Int J Clin Exp Med 2016;9(11):21756-21763
www.ijcem.com /ISSN:1940-5901/IJCEM0035888

Original Article

Polymorphisms of IL-1β and IL-1α genes and susceptibility to low back pain: a systematic review and meta-analysis

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Received July 15, 2016; Accepted September 5, 2016; Epub November 15, 2016; Published November 30, 2016

Abstract: Low back pain (LBP) belongs to the common spinal disorders, and the associations of IL-1β (+3594 T/C) and IL-1α (+889 C/T) polymorphisms with LBP have been investigated. However, results from different institutions were not identical. This meta-analysis was performed to provide a systematical assessment on the association of IL-1α (+889 C/T) and IL-1β (+3594 T/C) polymorphisms with low back pain. PubMed, EMBASE, Chinese Biomedical Literature Database in February 2016 were retrieved for the potential case-control studies which mainly focused on the relationship between IL-1β (+3594 T/C) and IL-1α (+889 C/T) polymorphisms and the susceptibility to LBP. The pooled odds ratio (OR) coupled with 95% confidence interval (95% CI) was employed to assess the associations. Firstly there existed 37 articles retrieved, 6 of which comprised of 669 cases and 948 controls met the inclusion criteria. Subgroup meta-analyses were performed according to the ethnicity. Overall, there was no significant association between IL-1β (+3594 T/C) polymorphism with LBP under five models. Subgroup analysis showed that significant association was observed in Asian, while in Caucasian populations there was no positive association. As to IL-1α (+889 C/T) polymorphism, significant association was observed with LBP in alleles, homozygote and recessive models, respectively. IL-1α (+889 C/T) alleles T may increase the susceptibility to LBP in Caucasian populations. No significant association was found between IL-1β (+3594 T/C) polymorphism, while exposure to alleles T may decrease the LBP risk in Asian.

Keywords: Low back pain, Interleukin 1, polymorphism, meta-analysis, IL-1β (+3594 T/C), IL-1α (+889 C/T)

Introduction

Low back pain (LBP) with or without being coupled with sciatica belongs to major health problems globally [1]. According to a retrospective study conducted in Switzerland, in 2005 direct expenditure on LBP reached the unprecedented 2.6 billion euros, which approximately consumed 6.1% of the whole healthcare budget. Furthermore, incremental losses of productivity were estimated at 2.2 billion euros by the friction cost approach, while the figure soared to 4.1 billion euros by the human capital method [2]. Recently, more and more reports have suggested that the pathogenic factors comprised of histological, psychosocial, occupational and inherited components can lead to LBP [3]. Genes affecting intervertebral disc degeneration (IDD) or the immune response are always involved LBP [4]. Several studies have been conducted to explore the accurate etiology of LBP at the molecule level such as DNA variations. The classic twin study showed that heritability estimates for back pain varied from 30% to 45% and disc degeneration (DD) was one pathway through which genes exerted influence on low back pain [5]. Intervertebral disc degeneration (IDD) is one of the most common musculoskeletal diseases associated with LBP. Therefore, genetic components related to IDD have been the most well-established genetic biomarkers closely associated with LBP [6]. Correspondingly, the interleukins such as interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-20 (IL-20) have been reported to play an important role in IDD [7]. Therefore genetic polymorphisms within those interleukins genes can integrate the underlying linkage between

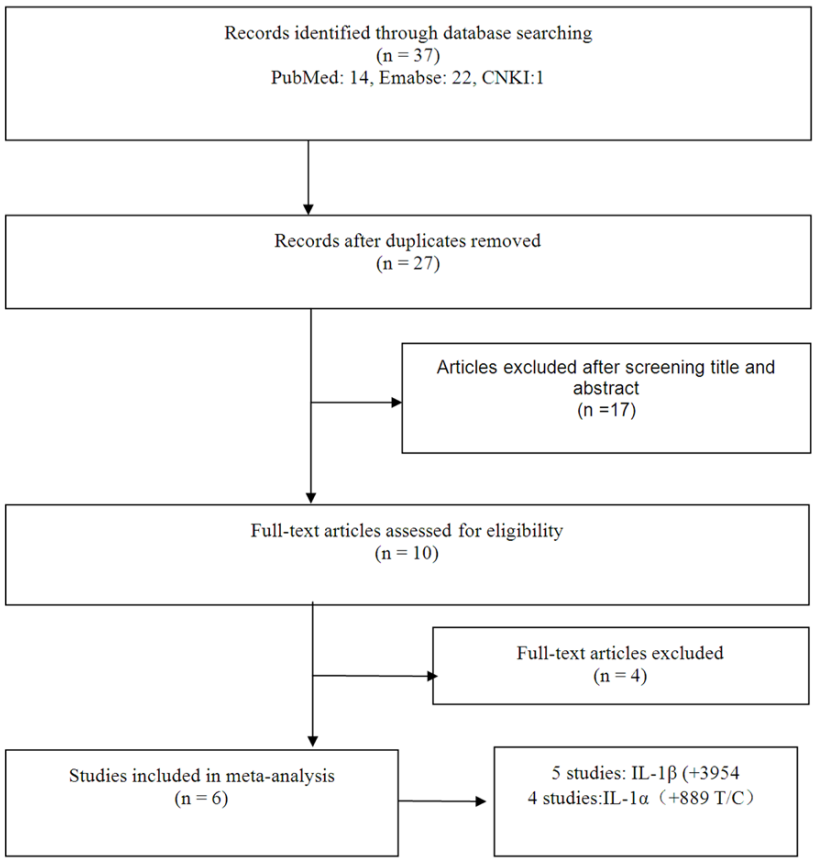

Figure 1. The study selection and inclusion process.

IDD and LBP, and a series of studies have shown that genetic factors such as IL-1 may play a vital role in the pathogenesis of LBP.

Inflammation response plays an important role in the pathogenesis of many diseases and IL-1 is such a multifunctional cytokine. With regard to IL-1, there exist 3 members in the IL-1 family: IL-1β, IL-1α, and interleukin-1 receptor antagonist (ILRN). IL-1β and IL-1α play an important role in the proinflammatory process, and both of them are critical molecules in the stimulation of enzymes that degrade proteoglycans [8]. To date, several common variants located within the IL-1β and IL-1α genes have been investigated. The most widely studied variants are the IL-1α (+889 C/T) [9, 10], IL-1β (+3593 T/C) [11], 86 base pair variable number tandem repeat (VNTR) polymorphism of IL-1 receptor antagonist [12, 13], IL-1α (511-C/T), IL-1α (949-C/T) [14], IL-1β (+3594 T/C) [15] polymorphisms. Besides, plasma levels and biological activities of IL-1α and IL-1β are highly genetically influenced. Subquently single nucleotide polymorphisms (SNPs) of IL-1α and IL-1β have been identified to be significantly associated with LBP susceptibility with or without being associated with IDD, and could account for the histopathological mechanism of this disease. Among above mentioned variants IL-1β (+3594 T/C) and IL-1α (+889 C/T) should be the most thoroughly researched. Solovieva, S et al. [10] conducted a case-control study to investigate whether the IL-1β (+3594 T/C) and IL-1α (+889 C/T) gene polymorphisms were associated with susceptibility to LBP. They found that The IL-1α (+889 C/T) allele T and the IL1-β (+354) allele T frequencies were higher in the individuals with LBP when compared with the counterparts. However, results from other recent researches remain inconsistent [15-17]. Given these contradictory reports, we performed this meta-analysis to provide a comprehensive and systematical assessment of the associations of IL-1α (+889 C/T) and the IL1-β (+3954 T/C) genes polymorphisms with LBP risk.

Materials and methods

Search strategy

PubMed, EMBASE and Chinese Biomedical Literature Database were retrieved in February 2016 for potential studies investigating the relationship between IL-1β (+3594 T/C) and IL-1α (+889 C/T) gene polymorphisms and the susceptibility to LBP with the following search terms: (“low back pain” OR “degeneration” OR “disc”) AND (“interleukin-1” OR “IL-1” OR “IL1” OR “IL-1β (+3594 T/C)” OR “IL-1α (+889 C/T)”) AND (‘polymorphism’ OR ‘single nucleotide polymorphism’ OR ‘SNP’ OR ‘variation’). There was no language restriction in the literature

Table 1. Descriptive characteristics of studies included in the meta-analysis

Author	Year	Country	Ethnicity	Method	Group	Size	IL-1β (+3954 T/C) Alleles		IL-1β (+3954 T/C) Genotypes			IL-1α (+889 C/T) Alleles		IL-1α (+889 C/T) Genotypes		
							T	C	TT	TC	CC	T	C	TT	TC	CC
Ye et al.	2007	China	Asian	PCR-RFLP	Case	81	4	158	0	4	77					
					Control	101	12	190	0	12	89					
Mu et al.	2013	China	Asian	ABI3730	Case	305	22	588	0	22	283					
					Control	587	63	1111	1	61	525					
Paz Aparicio, et al.	2011	Finland	Caucasian	PCR-RFLP	Case	50						31	69	3	25	22
					Control	129						71	187	5	61	63
Karppinen, et al.	2009	Finland	Caucasian	SNP-TRAP	Case	45	30	60	5	20	20	40	50	7	26	12
					Control	63	36	88	6	24	32	38	88	5	28	30
Solovieva, et al.	2004	Finland	Caucasian	SNP-TRAP	Case	97						80	144	13	54	30
					Control	34						20	48	1	18	15
Solovieva, et al.	2004	Finland	Caucasian	SNP-TRAP	Case	87						65	109	11	43	33
					Control	34						25	43	3	19	12
Solovieva, et al.	2004	Finland	Caucasian	SNP-TRAP	Case	94	65	123	12	41	41					
					Control	34	15	55	1	13	21					
Solovieva, S et al.	2004	Finland	Caucasian	SNP-TRAP	Case	94	56	132	8	40	46					
					Control	34	24	44	5	14	15					

Table 2. Results of genetic models for IL-1β (+3954 T/C) and IL-1α (+889 C/T) polymorphisms and low back pain

Comparison	Test of association			Model	Test of heterogeneity	
	OR	95% CI	*P* value		*P*	I^2 (%)
IL-1β (+3954 T/C)						
Overall						
T vs. C	0.926	0.586-1.463	0.742	R	0.039	60.2
TT vs. CC	1.290	0.607-2.738	0.508	F	0.231	30.2
TC vs. CC	0.863	0.624-1.195	0.375	F	0.186	35.2
TT/TC vs. CC	0.920	0.564-1.500	0.737	R	0.086	50.9
TT vs. TC/CC	1.173	0.565-2.436	0.668	F	0.306	17.1
Caucasian						
T vs. C	1.209	0.728-2.009	0.463	R	0.121	52.6
TT vs. CC	1.353	0.619-2.957	0.449	R	0.124	52.1
TC vs. CC	1.271	0.791-2.042	0.322	F	0.648	0.0
TT/TC vs. CC	1.287	0.795-2.083	0.305	F	0.321	12.0
TT vs. TC/CC	1.217	0.572-2.592	0.610	F	0.169	43.7
Asian						
T vs. C	0.610	0.387-0.962	0.034	F	0.436	0
TT vs. CC	0.618	0.025-15.217	0.768	F	-	-
TC vs. CC	0.610	0.383-0.972	0.038	F	0.397	0
TC/TT vs. CC	0.605	0.380-0.964	0.034	F	0.411	0
TT vs. TC/CC	0.640	0.026-15.756	0.785	F	-	-
IL-1α (+889 C/T)						
Overall (Caucasian)						
T vs. C	1.383	1.048-1.825	0.022	F	0.417	0.0
TT vs. CC	2.559	1.208-5.417	0.014	F	0.571	0.0
TC vs. CC	1.333	0.902-1.968	0.149	F	0.383	1.9
TT/TC vs. CC	1.160	0.996-1.350	0.056	F	0.330	12.5
TT vs. TC/CC	1.993	1.027-3.866	0.041	F	0.784	0.0

F: fixed effect model *R*: random effect model.

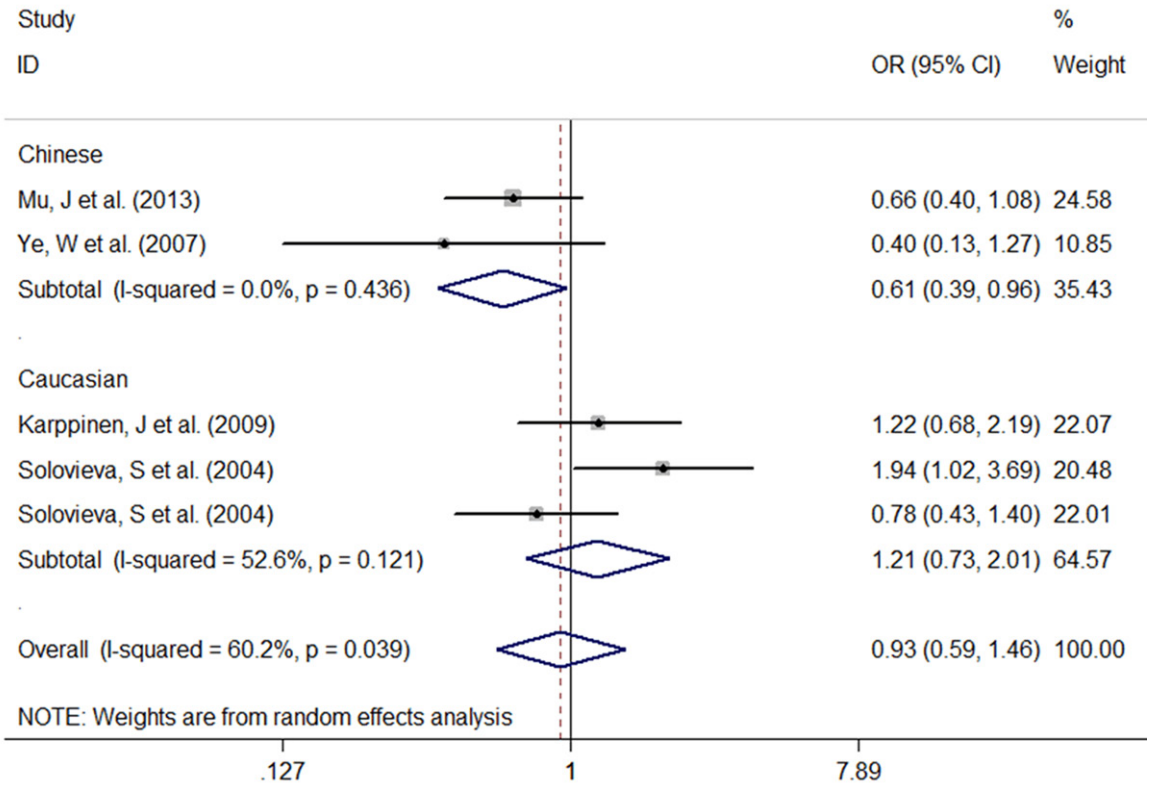

Figure 2. Forest plot describing the meta-analysis under alleles contrast model for the association between 1β (+3594 T/C) polymorphism and the risk of low back pain (T vs. C).

search. Secondary searches of unpublished literature were performed and the reference lists of the selected articles and reviews were also checked for the purpose of more potential studies.

Inclusion and exclusion criteria

The inclusion criteria of this meta-analysis were as follows: (1) case-control study; (2) estimating the risk of LBP and IL-1β (+3594 T/C)) polymorphism or IL-1α (+889 C/T) polymorphism; (3) sufficient data, including exact number or frequency of alleles and genotypes; (4) the Hardy-Weinberg equilibrium (HWE) was guaranteed in the control group. Exclusion criteria: (1) reviews or meta-analysis or not case-control design; (2) no available data; (3) genotype frequency distributions in the control group were not satisfied with the HWE; (4) duplicated reports based on the same population.

Data extraction

Data from the eligible studies were extracted according to the inclusion criteria and exclusion criteria by two reviewers (Jian, Zhao and Yunfei Zhao) independently. Any disagreement was removed through discussion between the two reviewers and then a consensus was achieved. For each study included in this meta-analysis the following characteristics were extracted: name of the first author, year of publication, country of origin, ethnicity, genotyping methods, group, sample size, alleles and genotypes of IL-1β (+3594 T/C) polymorphism or IL-1α (+889 C/T). If more than one paper published based on the same population, the paper with a larger sample size was included. Furthermore, we also evaluated whether the genotype distributions followed the Hardy-Weinberg equilibrium (HWE).

Data synthesis and statistical analysis

Pooled odds ratios (OR) coupled with 95% confidence intervals (CIs) were calculated to evaluate the association between IL-1β (+3594 T/C) or IL-1α (+889 C/T) polymorphisms and LBP according to allele contrast (T versus C), heterozygote (TC versus CC), homozygote (TT versus CC), dominant (TC/TT versus CC), and recessive (TT versus TC/CC) models for IL-1β (+3594 T/C) polymorphism, and the strength of associ-

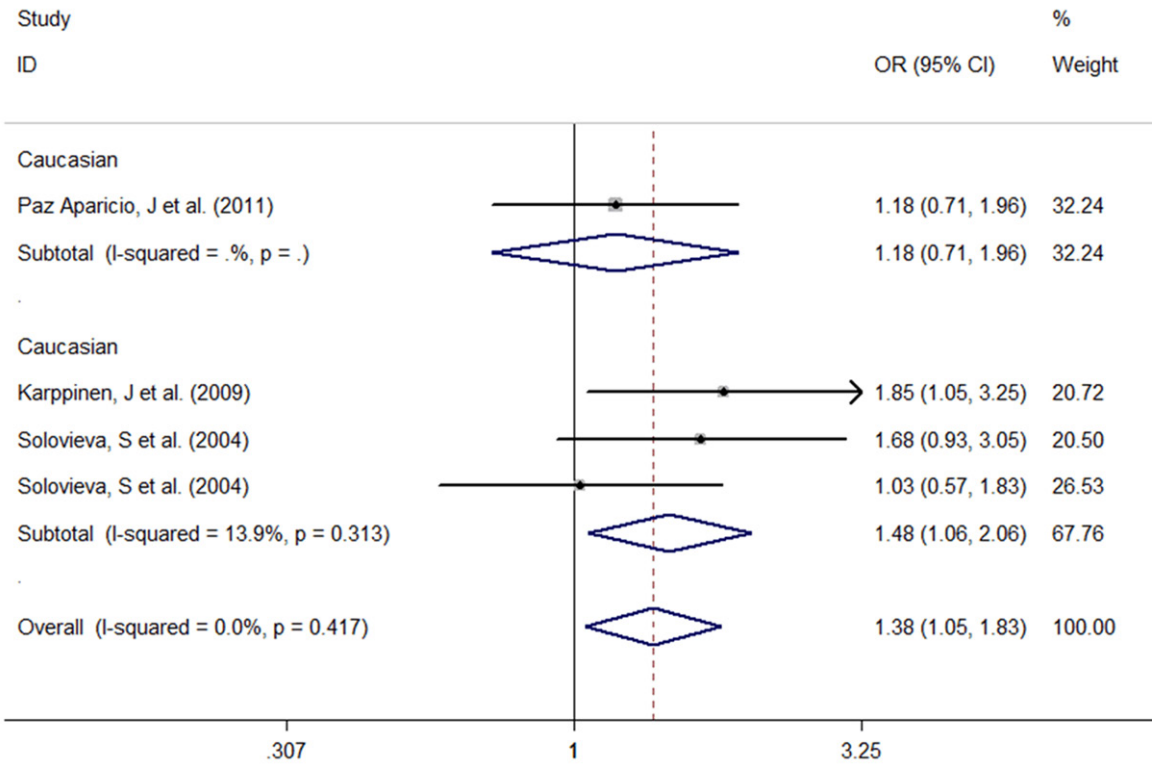

Figure 3. Forest plot describing the meta-analysis under alleles contrast model for the association between IL-1α (+889 C/T) polymorphism and the risk of low back pain (C vs. T).

ation between the IL-1α (+889 C/T) polymorphism and LBP susceptibility was evaluated by OR combined with 95% CI calculated by allele contrast (T versus C), homozygote (TT versus CC), heterozygote (TC versus CC), dominant (TC/TT versus CC), and recessive (TT versus TC/CC) models. All meta-analyses were performed using Stata 12.0 and the two tailed *P* value below 0.05 was statistically significant. Heterogeneity assessment was conducted by Chi-square-based Q statistic test and quantified by I^2 metric value. If I^2 value is >50% or P<0.10, ORs were pooled by random effect model for that an obvious heterogeneity existed. On the contrary, the fixed effect model was employed. Sensitivity analysis was performed in order to assess the impact of each study on the combined effect of the present meta-analysis and subgroup analysis was performed according to different ethnicity.

Results

Study characteristics

A total of 37 articles were initially retrieved, among which 6 studies consisted of 669 cases and 948 controls eventually were satisfied with the eligibility criteria (**Figure 1**). In these studies, only two experiments [16, 17] were conducted in Asian, while the rest were conducted in Caucasian [10, 11, 15, 18]. There were three studies [10, 15, 18] reporting both IL-1β (+3594 T/C) and IL-1α (+889 C/T) polymorphisms' alleles and genotypes, two study reported genotypes of IL-1β (+3594 T/C) polymorphism, and only one study reported IL-1α (+889 C/T) polymorphism's genotype. The generally descriptive characteristic of studies included in this meta-analysis was showed in **Table 1**. The HWE was guaranteed in each group.

Meta-analysis results

Data extracted from 6 case-control studies were pooled together for estimation of the potential association. This pooled results suggested that there was no significant association between IL-1β (+3594 T/C) polymorphism and LBP risk in five given models (T versus C: OR=0.926, 95% CI=0.586-1.463, P=0.742; TT verse CC: OR=1.290, 95% CI=0.607-2.738, P=0.508; TC verse CC: OR=0.863, 95%

CI=0.624-1.195, P=0.375; TC/TT versus CC: OR=0.920, 95% CI=0.564-1.500, P=0.737; TT versus TC/CC: OR=1.173, 95% CI=0.565-2.436, P=0.668), as indicated in **Table 2**. Besides, subgroup analysis showed that IL-1β (+3594 T/C) polymorphism was also significantly associated with risk of LBP in Asians in alleles contrast, heterozygote and dominant model, respectively (T versus C: OR=0.610, 95% CI =0.387-0.962, P=0.034; TC verse CC: OR= 0.610, 95% CI=0.387-0.962, P=0.038; TC/TT versus CC: OR=0.605, 95% CI=0.380-0.964, P=0.034), while no statistical significance was detected in Caucasians, as indicated in **Table 2** and **Figure 2**.

With regard to IL-1α (+889 C/T) polymorphism, significant association was observed in alleles contrast, homozygote, recessive models (T versus C: OR=1.383, 95% CI=1.048-1.825, P= 0.022; TT verse CC: OR=2.559, 95% CI=1.208-5.417, P=0.014; TT versus TC/CC: OR=1.993, 95% CI=1.027-3.866, P=0.041; as shown in **Table 2**, and **Figure 3**.

Sensitive analysis and publication bias

Through rejecting each article one by one we performed the sensitivity analysis to assess the sensitivity of our meta-analysis. No matter which single study was removed, the pooled OR did not fluctuate fiercely, which meant that the results were of significant stability. Therefore, in this meta-analysis stability and credibility should be guaranteed. However, publication bias was not assessed for the reason that it might not be suitable to perform it when the number of including studies was less than 10.

Discussion

Low back pain (LBP) is one of the most common healthy disorders, and the etiology and pathogenesis of this syndrome belongs to the common mechanisms shared by environment and heritability [19]. As one of the core cytokines in response to stress, IL-1 functions as an important trigger molecule on systemic metabolic reaction and is strongly associated with maintenance of homeostasis [20]. On the one hand, IL-1 stimulates tissue degrading enzymes to breakdown the extracellular matrix such as proteoglycan in the components of a disc and suppresses the synthesis process [21]. On the other hand, IL-1 can provokes pain reaction in IDD through un-regulating transcript of prostaglandin E2. Subsequently, cyclooxygenase-2 activities are bound to be elevated.

The polymorphisms of the IL-1 gene cluster ranged from IL-1α (+889 C/T), single-nucleotide polymorphisms of exon5 IL-1β (+3594 T/C) to 86 base pairs variable number tandem repeat (VNTR) of intron 2 of IL1RN. The polymorphisms have been reported as a molecule factor that involves in a group of diseases such as inflammatory intestinal diseases [22], schizophrenia [23], periodontitis [24], immunologic diseases [25], small cell lung cancer [26], and sickle cell anemia [27]. There were a cluster of studies that have focused on the association between the IL-1β (+3594 T/C) and IL-1α (+889 C/T) polymorphisms and LBP susceptibility, while the results reported were inconsistent or conflicting [9-11, 15-18]. To the best of our knowledge, no meta-analysis has previously been performed to summarize the associations between IL-1β (+3594 T/C) and IL-1α (+889 C/T) polymorphisms and LBP risk. Therefore, we performed this meta-analysis to provide a comprehensive and systemic assessment on the associations of IL-1β (+3594 T/C) and IL-1α (+889 C/T) polymorphisms with risk of LBP.

In this meta-analysis, there was no significant association between IL-1β (+3594 T/C) polymorphism between patients and healthy controls in any model, which was consistent with several individual studies included in the present meta-analysis [15-18] except one study [10]. Subgroup analysis also suggested the same results in Caucasian. However, the pooled results showed that the prevalence allele T was significantly higher in the control group and significant associations were observed in alleles contrast, heterozygote and dominant model, respectively (T versus C: OR=0.610, 95% CI= 0.387-0.962, P=0.034; TC verse CC: OR=0.610, 95% CI=0.387-0.962, P=0.038; TC/TT versus CC: OR=0.605, 95% CI=0.380-0.964, P= 0.034). With regard to IL-1α (+889 C/T), only four studies conducted in Caucasian were included in our meta-analysis and the pooled results suggested that there existed significant associations between IL-1α (+889 C/T) polymorphism and LBP in alleles contrast, homozygote, recessive models (T versus C: OR=1.383, 95% CI=1.048-1.825, P=0.022; TT verse CC: OR=2.559, 95% CI=1.208-5.417, P=0.014; TT versus TC/CC: OR=1.993, 95% CI=1.027-3.866, P=0.041, respectively), which was in

accord with the reports of Karppinen, J et al. [15] and Solovieva, S et al. [10]. Correspondingly, Schistad et al. [28] had reported that CT/TT genotype IL-1α (+889 C/T) might be associated with elevated pain intensity within the first year of disc herniation. On the other hand, patients suffering from LBP may have different pain thresholds among different populations. Pain such as LBP can be strongly influenced by culture, socioeconomic status, occupation and other covariates [29]. Therefore, the underlying reason of those controversial findings could be the heterogeneous genetic backgrounds and environment they exposed to.

Even through comprehensive and systematical met-analysis was performed to investigate the association between IL-1β (+3594 T/C) and IL-1α (+889 C/T) gene polymorphisms and LBP risk, there still existed many limitations that should be taken into serious consideration. First of all, the number of studies with 864 cases and 1017 controls eventually satisfied the eligibility criteria was only six, which could not guarantee statistical power to reveal the possible effects of IL-1β (+3594 T/C) polymorphism and IL-1α (+889 C/T) genes polymorphisms on LBP. Secondly, the sample sizes of some of studies in our meta-analysis were relatively small, which might contribute to controversial results in each study and have a negative influence on total consequences. Thirdly, only studies conducted in Asian and Caucasian were included in this meta-analysis, which, more or less, misrepresent the associations in other peoples. Therefore, larger-scale and well-designed studies are necessary to estimate the association between IL-1β (+3594 T/C) and IL-1α (+889 C/T) genes polymorphisms and LBP risk.

In conclusion, this meta-analysis had pooled the totality of evidence related to IL-1β (+3594 T/C) and IL-1α (+889 C/T) genes polymorphisms and LBP, and indicated that IL-1α (+889 C/T) gene polymorphismallele T may be involved in the susceptibility to LBP in Caucasian populations, while no significant association was detected between IL-1β (+3594 T/C) polymorphism and LBP susceptibility with the exception that exposure to the alleles T may decrease the risk of LBP in Asian. Considering the limitations above mentioned, the future studies are needed to further assess the associations of IL-1β (+3594 T/C) and IL-1α (+889 C/T) with risk of LBP.

Acknowledgements

The present study was supported by the Science & Technology Commission of Shanghai Municipality, China (Grant No. 15ZR1412700).

Disclosure of conflict of interest

None.

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