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Meta-Analysis of the Association Between FAS Ligand and TRAIL Genetic Polymorphisms and Intervertebral Disc Degeneration Susceptibility in Chinese Han population

Xin Huang, MD,* Weiyue Zhang, MD,[†] and Zengwu Shao, PhD*

Study Design. Meta-analysis to collect all the relevant studies to further investigate whether or not the FAS ligand (FASL) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) genetic polymorphisms are associated with susceptibility to intervertebral disc degeneration (IDD) in Chinese Han population.

Objective. To investigate whether or not the FASL and TRAIL genetic polymorphisms are associated with susceptibility to IDD in Chinese Han population.

Summary of Background Data. FASL and TRAIL are both apoptotic gene. Several studies have assessed the associations of FASL and TRAIL gene with risk of IDD in Chinese Han population, but the results are inconsistent.

Methods. We systematically searched the PubMed, EMBASE, Medline, Scopus, Web of Science, CBM, and the Cochrane Library databases. Eligible studies assessing the polymorphisms in the FASL and TRAIL gene and risk of IDD were incorporated. The pooled odds ratio (OR) with its 95% confidence intervals (95% CI) was used.

Results. Six studies with a total of 1766 IDD cases and 1533 controls were finally included in the meta-analysis. Meta-analysis of FASL-844C/T (rs763110) polymorphism was statistically associated with decreased IDD risk under all genetic models (allele model: OR = 0.68, 95% CI 0.59–0.80, $P = 0.000$; homozygote model: OR = 0.35, 95% CI 0.25–0.53, $P = 0.000$; dominant model: OR = 0.38, 95% CI 0.25–0.58, $P = 0.000$; recessive model: OR = 0.69, 95% CI 0.58–0.84, $P = 0.000$). There was a significant association between TRAIL-1595C/T (rs1131580) polymorphism with increased IDD risk under each genetic model (allele model: OR = 1.77, 95% CI 1.47–2.13, $P = 0.000$; homozygote model: OR = 2.44, 95% CI 1.70–3.51, $P = 0.000$; dominant model: OR = 1.67, 95% CI 1.22–2.29, $P = 0.002$; recessive model: OR = 3.13, 95% CI 2.40–4.08, $P = 0.000$). In addition, the association between TRAIL-1525G/A (rs1131568) polymorphism and the susceptibility of IDD was statistically significant under all genetic models.

Conclusion. The present meta-analysis demonstrated that FASL and TRAIL polymorphisms were significantly associated with susceptibility to IDD in Chinese Han population.

Key words: FAS ligand, gene polymorphism, intervertebral disc degeneration, meta-analysis, TRAIL.

Level of Evidence: 1

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Low back pain (LBP) is a prevalent health problem which affects about 80% of people worldwide.¹ Intervertebral disc degeneration (IDD) or lumbar disc degeneration (LDD) is a major pathological process that contributes to LBP.² Lumbar disc herniation (LDH) is induced mainly by LDD because of degeneration and herniation of the nucleus pulposus of intervertebral disc of the lumbar spine.³ And LDH is also one of the common causes of LBP and sciatica. In addition to environmental and behavioral factors, genetic factor has been implicated to be associated with the risk for the development of disc degeneration.⁴ It has been demonstrated that intervertebral

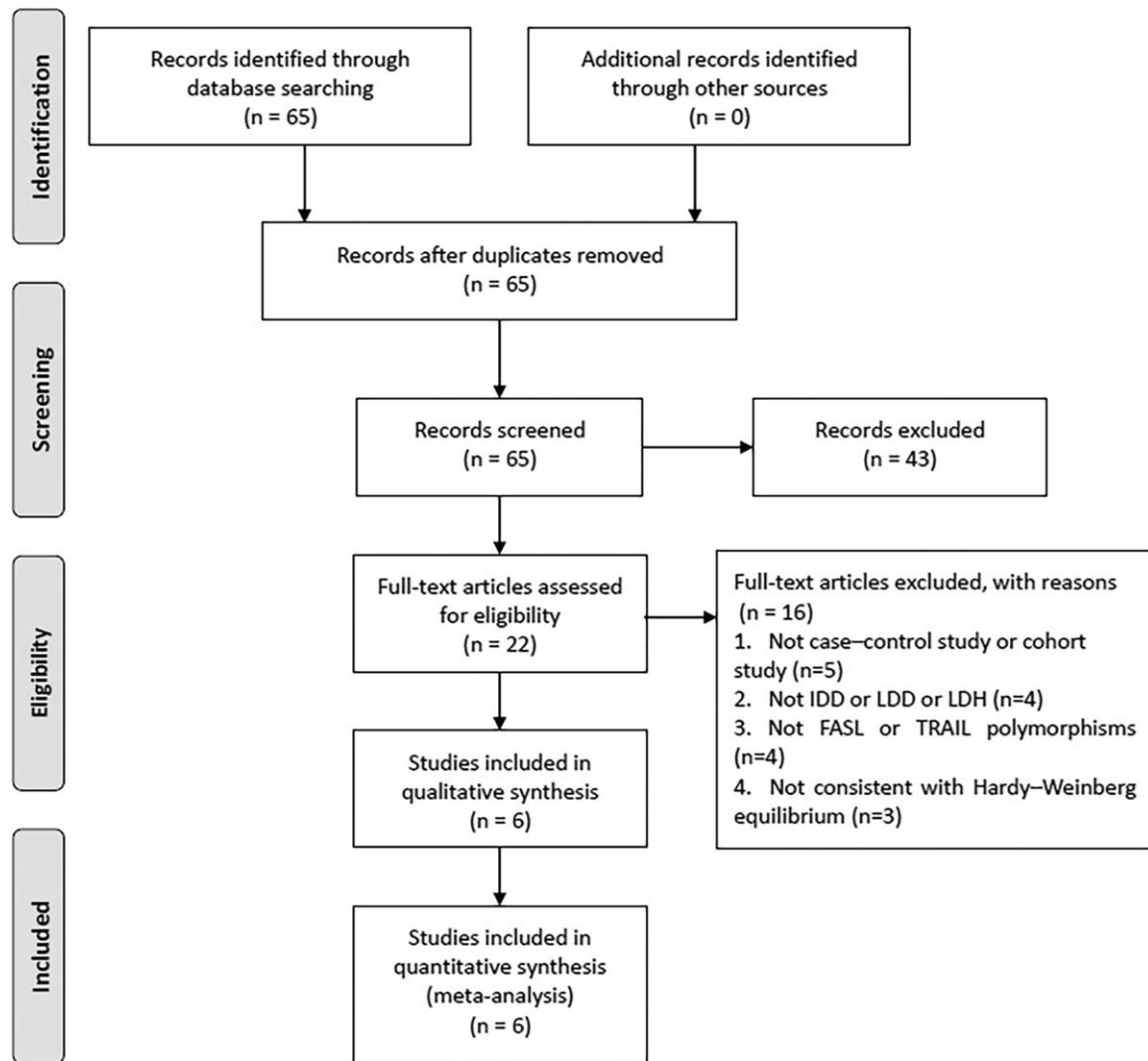


Figure 1. Flowchart of the study selection process.

cell loss resulting from apoptosis plays a vital role in promoting the progression of IDD.⁵

Recent studies revealed the association between different apoptosis-related genes polymorphisms with the risk of IDD, including caspase 9 gene,⁶ FAS and FAS ligand (FASL)⁷ and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) gene.⁸ The apoptotic pathways involved in IDD include the FAS/FASL-mediated death receptor pathway (exogenous pathway) and the mitochondrial pathway (endogenous pathway).^{9,10} FASL always appears in a trimer form, in which three FAS receptors bind to one FASL. And TRAIL induces apoptosis in transformed and cancer cells through its receptors TRAIL-R1/DR4 and TRAIL-R2/DR5.¹¹ It is suggested that the expression of TRAIL gene may play a role in IDD mechanism.¹²

There are several studies published to assess the link between FASL and TRAIL genetic polymorphisms with risk of IDD, but they failed to confirm a strong and consistent association. Thus, we conducted a meta-analysis of epidemiological studies to shed some light on the associations between FASL and TRAIL genetic polymorphisms and the susceptibility of IDD.

MATERIALS AND METHODS

Search Strategy

A computerized literature search was performed in the PubMed, EMBASE, Medline, Scopus, Web of Science, CBM, and the Cochrane Library databases up to February 20, 2018. The search strategy included the terms (“IDD” or “LDD” or “LDH” or “Intervertebral Disc Degeneration”) and (“apoptotic gene” or “FASL” or “TRAIL”) and (“polymorphisms” or “variants” or “variation” or “SNP”). All studies matching the eligibility criteria were retrieved, and bibliographies were checked for other relevant publications. No language or other restrictions were placed on the search. Furthermore, the reference lists of all the full-text articles were examined to identify any initially omitted studies.

Inclusion and Exclusion Criteria

To be eligible for inclusion in the meta-analysis, a study must meet the following criteria: (1) case-control study or cohort study, (2) the outcome was evaluation of the correlation between FASL or TRAIL polymorphisms and IDD risk, (3)

TABLE 1. Main Characteristics of the Studies Included in This Meta-Analysis

Study ID	Year	Country	Disease	Sex	Age (y)	Case Group			Control Group			P for HWE	Quality
						CC	CT	TT	CC	CT	TT		
FASL (844C/T) rs763110						CC	CT	TT	CC	CT	TT		
Sun ZM ⁷	2012	China	LDH	Both	49.7	236	188	48	308	200	20	0.072	Y
Zhang YG ¹⁵	2012	China	LDH	Both	46.2	64	51	13	77	50	5	0.368	Y
Zhu GB ¹⁶	2011	China	LDD	Both	50.2	175	148	25	131	76	8	0.455	Y
TRAIL (1595C/T) rs1131580						CC	CT	TT	CC	CT	TT		
Zhang CL ⁸	2015	China	LDD	Both	49.5	192	79	41	70	88	38	0.278	Y
Xu SM ¹⁷	2015	China	IDD	Both	59.0	37	46	17	29	42	29	0.110	Y
Du H ¹⁸	2015	China	LDD	Both	40.2	46	71	36	22	66	43	0.695	Y
TRAIL (1525G/A) rs1131568						GG	GA	AA	GG	GA	AA		
Xu SM ¹⁷	2015	China	IDD	Both	59.0	38	45	17	29	42	29	0.110	Y
Du H ¹⁸	2015	China	LDD	Both	40.2	46	71	36	22	66	43	0.695	Y

HWE indicates Hardy–Weinberg equilibrium; IDD, intervertebral disc degeneration; LDD, lumbar disc degeneration; LDH, lumbar disc herniation; Y, yes.

having an available genotype or allele frequency for estimating an odds ratio (OR) with 95% confidence interval (95% CI) or hazard ratio (HR) with 95% CI, (4) genotype frequencies in controls were consistent with those expected from Hardy–Weinberg equilibrium ($P > 0.05$). However, case reports, reviews, or studies containing overlapping data were all excluded. We also excluded those studies that contain frequency of genotype not in Hardy–Weinberg equilibrium in controls.¹³

Data Extraction and Quality Assessment

Two investigators (X.H. and W.Z.) evaluated the eligibility of all retrieved studies and extracted the relevant data independently. Extracted databases were then cross-checked between the two authors to rule out any discrepancy. Disagreement was resolved by consulting with a third investigator (Z.S.). The following data of each eligible study were extracted independently: name of first author, year of publication, countries, ethnicity, genotype or allele frequencies of FASL or TRAIL polymorphisms, and OR with its 95% CI. The study quality was assessed in accordance with the Newcastle–Ottawa Scale (NOS). Nine items were extracted, and each item scored 1. The total scores ranged from 0 to 8. If the scores were ≥ 7 , then the study was considered high quality.

Statistical Analysis

The statistical analysis was performed using STATA 14. Estimates were summarized as odds ratios (ORs) with 95% confidence intervals (CIs) for each study. The between-study heterogeneity was evaluated by using the chi-square test and the I^2 statistic. An I^2 value of $>50\%$ of the I^2 statistic was considered to indicate significant heterogeneity.¹⁴ When a significant heterogeneity existed across the included studies, a random effects model was used for the analysis. Otherwise, the fixed effects model was used. Subgroup analyses were performed to detect the source of heterogeneity. We further conducted sensitivity analyses to substantiate the stability of results and detect the potential source of heterogeneity. Publication bias was evaluated qualitatively by inspecting funnel plots and quantitatively through the Begg and Egger test. A two-tailed P value < 0.05 implies a statistically significant publication bias.

RESULTS

Search Results

The study selection process is illustrated in Figure 1. A total of 65 potential articles were identified from the databases search. Among these articles, 43 were excluded after abstract review, leaving 22 articles for the full-text review. In the review, 16 studies were excluded for the reasons as follows: five were eliminated because they were neither case-control study or cohort study, four were irrelevant to IDD or LDD or LDH, four studies were not studies on the role of FASL or TRAIL polymorphisms on IDD risk, three were not consistent with Hardy–Weinberg equilibrium. Finally, six studies with a total of 1766 IDD cases and 1533 controls that met the inclusion criteria were included in this meta-analysis.

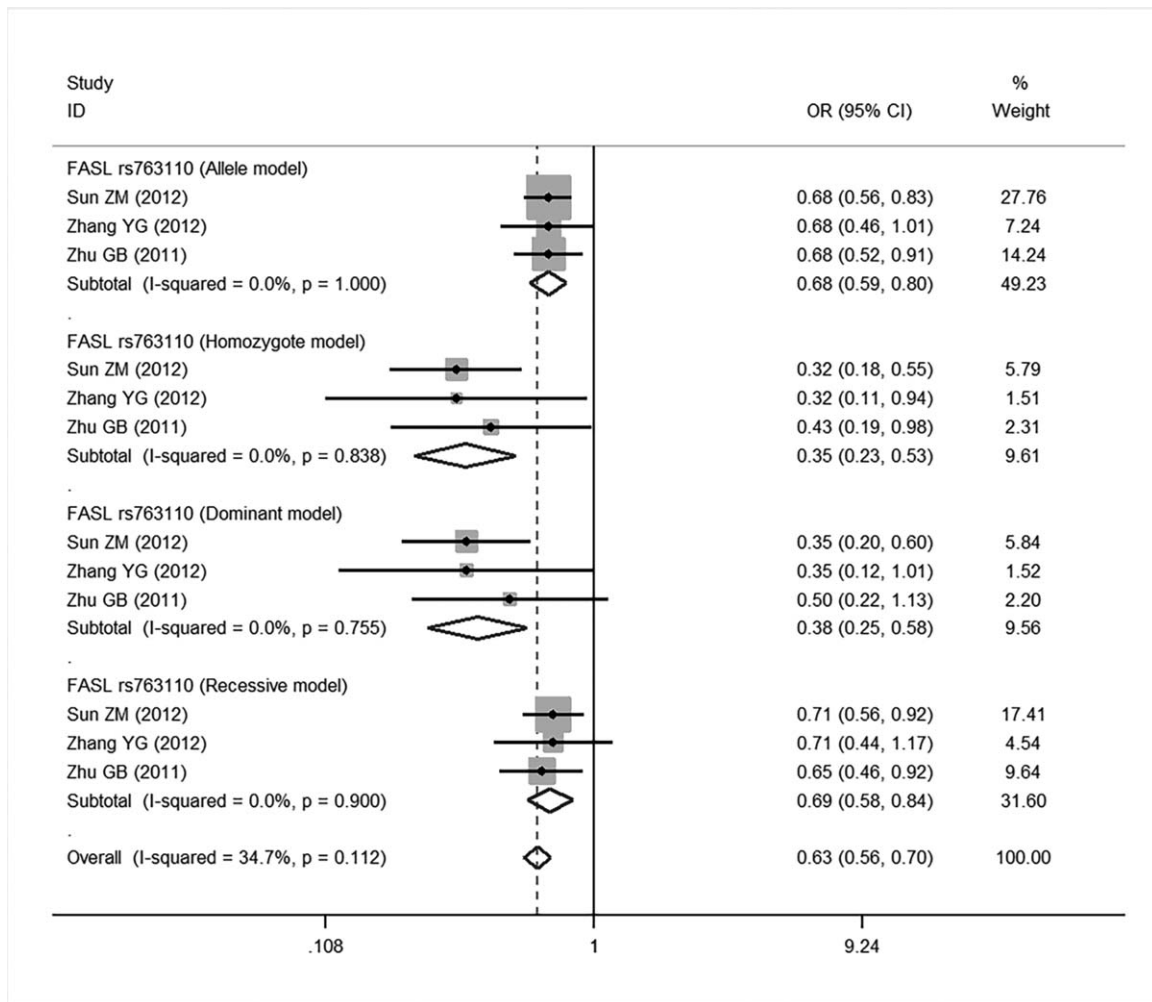


Figure 2. Meta-analysis for FASL rs763110 polymorphism under four genetic models in IDD.

Study Selection and Characteristics

Baseline characteristics of the included studies are presented in Table 1.^{7,8,15–18} Among these eligible studies, three studies investigated role of FASL-844C/T (rs763110) in IDD risk among Chinese Han population. In addition, three studies examined effects of TRAIL-1595C/T (rs1131580) on the risk of IDD and two for TRAIL-1525G/A (rs1131568) polymorphism. All the studies had been conducted in China, and all the enrolled subjects were Han Chinese. The publication years of the eligible studies ranged from 2011 to 2015. In all these studies, genotype frequencies in controls were consistent with those expected from Hardy-Weinberg equilibrium ($P > 0.05$). According to the Newcastle-Ottawa Scale (NOS), the quality scores of the included trials ranged from 7 to 8, which indicated a high quality (Supplementary Table 1, <http://links.lww.com/BRS/B351>).

Quantitative Data Synthesis

Meta-Analysis of the Association Between FASL rs763110 Polymorphism and IDD

The meta-analysis on rs763110 included a total of 948 IDD patients and 875 controls. Overall, the results indicated that

this polymorphism was statistically associated with decreased IDD risk under all genetic models studied (allele model: OR = 0.68, 95% CI 0.59–0.80, $P = 0.000$; homozygote model: OR = 0.35, 95% CI 0.25–0.53, $P = 0.000$; dominant model: OR = 0.38, 95% CI 0.25–0.58, $P = 0.000$; recessive model: OR = 0.69, 95% CI 0.58–0.84, $P = 0.000$) (Figure 2). No heterogeneity of studies on this polymorphism was observed under any genetic model ($P > 0.05$, $I^2 = 0.0\%$) and the fixed effects model was used.

Meta-Analysis of the Association Between TRAIL rs1131580 Polymorphism and IDD

A total of 565 IDD patients and 427 controls were included in our meta-analysis on TRAIL rs1131580 polymorphism. There was a significant association between TRAIL rs1131580 polymorphism with increased IDD risk under each genetic model (allele model: OR = 1.77, 95% CI 1.47–2.13, $P = 0.000$; homozygote model: OR = 2.44, 95% CI 1.70–3.51, $P = 0.000$; dominant model: OR = 1.67, 95% CI 1.22–2.29, $P = 0.002$; recessive model: OR = 3.13, 95% CI 2.40–4.08, $P = 0.000$) (Figure 3). The heterogeneity of studies on this polymorphism was $< 25\%$, under allele, homozygote, and dominant models.

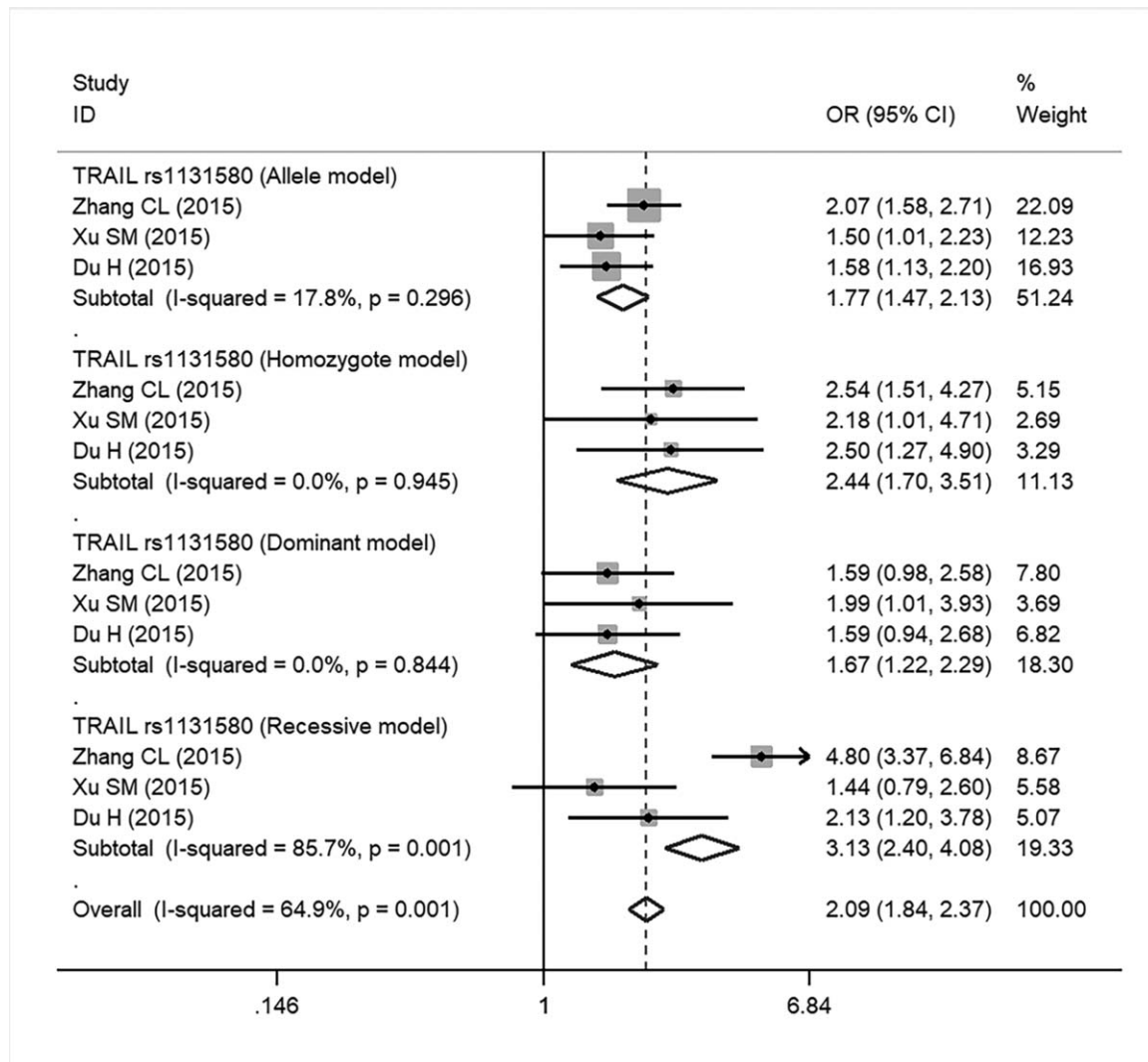


Figure 3. Meta-analysis for TRAIL rs1131580 polymorphism under four genetic models in IDD.

Meta-Analysis of the Association Between TRAIL rs1131568 Polymorphism and IDD

The results displayed that TRAIL rs1131568 polymorphism was associated with the susceptibility to IDD with a total of 253 cases and 231 controls. Moreover, the association was statistically significant under all genetic models (allele model: OR = 1.55, 95% CI 1.20–2.00, $P = 0.001$; homozygote model: OR = 2.38, 95% CI 1.43–3.95, $P = 0.001$; dominant model: OR = 1.73, 95% CI 1.15–2.62, $P = 0.010$; recessive model: OR = 1.80, 95% CI 1.20–2.72, $P = 0.005$) (Figure 4). No heterogeneity of studies on this polymorphism was observed under any genetic model ($P > 0.05$, $I^2 = 0.0\%$) and the fixed effects model was used.

Publication Bias and Sensitivity Analysis

The funnel plot did not indicate any evidence of publication bias in this analysis (Supplementary Figure 2, <http://links.lww.com/BRS/B351>). No evidence of publication bias was observed from Begg funnel plot ($P = 1.000$ for

FASL, $P = 0.296$ for TRAIL respectively) (Supplementary Figure 3, <http://links.lww.com/BRS/B351>) and Egger test ($P = 0.915$, $P = 0.507$ respectively) (Supplementary Figure 4, <http://links.lww.com/BRS/B351>). To sum up, the possibility of publication bias could be excluded. The sensitivity analysis showed that the results of the meta-analysis did not change when studies were omitted one by one (Supplementary Figure 5, <http://links.lww.com/BRS/B351>).

DISCUSSION

LBP is one of the most common spinal disorders.¹⁹ Recent researches have indicated that a number of genetic risk factors may be responsible for the leading causes of LBP and IDD.^{20,21} Previous studies have reported FASL or TRAIL polymorphisms to be associated with IDD, but with inconsistent results. Therefore, our meta-analysis was performed to examine the association between FASL and TRAIL genetic polymorphisms and susceptibility to IDD in Chinese Han population. Six studies with a total of 1766

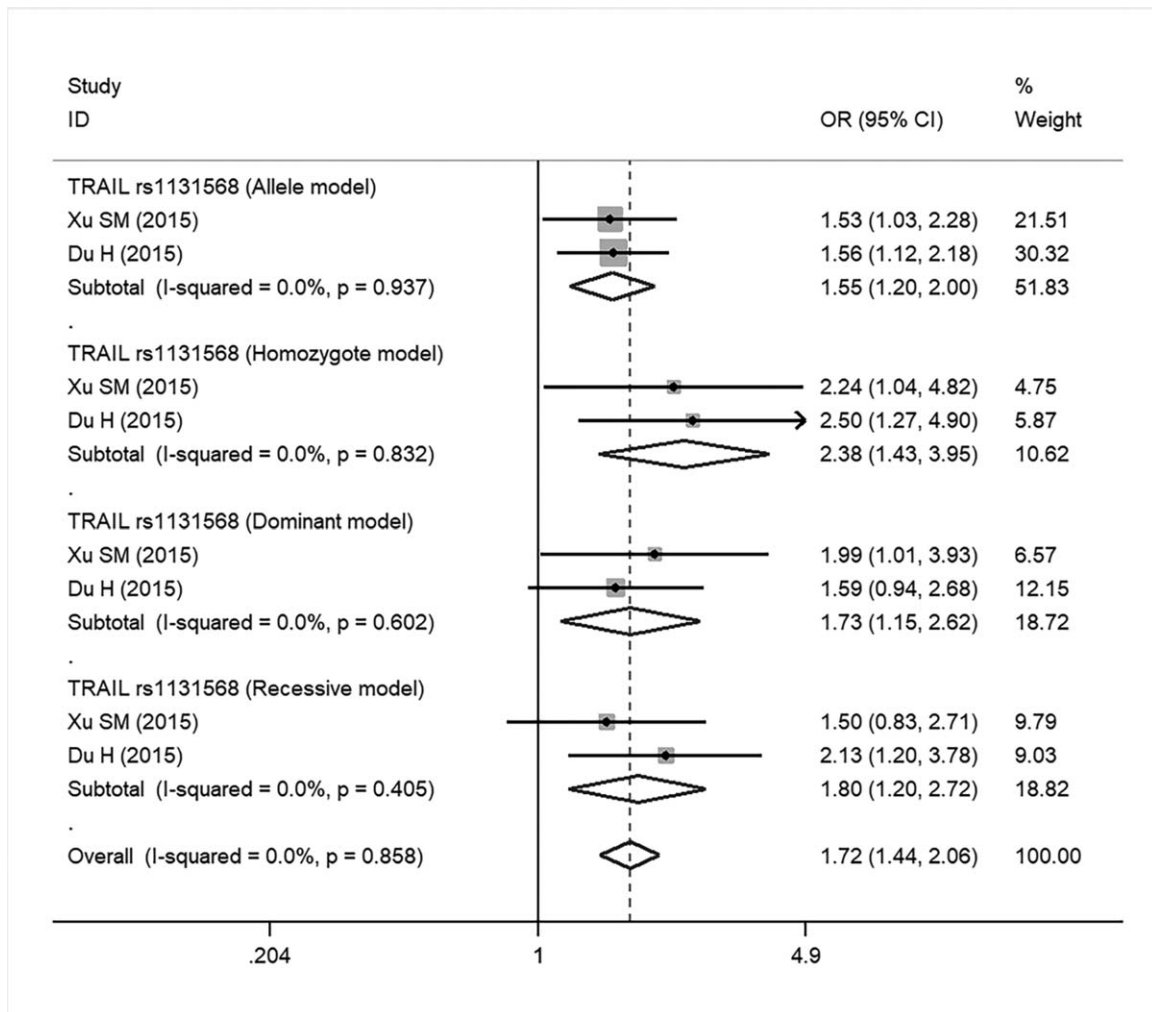


Figure 4. Meta-analysis for TRAIL rs1131568 polymorphism under four genetic models in IDD.

IDD cases and 1533 controls were finally included in the meta-analysis. Eligible studies included three studies on FASL rs763110, three studies on TRAIL rs1131580, and two studies on TRAIL rs1131568.

The pooled ORs and 95% CIs showed that FASL rs763110 polymorphism was significantly associated with decreased IDD risk under all genetic models studied. In contrast, TRAIL rs1131580 and TRAIL rs1131568 polymorphisms with increased IDD risk under each genetic model were observed in our study. The FAS and FASL system plays a key role in the apoptotic signaling pathway. Recently, FAS and FASL were suggested to be involved in the pathophysiological mechanism of LDD. A higher degree of FASL expression in disc cells was found in noncontained discs than in contained discs.²² TRAIL is a potent apoptosis inducer in cancer cells. It has been found that TRAIL also exists in the vertebral endplates, nucleus pulposus, and annulus fibrosus of normal intervertebral disc tissues.¹² The percentage of TRAIL-positive cells was higher in the intervertebral disc tissues of patients compared with the control.¹⁸ Our present meta-analysis demonstrated that

FASL rs763110, TRAIL rs1131580, and TRAIL rs1131568 polymorphisms were significantly associated with susceptibility to IDD in Chinese Han population. Given that all eligible studies included were performed in Chinese populations, subgroup analyses of different ethnicity could not be conducted and more studies should be designed to analyze these conditions.

In addition to TRAIL rs1131580 ($I^2 = 17.8%$ under allele model and $I^2 = 85.7%$ under recessive model), there were no heterogeneities in the overall comparisons for FASL rs763110 and TRAIL rs1131568 polymorphism and IDD risk. To explore the source of heterogeneity, we performed sensitivity analysis and found that none of those studies altered the pooled OR significantly, indicating that other unknown factors might be the cause. And we predicted that ethnicity may account for the heterogeneity. Neither the Egger test nor the Begg funnel plot showed significant publication bias for the IDD risk associated with FASL and TRAIL polymorphism. Although the results are reliable, more studies are warranted to confirm the findings of this meta-analysis.

Taken all these data in consideration, our meta-analysis has several strengths. First, we used a comprehensive search strategy with well-defined inclusion and exclusion criteria. Second, two reviewers performed the study selection and data extraction independently and discrepancies were resolved by consensus. Third, we assessed the quality of the included studies by predefined criteria and the score of included studies here was high. Finally, all genotype data extracted from the studies are reported in the meta-analysis.

Nevertheless, there are still some limitations. First, the number of cases is still relatively small. Some unpublished reports, non-English and Chinese articles, and studies without sufficient information were not included in our meta-analysis, which may have biased our results. Second, most of the studies included only assessed the association of gene polymorphisms with IDD risk, and more precise OR adjusted for other covariates such as age, sex, and environmental factors were unavailable. Finally, all eligible studies included were performed in Chinese populations. Therefore, additional studies with other ethnic populations are warranted to investigate the effects among overall populations.

CONCLUSION

The present meta-analysis demonstrated that FASL rs763110, TRAIL rs1131580, and TRAIL rs1131568 polymorphisms were significantly associated with susceptibility to IDD in Chinese Han population. Future research on FASL and TRAIL polymorphisms and IDD susceptibility should be discouraged and more promising potential sources of variation in other genes should be investigated.

➤ Key Points

- ❑ To date, growing numbers of studies have revealed the association between FASL and TRAIL polymorphisms and susceptibility to IDD. However, those studies have yielded inconsistent results.
- ❑ Meta-analysis of six eligible studies with a total of 1766 IDD cases and 1533 controls showed that the FASL rs763110, TRAIL rs1131580, and TRAIL rs1131568 polymorphisms were significantly associated with susceptibility to IDD in Chinese Han population.
- ❑ More studies based on larger sample sizes and homogeneous samples of patients with IDD are warranted to confirm these findings.

Supplemental digital content is available for this article. Direct URL citations appearing in the printed text are provided in the HTML and PDF version of this article on the journal's Web site (www.spinejournal.com).

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