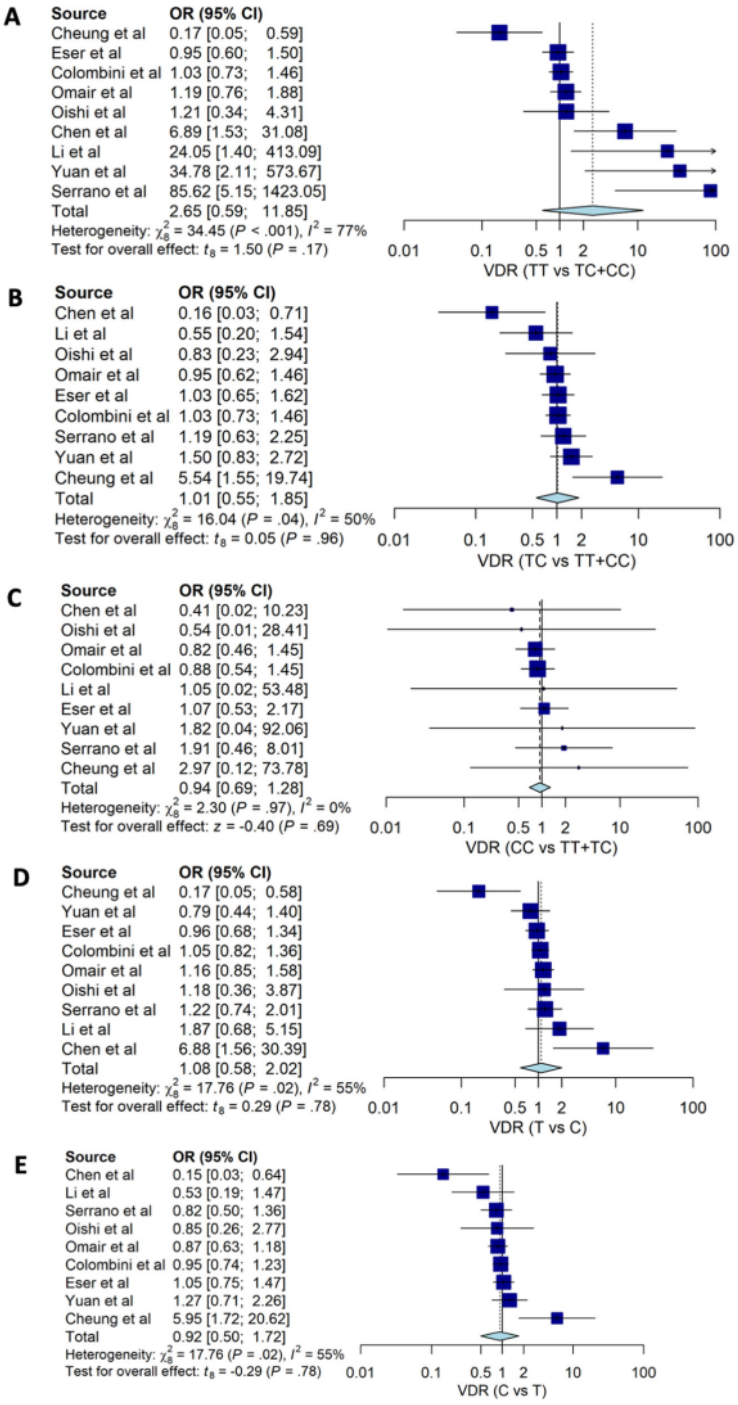

Figure 4. The forest plot of the association of *VDR TaqI* (rs731236) and HNP. (A) TT vs TC+CC (OR: 2.65; CI95%: 0.60, 11.85); p-value 0.172, p-Het <0.001, p-Egger 0.986, (B) TC vs TT+CC (OR1.01; CI95%: 0.55, 1.85); p-value 0.964, p-Het 0.041, p-Egger 0.791, (C) CC vs TC+TT (OR 0.94; CI95%: 0.69, 1.28); p-value 0.688, p-Het 0.970, p-Egger 0.387, (D) T vs C (OR: 1.06; CI95%: 0.91, 1.22); p-value 0.775, p-Het 0.023, p-Egger 0.874), (E) C vs T (OR: 0.92; 95%CI: 0.50, 1.72); p-value 0.775, p-Het 0.023, p-Egger 0.874.

and/or in synthesis and/or degradation of those structural proteins could lead to herniated disc problems. For example, hypoxic and acidic conditions could repress the synthesis of the matrix leading to the dysfunctionalities of the cells of the disc.[59,60]

The role of inflammation in predisposing the disc to damage has also been revealed. Specifically, proinflammatory cytokines are found to play a specific role in herniated and degenerated discs.[58,61-63] A controlled immunohistochemical study observed the accumulation of inflammatory cells, mainly macrophages, in herniated disc cells indicating the role of proinflammatory cytokines in the disease.[62] For example, IL-1β could induce the annulus fibrosus to generate inflammatory factors leading to the impairment of proteoglycan aggregation.[63] Another cytokine, TNF-α, is also involved in the development of intervertebral disc problems.[64] However, it seems that its effect is less significant than IL-1.[65] This finding may be related to its relatively lower expression compared to IL-1 in the normal and healthy disc.[56,66]

Penetration of those inflammatory cells or proteins could be caused by matrix loss. In normal conditions, aggrecan should prevent the penetration of various compounds, especially serum proteins and cytokines.[67] Therefore, in addition to its pivotal role in maintaining sufficient hydration to the disc, proteoglycan loss could stimulate the movement of cytokines towards the disc activating the inflammation cascade.[56]

One of the mechanisms by which the proinflammatory cytokines, such as IL-1α and TNF-α, generate problems in the intervertebral disc is related to their effect on inducing MMP production.[68-71] The exaggerated activity of MMPs causes excessive degradation of collagen and proteoglycan.[58] Another mechanism is associated with the activity of the cytokines in inhibiting tissue inhibitors of MMPs (TIMPs) which are responsible for terminating the action of MMPs.[58] Taken together, those actions ultimately impair disc functionality.

As the normal intervertebral disc is relatively avascular and aneural,[56] the nutritional supply to the disc depends on the ability of the nutrients to diffuse from the closest vascularized structure outside the disc which are the vertebral bodies.[72] The nutrients then penetrate the cartilaginous endplate and finally reach the annulus fibrosus and nucleus pulposus.[72,73] Accordingly, calcification of the endplate would diminish diffusion of vital nutrients, leading to the death of the disc cells.[74] Therefore, VDR plays a critical role as this ligand-dependent transcription factor is involved in regulating calcium homeostasis and bone mineralization in the body, including in the intervertebral disc.[75,76] It has been known that genetic polymorphisms occurring in genes encoding VDR are associated with intervertebral disc problems,[76] including herniated disc.

Our current study had several limitations. First, the pertinent confounding factors that might affect the final findings of our study were not included in analysis, such as mechanical and behavioral factors and the levels of proteoglycans. Second, since the included articles in our current study were non-randomized controlled trials (RCTs), the final findings might have the higher risk of bias. Therefore, the up-coming meta-analysis was expected to involve only RCTs studies. Third, the limited reports on the context of gene polymorphism in HNP had made our study included the limited number of studies. Therefore, our findings should be interpreted with caution.

In conclusion, our results suggest that well-regulated IL-1A, TNF-A, and VDR are important for normal intervertebral discs and that dysregulation of these could negatively affect the intervertebral discs. Some individual studies found that SNPs in IL-1A (rs1800587), TNF-A (rs361525), and VDR (rs731236) were associated with the susceptibility to HNP, however, our meta-analysis suggested that the effects are not robust.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

Reporting guidelines

Figshare: PRISMA checklist for 'The role of single nucleotide polymorphisms of IL-1A -889C>T (rs1800587), TNF-A -238G>A (rs361525), and VDR TaqI (rs731236) on susceptivity of herniated nucleus pulposus', https://doi.org/10.6084/m9.figshare.14479233.[77]

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General remark:
- The title has been added and clarified with the study design "Systematic Review and Meta-Analysis" according to the previous comment.

Abstract:
- No further comment.

Introduction:
- No further comment.

Materials and Methods:
- No further comment.

Result and discussion:
- The discussion has been strengthened with comparison with previous studies that discussed about IL-1A, TNF-A, or VDR generally according to the previous comment.

Figures and Tables:
- No further comment.

Conclusion:

- No further comment.

Overall comments:

- This current manuscript version may be accepted for indexing.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Stem cell and Tissue Engineering

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 09 August 2021

https://doi.org/10.5256/f1000research.59208.r91376

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Ismail Hadisoebroto Dilogo
[1] Stem Cell Medical Technology Integrated Service Unit, Cipto Mangunkusumo Central Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[2] Stem Cell and Tissue Engineering Research Cluster Indonesian Medical Education and Research Institute (IMERI), Universitas Indonesia, Jakarta, Indonesia
[3] Department of Orthopaedic and Traumatology, Dr. Cipto Mangunkusumo General Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

General remark:

- The study design on the title has not been added, I noticed that there is already a design label “Systematic Review” written above the title from the F1000 platform but since this manuscript will be added to some online databases such as Pubmed and Scopus, I recommend to put the design on the title. Also, please clarify if this is a meta-analysis or systematic review. As it is still written “Systematic review” above the title.

Abstract:

- The problem that this review wants to answer is added “this study was to determine the role of single nucleotide polymorphisms (SNPs) in interleukin 1 alpha (*IL-1A*), tumor necrosis factor-alpha (*TNF-A*), and vitamin D receptor (*VDR*) genes on the susceptibility to herniated nucleus pulposus (HNP)” according to the previous comment.

- The study design of included samples in this study has been added according to the previous comment to show the level of evidence of this systematic review “three, two and nine case-control studies on *IL-1A* -889C>T, *TNF-A* -238G>A, and *VDR TaqI* were included, respectively, in our meta-analysis".

- For the conclusion, the author has stated the answer to the research question, although it is still inconclusive.

Introduction:
- No comment.

Materials and Methods:
- According to the previous comment, the author has clarified and stateD that there is no Randomized Controlled Trial and Cohort study about this topic in the limitation section.

Result and discussion:
- For the discussion, I noticed that author responded “To the best of our knowledge, our current study is the first study providing the holistic gene polymorphism in the case of HNP. Therefore, the comprehensive comparison in the context of methodological quality between our study and previous studies was unable to perform”. For comparing the result, you do not have to find the same method and result, please kindly compare it with similar or other previous studies that analyse similar variables. It doesn't have to be as specific as “IL-1A (rs1800587), TNF-A (rs361525), and VDR (rs731236)”. Please strengthen the discussion with comparison with previous studies that discussed IL-1A, TNF-A, or VDR as general.

Figures and Tables:
- No comment.

Conclusion
- The conclusion has been revised according to the previous comment, answering the research question. The conclusion is current existed studies are not strong enough to answer the question. Hence, further larger population and subgroup analyses are warranted to support these findings.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Stem cell and Tissue Engineering

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 10 Aug 2021

Azharuddin Azharuddin, Universitas Syiah Kuala, Banda Aceh, Indonesia

General remark:

- The study design on the title has not been added, I noticed that there is already a design label "Systematic Review" written above the title from the F1000 platform but since this manuscript will be added to some online databases such as Pubmed and Scopus, I recommend to put the design on the title. Also, please clarify if this is a meta-analysis or systematic review. As it is still written "Systematic review" above the title.

RESPONSE: We have added the a "systematic review and meta-analysis" in our title.

Abstract:

- The problem that this review wants to answer is added "this study was to determine the role of single nucleotide polymorphisms (SNPs) in interleukin 1 alpha (*IL-1A*), tumor necrosis factor-alpha (*TNF-A*), and vitamin D receptor (*VDR*) genes on the susceptibility to herniated nucleus pulposus (HNP)" according to the previous comment.

RESPONSE: Thank you. No comment. No further edit required.

- The study design of included samples in this study has been added according to the previous comment to show the level of evidence of this systematic review "three, two and nine case-control studies on *IL-1A* -889C>T, *TNF-A* -238G>A, and *VDR TaqI* were included, respectively, in our meta-analysis".

RESPONSE: Thank you. No further edit required.

- For the conclusion, the author has stated the answer to the research question, although it is still inconclusive.

RESPONSE: Thank you. No further edit required.

Introduction:

- No comment.

RESPONSE: No further edit required.

Materials and Methods:

- According to the previous comment, the author has clarified and stateD that there is no Randomized Controlled Trial and Cohort study about this topic in the limitation section.

RESPONSE: Thank you. No further edit required.

Result and discussion:

- For the discussion, I noticed that author responded "To the best of our knowledge, our current study is the first study providing the holistic gene polymorphism in the case of HNP. Therefore, the comprehensive comparison in the context of methodological quality between our study and previous studies was unable to perform". For comparing the result, you do not have to find the same method and result, please kindly compare it with similar or other previous studies that analyse similar variables. It doesn't have to be as specific as "IL-1A (rs1800587), TNF-A (rs361525), and VDR (rs731236)". Please strengthen the discussion with comparison with previous studies that discussed IL-1A, TNF-A, or VDR as general.

2

RESPONSE: Thank you for your suggestion. We have added some discussion based on previous studies.

Figures and Tables:
- No comment.

RESPONSE: Thank you. No further edit required.

Conclusion
- The conclusion has been revised according to the previous comment, answering the research question. The conclusion is current existed studies are not strong enough to answer the question. Hence, further larger population and subgroup analyses are warranted to support these findings.

RESPONSE: Thank you. No further edit required.

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 19 July 2021

https://doi.org/10.5256/f1000research.56597.r87698

Mahir Gachabayov
Section of Colorectal Surgery, Department of Surgery, Westchester Medical Center, New York Medical College, Valhalla, NY, USA

Thank you for the opportunity of reviewing this manuscript.
- This is a systematic review and meta-analysis aiming at evaluating the impact of SNPs on susceptibility to HNP.
- The research question makes sense. The gap in the literature was well presented and the objective of the review was well formulated.
- The protocol of the systematic review was prospectively developed and registered in PROSPERO.
- The search strategy was comprehensive.The screening and study selection process were well described and illustrated in a PRISMA flow diagram. Methodology of quality assessment and statistical analysis was adequate.
- The results are well presented, summarized in tables, and illustrated in forest plots.

- The Discussion is comprehensible, well-describes the findings of this systematic review in comparison with the current body of evidence.
- Conclusions are justified by the findings.

I have one minor comment:

- It seems like the limitations were presented in the conclusion. I would separate them from the conclusions and move them as the last paragraph of the Discussion.

4

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical outcomes research 1 and evidence synthesis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 03 Aug 2021

Azharuddin Azharuddin, Universitas Syiah Kuala, Banda Aceh, Indonesia

#Reviewer 2

I have one minor comment: It seems like the limitations were presented in the conclusion. I would separate them from the conclusions and move them as the last paragraph of the Discussion.
Response: The limitation has been provided in the end of discussion section. The conclusion has been revised as suggested.

1

Competing Interests: No competing interests were disclosed.

Reviewer Report 01 June 2021

https://doi.org/10.5256/f1000research.56597.r86114

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[2] Stem Cell and Tissue Engineering Research Cluster Indonesian Medical Education and Research Institute (IMERI), Universitas Indonesia, Jakarta, Indonesia
[3] Department of Orthopaedic and Traumatology, Dr. Cipto Mangunkusumo General Hospital, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

General remark:
- The title is descriptive about the manuscript, however, please state the study design on the title.
- To draw the interest of the reader, is it possible if the authors simplified the title from "IL-1A-889C>T(rs1800587)" to "IL-1A", and also the same for TNF-A and VDR?

Abstract:
- Line 31, please state the problem that this review will answer.
- Line 35, in the methods section, please state the study design of included samples in this study to show the level of evidence of this meta-analysis.
- Line 58, for the conclusion, please kindly state the answer and summary of the research question, instead of restating limitation and result.

Introduction:
- The Introduction is already well written. It gives enough information for the reader to understand the context. It also clearly explains why the study was necessary.

Materials and Methods:
- As all the studies included in this review are a case-control, though it is uncommon for a systematic review meta-analysis to use a case control as a sample, please clarify and state that there is no Randomized Controlled Trial and Cohort study about this topic.
- I noticed the authors used Newcastle Ottawa Score, please kindly check https://ebm.bmj.com/content/23/2/60 to review the methodological quality of a case series.
- Please define the primary outcome in this review.

Result and discussion:
- The results are presented clearly and accessibly, and it also supports the main conclusion.
- The discussion, has to be more detailed, from line 203- 244, the discussion mainly discusses the pathogenesis of the herniated nucleus pulposus. Please kindly deepen the

discussion based on the result of this review, compare it with previous study(s), and explain the finding from the authors' point of view.

Figures and Tables:
- Figures and Tables are adequately explained.

Conclusion:
- The limitations are well stated, however, line 286-288 "Therefore, studies with larger sample sizes and sub-analyses for different populations such as Asian, Caucasian, and other populations are warranted whenever more data are available." Please put in one paragraph before the conclusion to make the conclusion from your review stronger.

Overall comments:
- This manuscript may be considered for indexing after Major revisions.

4

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Yes

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Partly

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Stem cell 1 and Tissue Engineering

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 03 Aug 2021

Azharuddin Azharuddin, Universitas Syiah Kuala, Banda Aceh, Indonesia

#Reviewer 1

Abstract: Line 31, please state the problem that this review will answer.
Response: We have added the problem that underly our study in abstract: "The pathogenesis of herniated nucleus pulposus (HNP) is complex, and may involve the wide variety of gene polymorphism. However, the reports from the existing evidence revealed inconclusive findings."

Abstract: Line 35, in the methods section, please state the study design of included samples in this study to show the level of evidence of this meta-analysis.
Response: the study design of included articles has been added in the results section of abstract: "We screened 3,067 unique studies for eligibility and three, two and nine case-control studies on IL-1A -889C>T, TNF-A -238G>A, and VDR TaqI were included, respectively, in our meta-analysis."

Abstract: Line 58, for the conclusion, please kindly state the answer and summary of the research question, instead of restating limitation and result.
Response: The main findings of our study has been outlined in the conclusion section of abstract: "our data indicated that IL-1A -889C>T, TNF-A -238G>A, and VDR TaqI had weak association with HNP susceptibility in both genotypes and allele distributions." However, we also described about the clinical implication, limitation and future research direction to prevent the miss-understanding in interpretating the findings of our study.

Introduction: The Introduction is already well written. It gives enough information for the reader to understand the context. It also clearly explains why the study was necessary.
Response: thank you.

Materials and Methods: As all the studies included in this review are a case-control, though it is uncommon for a systematic review meta-analysis to use a case control as a sample, please clarify and state that there is no Randomized Controlled Trial and Cohort study about this topic.
Response: We agree that case-control studies are uncommon to include in meta-analysis. However, in the meta-analysis, we cannot manage the findings (the findings of article searching) as we expected if they are not supported by the available data. And unfortunately, in the searching strategy, we only found case-control studies. This point has also been included in the limitations of our study.

Materials and Methods: I noticed the authors used Newcastle Ottawa Score, please kindly check https://ebm.bmj.com/content/23/2/60 to review the methodological quality of a case series.
Response: We thank you for the suggestion. Case report and or case series studies may be possible to include in systematic review. However, they are not possible to include in meta-analysis (double arm calculation, as reported in our current study) because they do not have control.

Materials and Methods: Please define the primary outcome in this review.
Response: The primary outcomes have been provided in the Method section: "Covariates and sub-group analysis. The outcome measure in our study was the incidence of HNP while the predictor covariates were the gene polymorphisms of IL-1A (rs1800587), TNF-A (rs361525), and VDR (rs731236). All genetic models were applied to describe the role of each gene variant in the pathogenesis of HNP. For IL-1A (rs1800587), the allele models were C vs. T and T vs. C; and the genotype models were CC vs. CT + TT, CT vs. CC + TT, and TT vs. CC + CT. For TNF-A (rs361525), the allele models were G vs. A and A vs. G; and the genotype models were GG vs. GA + AA, GA vs. GG + AA, and AA vs. GG + GA. For VDR (rs731236), the allele models were T vs. C and C vs. T; and the genotype models were TT vs. TC + CC, TC vs. TT + CC, and CC vs. TT + TC."

Result and discussion: The results are presented clearly and accessibly, and it also supports the main conclusion.
Response: Thank you.

The discussion, has to be more detailed, from line 203- 244, the discussion mainly discusses the pathogenesis of the herniated nucleus pulposus. Please kindly deepen the discussion based on the result of this review, compare it with previous study(s), and explain the finding from the authors' point of view.
Response: The explanation on our main findings and the holistic comparison including the possible reason of our findings has been provided: "Our present study failed to clarify the role of IL-1A (rs1800587), TNF-A (rs361525), and VDR (rs731236) in the pathogenesis of HNP. To the best of our knowledge, our current study is the first study providing the holistic gene polymorphism in the case of HNP. Therefore, the comprehensive comparison in the context of methodological quality between our study and previous studies was unable to perform. However, several possible reason for the negative findings in our study might be proposed. First, HNP is a complex disease and is cause by multiple factors. Thus, no single factor such as a single SNP is responsible for the whole pathogenesis. Second, large variations in the number of samples or allele frequencies among studies in our meta-analysis also contribute to the findings. This probably relates to differences in populations where study data were collected. Finally, the small number of samples significantly influenced the results of our meta-analysis. Therefore, studies with larger sample sizes and sub-analyses for different populations such as Asian, Caucasian, and other populations are warranted whenever more data are available."

Figures and Tables: Figures and Tables are adequately explained.
Response: Thank you.

Conclusion: The limitations are well stated, however, line 286-288 "Therefore, studies with larger sample sizes and sub-analyses for different populations such as Asian, Caucasian, and other populations are warranted whenever more data are available." Please put in one paragraph before the conclusion to make the conclusion from your review stronger.
Response: The conclusion has been revised as suggested.

Overall comments: This manuscript may be considered for indexing after Major revisions.
Response: Thank you.

Competing Interests: No competing interests were disclosed.

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