Association of IL-6 and MMP-3 gene polymorphisms with adolescent idiopathic scoliosis: A systematic review and meta-analysis

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Abstract. The pathogenesis of adolescent idiopathic scoliosis (AIS) remains unclear. It has been found that interleukin-6 (IL-6) rs1800795 locus and matrix metalloproteinase-3 (MMP-3) rs3025058 locus gene polymorphisms may be associated with AIS susceptibility, which has been controversial and needs to be further confirmed by updated meta-analysis. The aim of the present study was to investigate the association of MMP-3 rs3025058 and IL-6 rs1800795 single nucleotide polymorphisms (SNPs) with susceptibility to AIS. All relevant articles that met the criteria were retrieved and included, and the publication dates were limited from January 2005 to December 2023. The allele frequencies and different genotype frequencies of IL-6 rs1800795 and MMP-3 rs3025058 loci in each study were extracted and statistically analyzed by ReviewManager 5.4 software, and the odds ratio (OR) and 95% confidence interval (95% CI) of different genetic models were calculated. The results of the meta-analysis showed that there was no significant association between the gene polymorphism of IL-6 rs1800795 locus and the pathogenesis of AIS. The allele 5A and genotype 5A5A of MMP-3 rs3025058 SNP were associated with AIS susceptibility (5A vs. 6A, OR=1.18; 95% CI, 1.04-1.33; 5A5A vs. 6A6A, OR=1.65; 95% CI, 1.23-2.21; and 5A5A vs. 6A6A + 6A6A, OR=1.54; 95% CI, 1.19-1.99). Results of subgroup analysis revealed that the allele 5A and genotype 5A5A of MMP-3 rs3025058 SNP were associated with AIS susceptibility in the Caucasian population, and the susceptibility of AIS was associated with the genotype 5A5A of MMP-3 rs3025058 SNP in an Asian population. There was no significant association between the gene polymorphism of IL-6 rs1800795 locus and the pathogenesis of AIS, while the allele 5A of MMP-3 rs3025058 locus was associated with the susceptibility to AIS, especially in the Caucasian population.

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Abbreviations: AIS, adolescent idiopathic scoliosis; IL-6, interleukin-6; MMP-3, matrix metalloproteinase-3; SNP, single nucleotide polymorphism; 95% CI, 95% confidence interval; OR, odds ratio; HWD, Hardy-Weinberg disequilibrium; HWE, Hardy-Weinberg equilibrium; PRISMA, preferred reporting items for systematic review and meta-analysis

Key words: adolescent idiopathic scoliosis, IL-6, MMP-3, single nucleotide polymorphism, meta-analysis

Introduction

Adolescent idiopathic scoliosis (AIS) is a complex three-dimensional (3D) deformity of the spine that occurs during the rapid growth and development of adolescents. The prevalence of the condition is estimated to be between 2 and 4% among the ages of 10 to 18 (1,2). It is primarily a result of the difference in growth and development between the anterior and posterior vertebrae that causes the spine to have lordosis or kyphosis. There is a lordosis in AIS because the vertebral body grows faster than the posterior elements, and the ventral vertebral body has to twist and rotate to maintain its height, as the dorsal diminished growth makes it difficult to maintain its normal height (3).

To date, the pathogenesis of AIS is not clear. Numerous scholars have studied the histomorphology, biological macromolecules and gene levels, as well as microbial and environmental cues (4,5), and have put forward a number of hypotheses, including genetic factors, an imbalance of the growth and development of the skeletal muscle system (6,7), hormone level and metabolic disorders (8-10), and genetic complexity (11-13).

At present, researchers are focusing heavily on gene polymorphism, which is considered to play an important role in the pathogenesis of AIS. The single nucleotide polymorphism (SNP) of the estrogen receptor β (ESR2) gene (10,14,15), vitamin D receptor (16-18), insulin-like growth factor-1

(IGF1) (19,20), melatonin receptor (21), ADAMTS-like protein 2 (ADAMTSL2), latent transforming growth factor β-binding protein 4 (LTBP4), Ras homolog gene family, member A (RHOA) (12,22).

In 2007, Aulisa *et al* (23) reported a case-control study linking interleukin-6 (IL-6) and matrix metalloproteinase-3 (MMP-3) SNPs to susceptibility to AIS development, and this study was later replicated by several other scholars, however the conclusions were quite inconsistent. Zhao *et al* (24) conducted a meta-analysis in 2016 which included only five related studies. Due to the low number of related articles and the small sample sizes included in each study, the conclusion was controversial in some respects. The purpose of the present study was to use an updated meta-analytic method to conduct a systematic and comprehensive analysis of all the published studies on the role of the MMP-3 rs3025058 gene polymorphism and the IL-6 rs1800795 gene polymorphism in AIS, in order to obtain more concrete and reliable results, and subsequently to scientifically evaluate the role of IL-6 and MMP-3 SNPs in the pathogenesis of AIS.

Materials and methods

Search strategy. The present study conformed to preferred reporting items for systematic review and meta-analysis guidelines. The databases searched included PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com), EMBASE (https://www.embase.com), China National Knowledge Infrastructure (https://www.cnki.net/) and China Wanfang Data Knowledge Service Platform (https://www.wanfangdata.com.cn/) to analyze the relationship between MMP-3 rs3025058, IL-6 rs1800795 SNP and AIS. The search strategy included the following terms: 'Adolescent idiopathic scoliosis' or 'AIS' and 'matrixmetalloproteinase-3' or 'MMP-3' or 'interleukin-6' or 'IL-6' or 'rs3025058' or 'rs1800795' and 'polymorphism' or 'single nucleotide polymorphism' or 'SNP' or 'variation' or 'mutation'. There was no language limit, and the publication dates were limited from January 2005 to December 2023.

Selection criteria. Studies were selected for review if they met the following inclusion criteria: i) Case-control study; ii) the case group met the diagnostic criteria of AIS, there were no other underlying diseases and the control group was healthy; and iii) the full text of the original literature was available, involvement of MMP-3 rs3025058 and IL-6 rs1800795, and specific data on sample size, genotype and gene frequency in the case group and the control group. Studies were excluded if they met the following criteria: i) Other observational study design, pedigree correlation study, case report, clinical trial, review and comment; ii) the case group did not meet the diagnosis of AIS, or it met the diagnosis of AIS but was combined with one or more underlying diseases, and the control group was not healthy; iii) MMP-3 rs3025058 and IL-6 rs1800795 were not the SNPs of interest or AIS was not the phenotype of interest.

Data extraction. The abstracts and full texts of articles matching inclusion criteria were independently reviewed by two authors. To ensure all relevant studies had been searched and indexed, data were checked thoroughly and repeatedly. Differences in information extraction results were resolved through discussion between researchers or with a third party. The following information was extracted from studies included in the reviewing: i) Last name of the first author; ii) publication year; iii) the country in which the study was conducted; iv) ethnicity; and v) sample size, genotypes and alleles of the AIS group and the control group.

Quality assessment. The modified Newcastle-Ottawa scale (NOS) was employed to evaluate the quality of the included literature on the association between MMP-3 rs3025058/IL-6 rs1800795 SNP and AIS. The modified NOS has a total of 9 stars and includes three aspects: Selection, comparability and outcome. The item of 'selection' can be awarded at most 4 stars, the item of 'comparability' can be awarded at most 2 stars and the item of 'outcome' can be awarded at most 3 stars. The specific scoring criteria are shown in Table I and the relative threshold may be adjusted depending on applicable technologies (25).

Statistical analysis. Review Manager 5.4 software provided by The Cochrane Collaboration network was used to analyze the extracted data by meta-analysis. Notably, dichotomous variables were expressed by the odds ratio (OR) and 95% confidence interval (CI). The OR and 95% CI of the IL-6 rs1800795 and the MMP-3 rs3025058 allele model (IL-6: C vs. G; MMP-3: 5A vs. 6A), codominant model (IL-6: CC vs. GG, CG vs. GG; MMP-3: 5A5A vs. 6A6A, 5A6A vs. 6A6A), dominant model (IL-6: CC + CG vs. GG; MMP-3: 5A5A + 5A6A vs. 6A6A) and recessive model (IL-6: CC vs. CG + GG; MMP-3: 5A5A vs. 5A6A + 6A6A), and it was considered statistically significant when the P-value was <0.05. A Hardy-Weinberg equilibrium (HWE) calculation was performed on the gene frequency of the control group included in the literature. P>0.05 indicated that the gene frequency distribution of the control group conformed to HWE, while P<0.05 indicated that it did not. According to ethnicity, the included population was divided into Asian and Caucasian subgroups for analysis. Heterogeneity was evaluated by I^2: I^2<50%, the heterogeneity is small and a fixed effect model was used; I^2≥50%, heterogeneity is large and a random effect model was adopted. Trim funnel plots were used to analyze the publication bias of the article, and Egger's test and Begg's test were used to test the publication bias; if P>0.05, the publication bias was not significant.

Results

Description of included studies. According to the aforementioned retrieval strategy, a total of 154 related articles were retrieved. By reading the titles and abstracts, a total of 95 non-case-control studies, repeated publications and articles not related to the purpose of the study were excluded. Subsequently, 59 related articles were screened out, and the full text was further read and screened strictly according to the inclusion criteria and exclusion criteria. Finally, a total of seven English articles and two Chinese articles were included. The nine articles included 1,601 patients with AIS (case group) and 1,899 controls (control group). The literature screening process and results are presented in Fig. 1, and the basic characteristics included in the literature research are presented in Table II.

Table I. Scoring criteria of the modified Newcastle-Ottawa scale.

Quality assessment	Selection (maximum score: 4 stars)	Comparability (maximum score: 2 stars)	Outcome (maximum score: 3 stars)
Good quality	3/4 stars	1/2 stars	2/3 stars
Fair quality	2 stars	1/2 stars	2/3 stars
Poor quality	0/1 star	0 stars	0/1 star

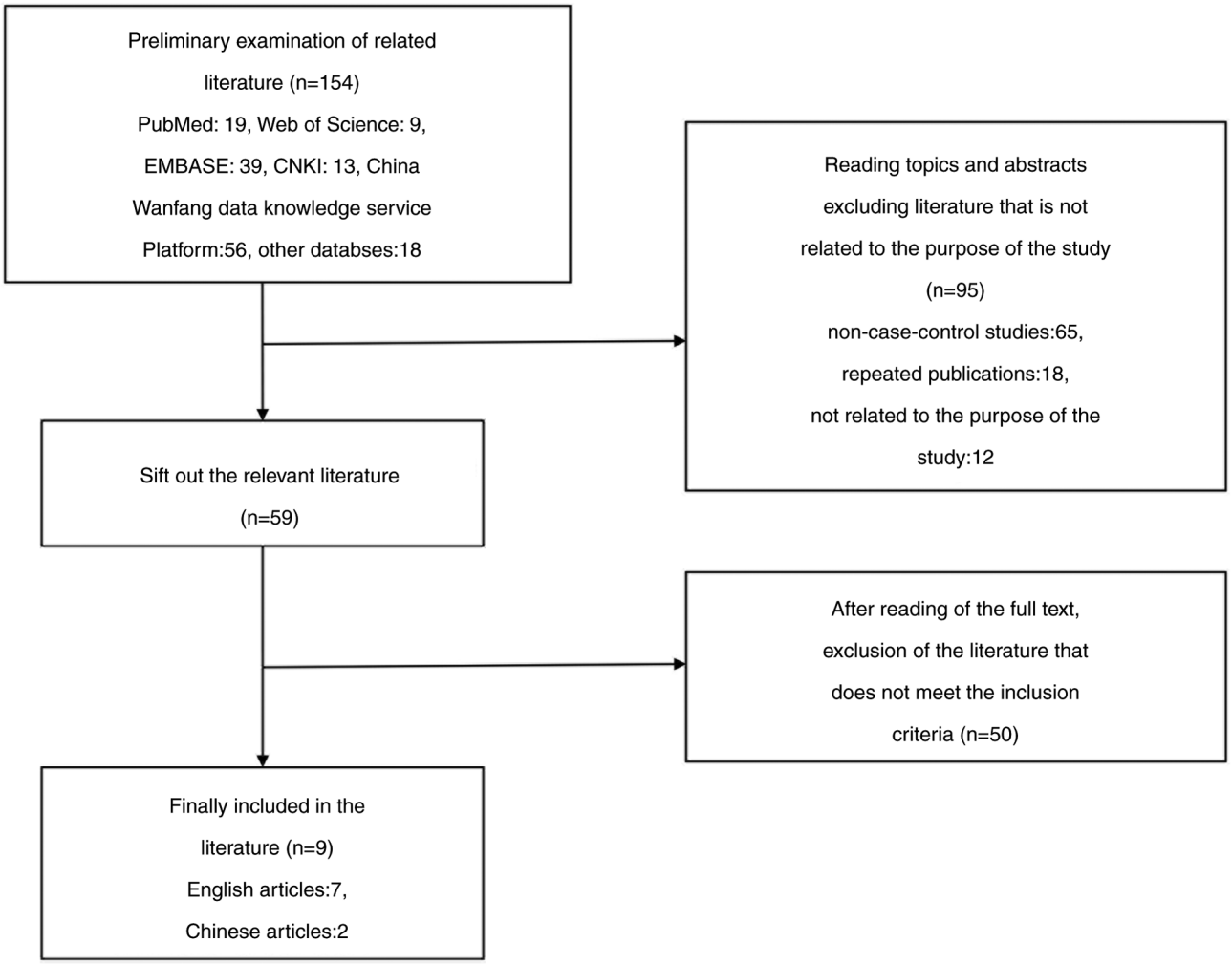

Figure 1. Flow diagram of the literature search.

Quality evaluation of included literature. In the present study, the quality of literature was evaluated using the modified NOS, and nine articles received research quality scores >5 stars (Table III), indicating higher overall quality. All the inclusion studies were case-control studies, and all met the aforementioned inclusion and exclusion criteria.

Meta-analysis results. The nine articles (23,26-33) included in this meta-analysis examined the association between IL-6 rs1800795 SNP and AIS, involving 1,214 patients with AIS (case group) and 1,505 controls (control group). A total of six (23,27-29,31,32) out of the nine articles investigated the relationship between MMP-3 rs3025058 SNP and AIS, including 1,143 patients with AIS (case group) and 1,517 controls (control group).

In the study of the association between IL-6 rs1800795 SNP and AIS, the meta-analysis showed that the allele model (C vs. G), codominant model (CC vs. CG and CG vs. GG), dominant model (CC + CG vs. GG) and recessive model (CC vs. CG + GG) were not associated with AIS susceptibility (Figs. 2-6). Subgroup analysis showed that there was an association between the dominant model (CG vs. GG, OR=0.71; 95% CI: 0.52-0.97) and AIS susceptibility in the Caucasian population (Fig. 4). The specific results are shown in Table IV.

In the study of the association between the MMP-3 rs3025058 SNP and AIS, the meta-analysis showed that the

Table II. Basic characteristics of the selected studies.

			Groups							
			IL-6 rs1800795				MMP-3 rs3025058			
First author, year	Country	Ethnicity	Case (n)	C/G/ CC/CG/GG	Control (n)	C/G/CC/CG/GG	Case (n)	5A/6A/5A5A/ 5A6A/6A6A	Control (n)	5A/6A/5A5A/ 5A6A/6A6A	(Refs.)
Sobhan *et al*, 2020	Iran	Asian	80	7/153/1/5/74	80	4/156/0/4/76	-	-	-	-	(26)
Gao, 2019	China	Asian	172	62/282/10/42/120	210	88/332/14/60/136	172	73/271/11/51/110	210	79/341/10/59/141	(27)
Sui *et al*, 2017	China	Asian	200	5/395/0/5/195	200	4/396/0/4/196	200	188/212/38/112/50	200	159/241/19/121/60	(28)
Nikolova *et al*, 2016	Bulgaria	Caucasian	105	62/148/11/40/54	210	200/220/53/94/63	105	98/112/25/48/32	210	190/230/41/108/61	(29)
Liu, 2015	China	Asian	180	5/355/0/5/175	182	3/361/0/3/179	-	-	-	-	(30)
Mórocz *et al*, 2011	Hungary	Caucasian	126	117/135/25/67/34	197	169/225/36/97/64	126	134/118/33/68/25	197	194/200/50/94/53	(31)
Liu *et al*, 2010	China	Asian	100	0/200/0/0/100	100	0/200/0/0/100	487	183/791/17/149/321	494	180/808/13/154/327	(32)
Lee *et al*, 2010	South Korea	Asian	198	1/395/0/1/197	120	1/239/ 0/1/119	-	-	-	-	(33)
Aulisa *et al*, 2007	Italy	Caucasian	53	28/78/3/22/28	206	214/198/62/90/54	53	56/50/16/24/13	206	165/247/23/119/64	(23)

allele model (5A vs. 6A, OR=1.18; 95% CI: 1.04-1.33), codominant model (5A5A vs. 6A6A, OR=1.65; 95% CI: 1.23-2.21) and recessive model (5A5A vs. 5A6A + 6A6A, OR=1.54; 95% CI: 1.19-1.99) were associated with the susceptibility to AIS. There was no significant association between the codominance model (5A6A vs. 6A6A) and dominance model (5A5A + 5A6A vs. 6A6A) and susceptibility to AIS. The results of subgroup analysis revealed that the codominant model (5A5A vs. 6A6A, OR=1.73; 95% CI: 1.13-2.67) and implicit model (5A5A vs. 5A6A + 6A6A, OR=1.73; 95% CI: 1.15-2.59) were associated with the susceptibility to AIS in the Asian population, while the allele model (5A vs. 6A, OR=1.22; 95% CI: 1.00-1.49), codominant model (5A5A vs. 6A6A, OR=1.57; 95% CI: 1.05-2.36) and recessive model (5A5A vs. 5A6A + 6A6A, OR=1.41; 95% CI: 1.01-1.98) were associated with the susceptibility to AIS in the Caucasian population (Figs. 7-9). The specific results are presented in Table IV.

Heterogeneity and sensitivity analyses. As a result of the meta-analysis, heterogeneity was observed. There are a number of factors that can explain heterogeneity, including HWE, studies conducted in different countries and sample size limitations. There was no significant change in genotypes studied when the studies selected were limited to high quality and HWE studies. In addition, when analyzing the relationship between IL-6 rs1800795SNP and AIS, evident heterogeneity was detected, and the heterogeneity mainly emerged from the study of Mórocz *et al* (31), and it is hypothesized that this heterogeneity may be caused by ethnic differences and the weight of the number of cases. Following further careful reading and analysis of the literature, it was found that the study was carried out in the Hungarian population, and the gene frequency of risk gene (C) reported by the authors was much higher than that of other studies, suggesting that the occurrence of this phenomenon may be related to race specificity. Concurrently in this study, there were 126 cases in the case group and 197 cases in the control group. The weight of the number of cases in this study was larger, and the conclusion of this study was opposite to that of the other two (27,28), thus it greatly increased the heterogeneity of meta-analysis. However, considering the large sample size and high quality of the study conducted by Mórocz *et al* (31) it was not excluded from the present study. In the subgroup analysis, no significant heterogeneity was detected in several studies of the Asian subgroup, indicating a good consistency. At the same time, a sensitivity analysis was conducted, and when any study was removed, there was no significant difference in the results of meta-analysis, therefore it was finally concluded that the results were stable and the meta-analysis results were accurate. The detailed results are shown in Table IV.

Publication bias. All comparisons were included and publication bias was estimated using trim funnel plots test (Fig. 10). For statistical evidence, Egger's and Begg's tests (P>0.05) were conducted, and indicated that publication bias was not apparent. Although funnel plots are symmetrical, publication bias may be present because of the few related studies on the whole.

The comparisons were the following: i) The allelic comparison (C vs. G); ii) the codominance model comparison (CC vs. GG); iii) the codominance model comparison (CG vs.

Table III. Quality assessment of studies using a modified Newcastle-Ottawa scale.

First author, year	Selection (maximum score: 4 stars)	Comparability (maximum score: 2 stars)	Outcome (maximum score: 3 stars)	Overall	(Refs.)
Sobhan *et al*, 2020	☆☆☆	☆	☆☆	☆☆☆☆☆☆	(26)
Gao, 2019	☆☆☆☆	☆	☆☆	☆☆☆☆☆☆☆☆	(27)
Sui *et al*, 2017	☆☆☆☆	☆	☆☆	☆☆☆☆☆☆☆☆	(28)
Nikolova *et al*, 2016	☆☆☆☆	☆	☆☆	☆☆☆☆☆☆☆☆	(29)
Liu, 2015	☆☆☆	☆	☆☆	☆☆☆☆☆☆	(30)
Mórocz *et al*, 2011	☆☆☆	☆	☆☆	☆☆☆☆☆☆	(31)
Liu *et al*, 2010	☆☆☆☆	☆	☆☆	☆☆☆☆☆☆☆☆	(32)
Lee *et al*, 2010	☆☆☆	☆	☆☆	☆☆☆☆☆☆	(33)
Aulisa *et al*, 2007	☆☆☆☆	☆	☆	☆☆☆☆☆☆	(23)

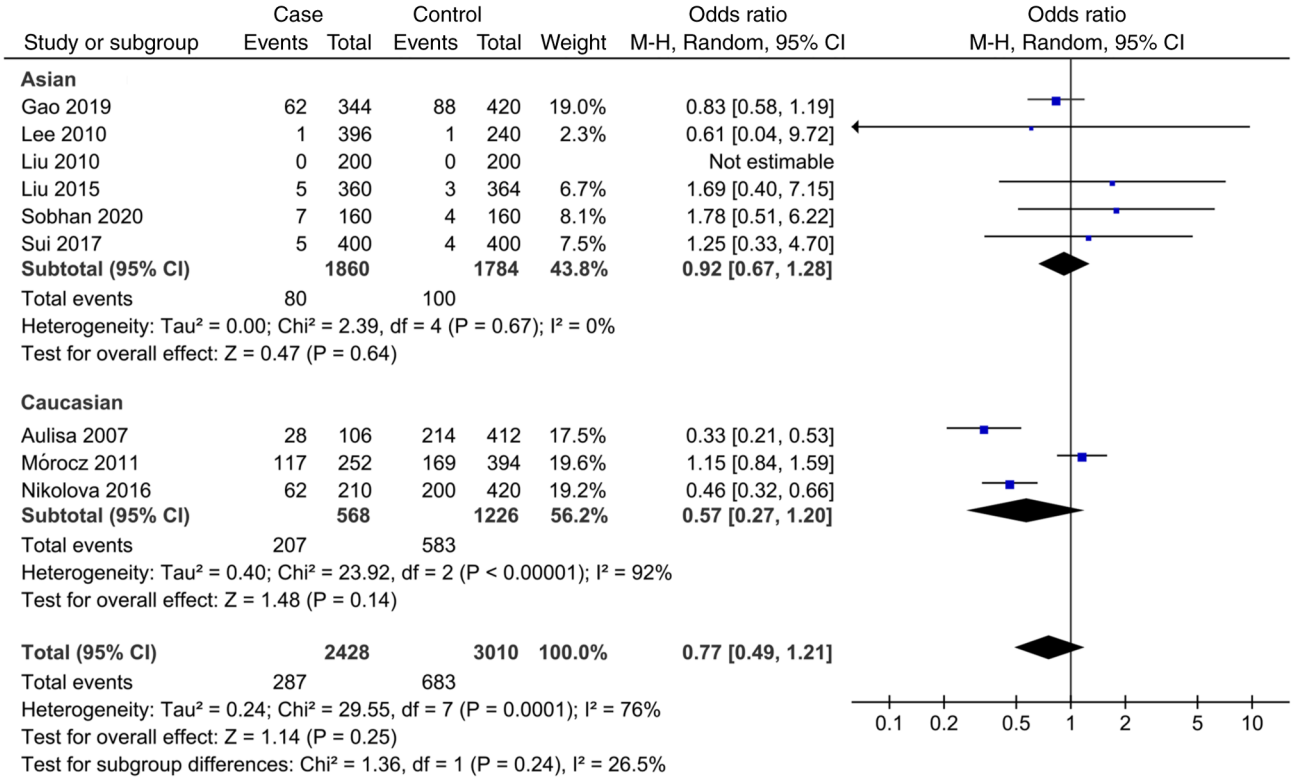

Figure 2. Forest plot of the association between IL-6 rs1800795 single nucleotide polymorphism and adolescent idiopathic scoliosis risk for the allelic comparison (C vs. G). MH, Mantel-Haenszel; CI, confidence interval.

GG); iv) the dominant model comparison (CC + CG vs. GG); v) the recessive model comparison (CC vs. CG + GG); vi) the allelic model comparison (5A vs. 6A); vii) the codominance model comparison (5A5A vs. 6A6A); and viii) the recessive model comparison (5A5A vs. 5A6A + 6A6A).

Discussion

Scoliosis is a 3D deformity of the spine with a complex etiology, which often occurs in adolescence. As the initial symptoms are not obvious, the occurrence and development of the disease are often ignored. If adolescent patients with idiopathic scoliosis do not receive effective prevention and timely treatment, a serious condition may develop, affecting the appearance of the spine, cardiopulmonary function and even threatening the patient's life. As adolescence is a stage of maturation with physical and psychological development, the occurrence of scoliosis may seriously harm the physical and mental health of adolescents. Thus, active measures should be taken to prevent the occurrence of AIS (34,35). Specific pathogenic genes of AIS remain inconclusive, and greater attention has been paid to its genetic factors, especially the relationship between candidate genes and AIS (36,37). In recent years, some studies on the correlation between IL-6 rs1800795,

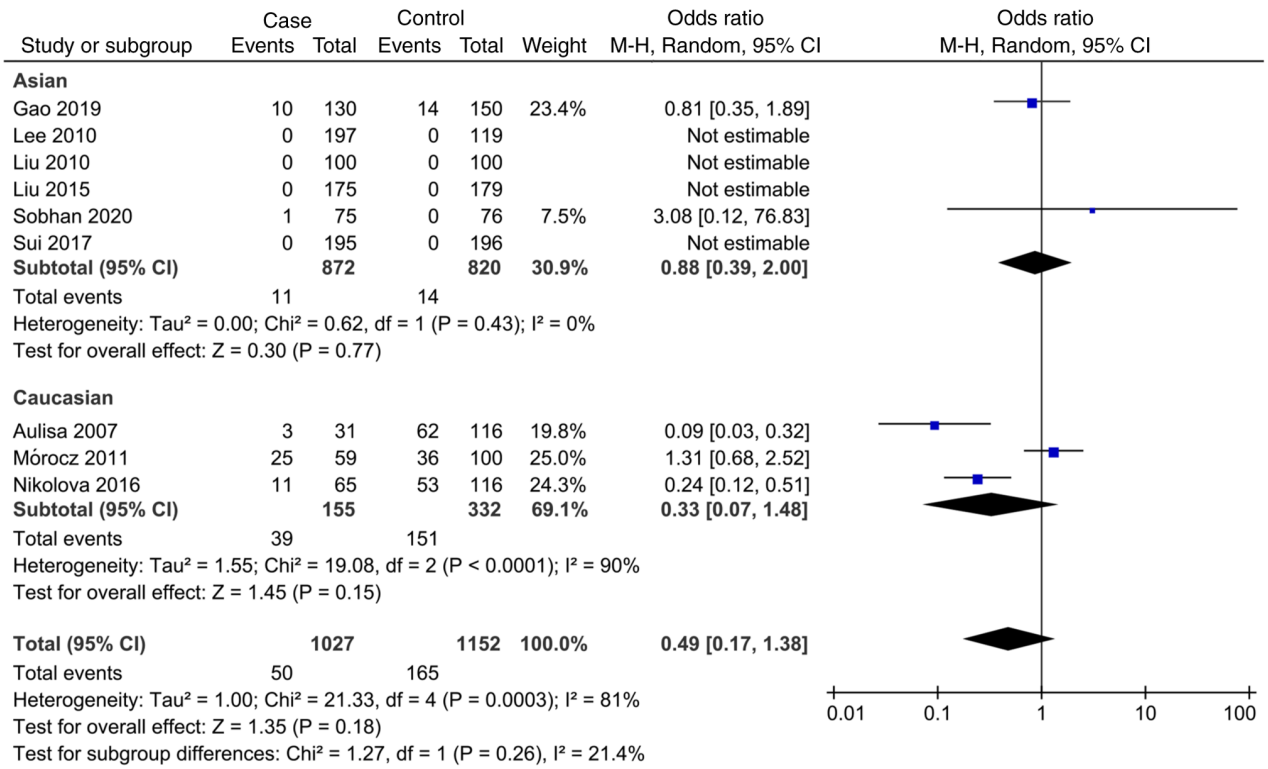

Figure 3. Forest plot of the association between IL-6 rs1800795 single nucleotide polymorphism and adolescent idiopathic scoliosis risk for the codominance model comparison (CC vs. GG). CI, confidence interval; MH, Mantel-Haenszel.

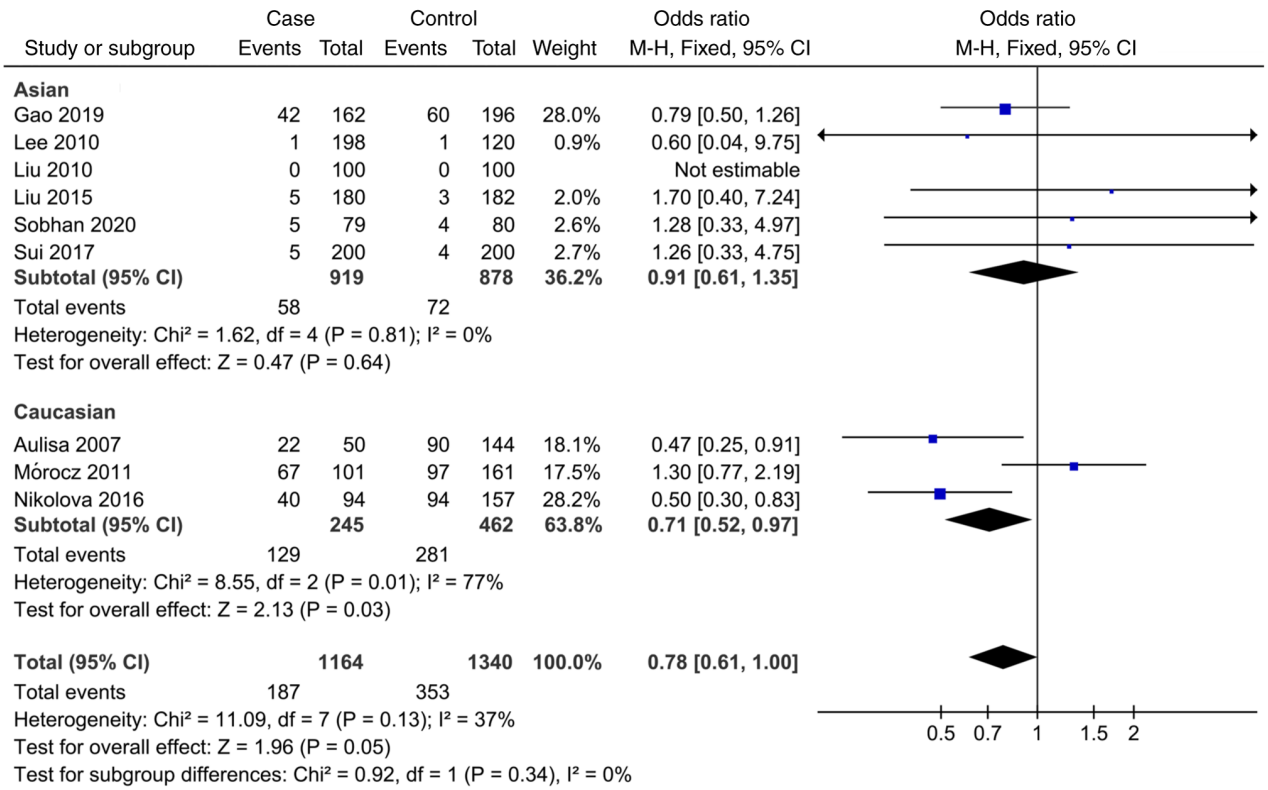

Figure 4. Forest plot of the association between IL-6 rs1800795 single nucleotide polymorphism and adolescent idiopathic scoliosis risk for the codominance model comparison (CG vs. GG). MH, Mantel-Haenszel; CI, confidence interval.

MMP-3 rs3025058 and AIS have emerged, but the conclusions are not consistent. At present, the total amount of research literature on the relationship between IL-6 rs1800795, MMP-3 rs3025058 and AIS remains limited.

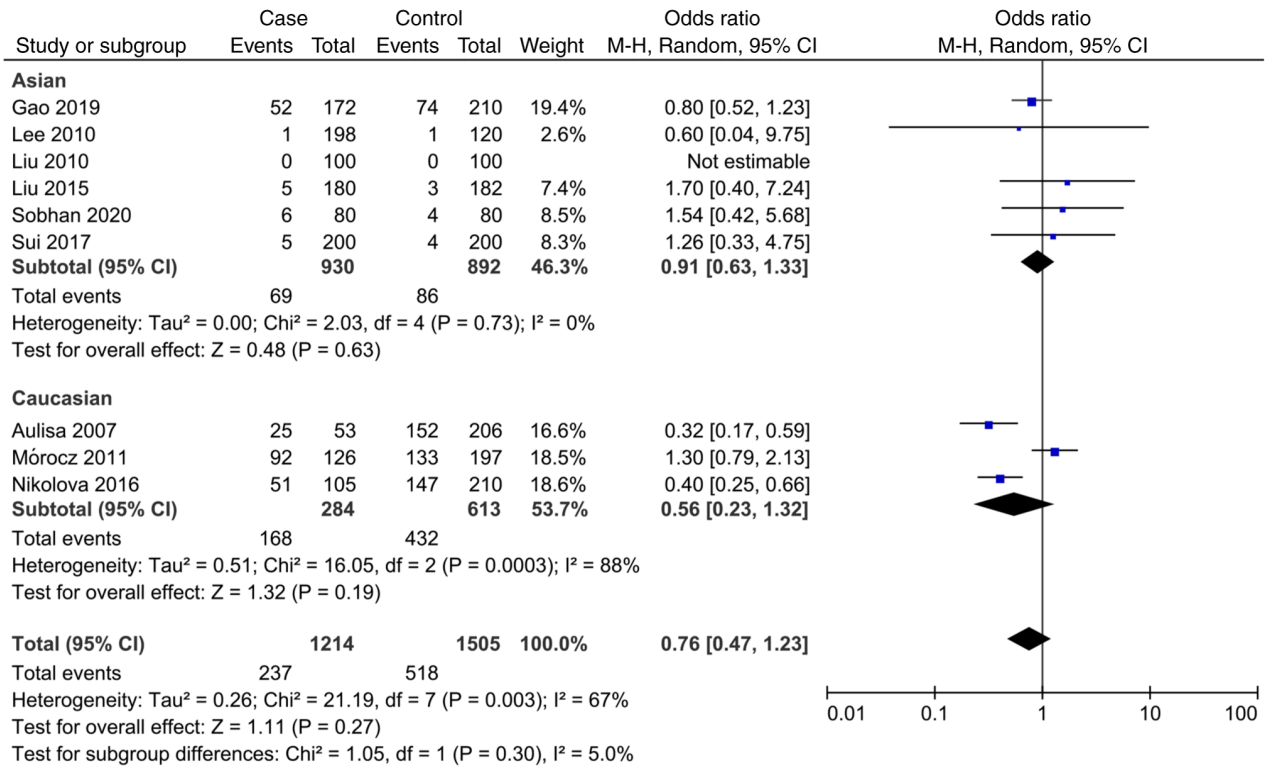

Figure 5. Forest plot of the association between IL-6 rs1800795 single nucleotide polymorphism and adolescent idiopathic scoliosis risk for the dominant model comparison (CC + CG vs. GG). MH, Mantel-Haenszel; CI, confidence interval.

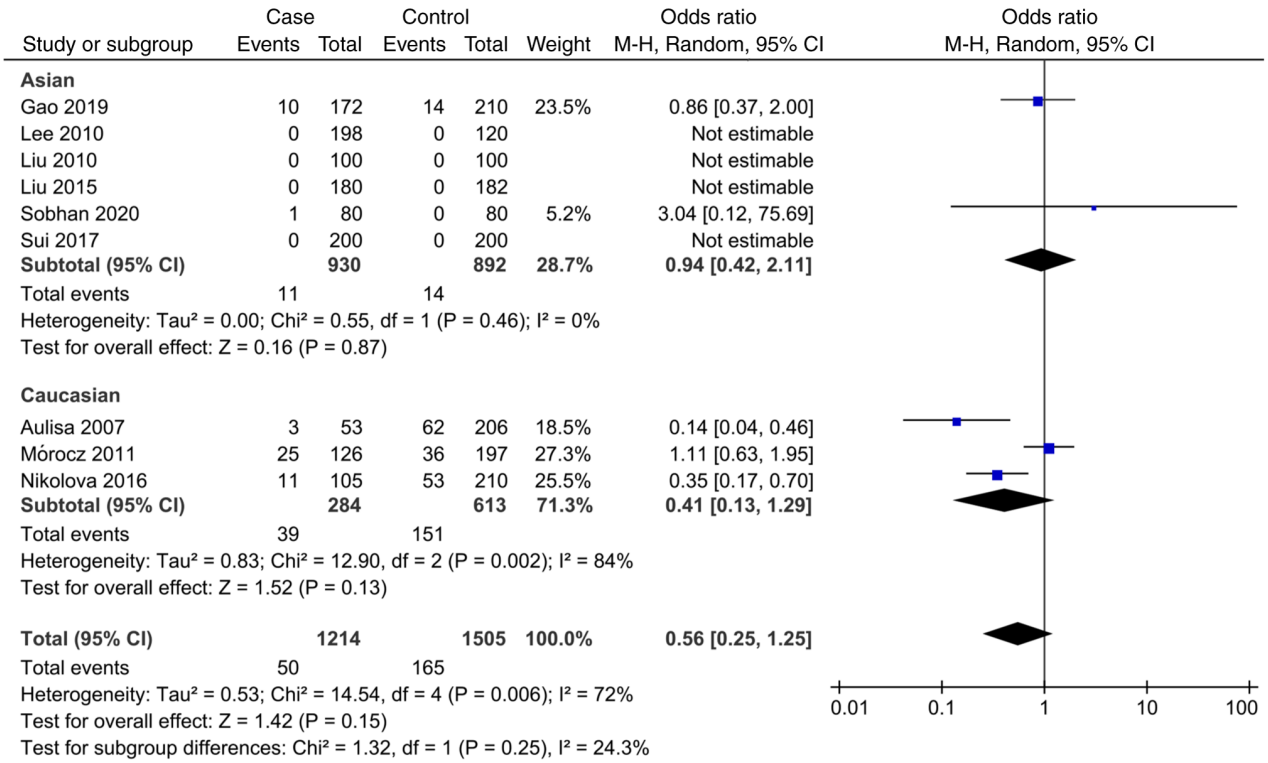

Figure 6. Forest plot of the association between IL-6 rs1800795 single nucleotide polymorphism and adolescent idiopathic scoliosis risk for the recessive model comparison (CC vs. CG + GG). MH, Mantel-Haenszel; CI, confidence interval.

IL-6 is a multifunctional cytokine from a wide range of sources. Current studies have shown that IL-6 has both pro-inflammatory and anti-inflammatory effects, and its main function is to mediate inflammatory response (38,39). A number of studies have revealed that the expression of IL-6 in herniation intervertebral disc cells was significantly

Table IV. Analysis of the genetic models on the association of MMP-3 rs3025058 and IL-6 rs1800795 polymorphism with adolescent idiopathic scoliosis.

A, IL-6 rs1800795

Allele gene and genotype	Odds ratio	95% Confidence interval	P-value	Model	I^2 (%)
Overall					
C vs. G	0.77	0.49-1.21	0.25	R	76
CC vs. GG	0.49	0.17-1.38	0.18	R	81
CG vs. GG	0.78	0.61-1.00	0.05	F	37
CC + CG vs. GG	0.76	0.47-1.23	0.27	R	67
CC vs. CG + GG	0.56	0.25-1.25	0.15	R	72
Asian					
C vs. G	0.92	0.67-1.28	0.64	R	0
CC vs. GG	0.88	0.39-2.00	0.77	R	0
CG vs. GG	0.91	0.61-1.35	0.64	F	0
CC + CG vs. GG	0.91	0.63-1.33	0.63	R	0
CC vs. CG + GG	0.94	0.42-2.11	0.87	R	0
Caucasian					
C vs. G	0.57	0.27-1.20	0.14	R	92
CC vs. GG	0.33	0.07-1.48	0.15	R	90
CG vs. GG	0.71	0.52-0.97	0.03[a]	F	77
CC + CG vs. GG	0.56	0.23-1.32	0.19	R	88
CC vs. CG + GG	0.41	0.13-1.29	0.13	R	84

B, MMP-3 rs3025058

Allele gene and genotype	Odds ratio	95% Confidence interval	P-value	Model	I^2 (%)
Overall					
5A vs. 6A	1.18	1.04-1.33	0.01[a]	F	0
5A5A vs. 6A6A	1.65	1.23-2.21	0.0009[a]	F	12
5A6A vs. 6A6A	1.05	0.88-1.26	0.57	F	0
5A5A + 5A6A vs. 6A6A	1.13	0.95-1.34	0.17	F	0
5A5A vs. 5A6A + 6A6A	1.54	1.19-1.99	0.001[a]	F	45
Asian					
5A vs. 6A	1.15	0.98-1.35	0.08	F	0
5A5A vs. 6A6A	1.73	1.13-2.67	0.01[a]	F	0
5A6A vs. 6A6A	1.04	0.84-1.27	0.74	F	0
5A5A + 5A6A vs. 6A6A	1.09	0.90-1.34	0.38	F	0
5A5A vs. 5A6A + 6A6A	1.73	1.15-2.59	0.008[a]	F	0
Caucasian					
5A vs. 6A	1.22	1.00-1.49	0.05	F	30
5A5A vs. 6A6A	1.57	1.05-2.36	0.03[a]	F	50
5A6A vs. 6A6A	1.10	0.78-1.55	0.59	F	12
5A5A + 5A6A vs. 6A6A	1.22	0.88-1.68	0.24	F	0
5A5A vs. 5A6A + 6A6A	1.41	1.01-1.98	0.04[a]	F	72

P-value, corresponding to the Z test for the summary effect estimate ([a]$P<0.05$ was considered to indicate a statistically significant difference). $I^2=0$, no heterogeneity; $I^2=25\%$, low heterogeneity; $I^2=50\%$, moderate heterogeneity; and $I^2=75\%$, high heterogeneity. IL-6, interleukin-6; MMP-3, matrix metalloproteinase-3; R, random effect model; F, fixed effect model.

increased, suggesting that IL-6 is involved in the pathogenesis of intervertebral disc degeneration to a certain extent (40-42). The 5A allele in the MMP-3 promoter sequence is a risk factor for lumbar degenerative diseases and is highly expressed in

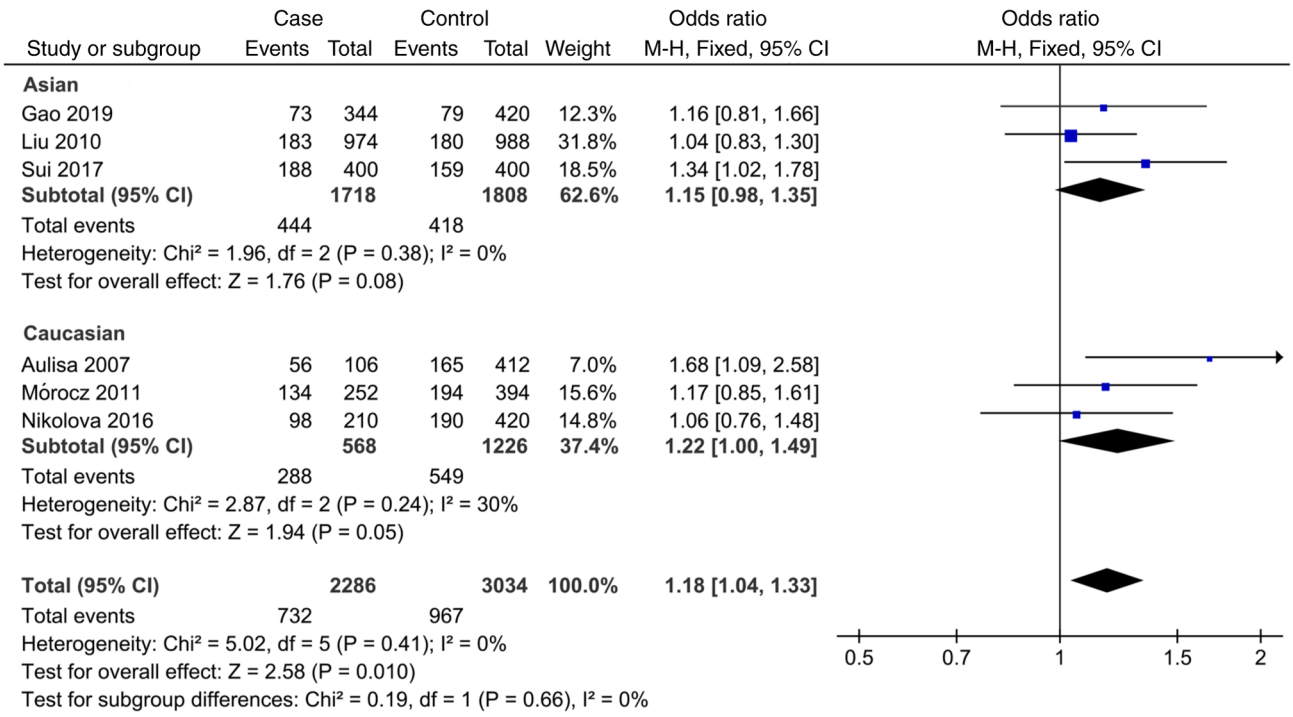

Figure 7. Forest plot of the association between MMP-3 rs3025058 single nucleotide polymorphism and adolescent idiopathic scoliosis risk for the allelic model comparison (5A vs. 6A). MH, Mantel-Haenszel; CI, confidence interval.

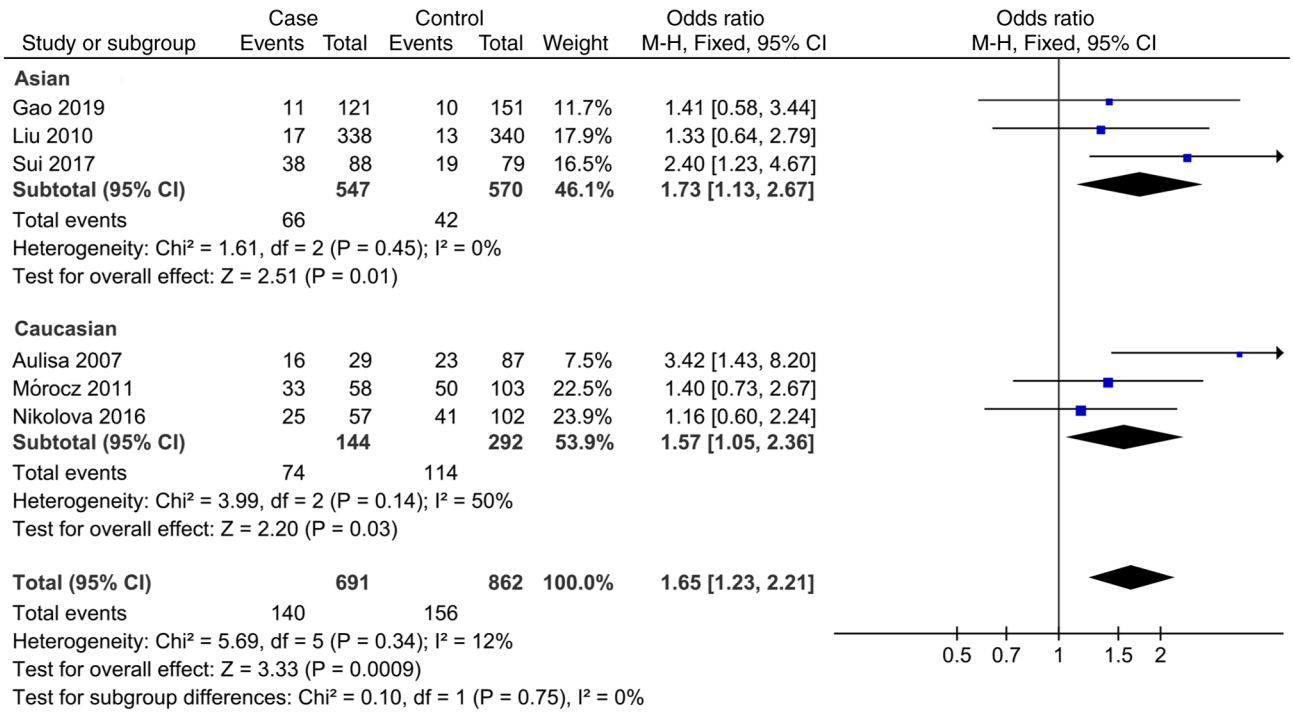

Figure 8. Forest plot of the association between MMP-3 rs3025058 single nucleotide polymorphism and adolescent idiopathic scoliosis risk for the codominance model comparison (5A5A vs. 6A6A). MH, Mantel-Haenszel; CI, confidence interval.

human degenerative intervertebral disc samples, suggesting that MMP-3 plays an important role in intervertebral disc degeneration (43,44). The upregulated expression of IL-6 and MMP-3 can promote intervertebral disc degeneration, and numerous studies have found that scoliosis areas of patients with AIS are more prone to intervertebral disc degeneration than normal areas, suggesting that MMP-3 and IL-6 may interact to induce intervertebral disc degeneration and participate in the occurrence of scoliosis (38,42-44).

Research in several countries has identified a relationship between IL-6 rs1800795 and MMP-3 rs3025058 SNPs and AIS incidence, gradually expanding evidence. However,

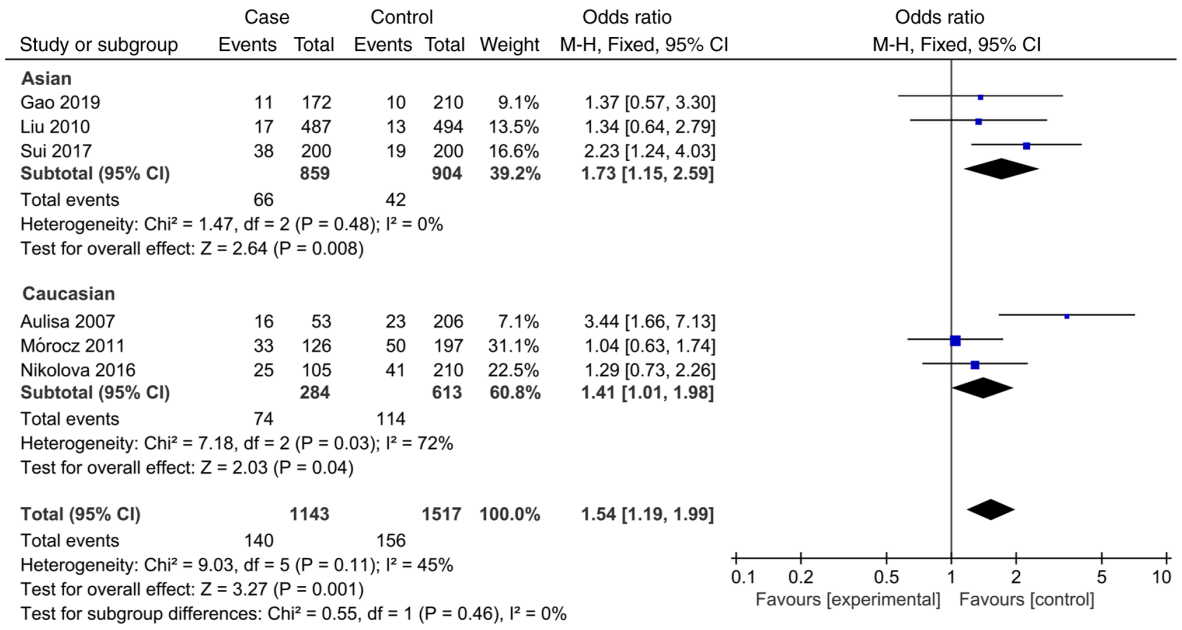

Figure 9. Forest plot of the association between MMP-3 rs3025058 single nucleotide polymorphism and adolescent idiopathic scoliosis risk for the recessive model comparison (5A5A vs. 5A6A + 6A6A). MH, Mantel-Haenszel; CI, confidence interval.

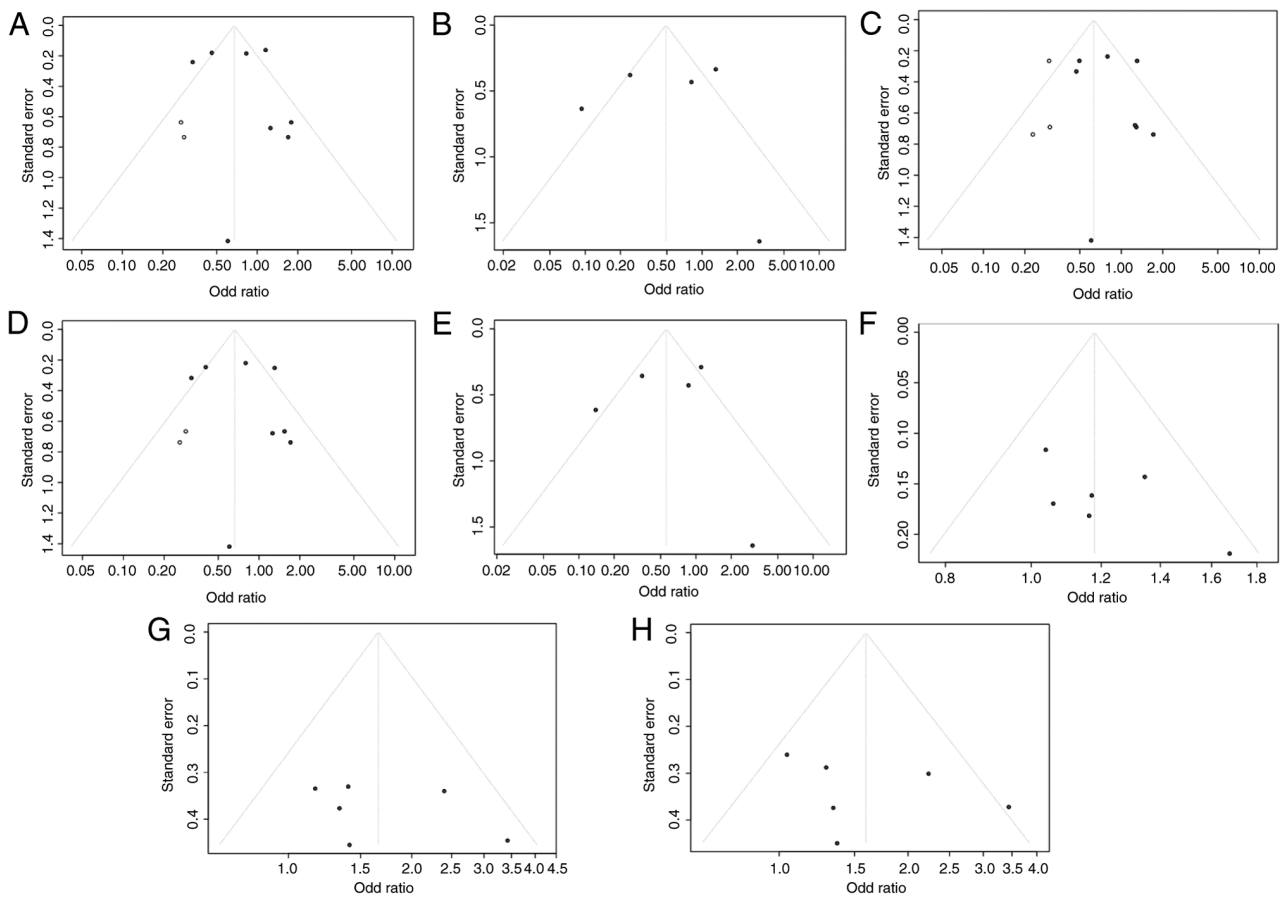

Figure 10. Trim funnel plots of publishing bias. (A) The allelic comparison (C vs. G). (B) The codominance model comparison (CC vs. GG). (C) The codominance model comparison (CG vs. GG). (D) The dominant model comparison (CC + CG vs. GG). (E) The recessive model comparison (CC vs. CG + GG). (F) The allelic model comparison (5A vs. 6A). (G) The codominance model comparison (5A5A vs. 6A6A). (H) The recessive model comparison (5A5A vs. 5A6A + 6A6A).

the conclusions remain uncertain, and controversial points continue to exist. According to the results of the present meta-analysis, the IL-6 rs1800795 gene polymorphism does not appear to be associated with AIS incidence. Based on a

meta-analysis published in 2020, Sobhan *et al* (26) found that the IL-6 rs1800795 SNP and AIS risk were statistically significant. In the subgroup analysis, the IL-6 rs1800795 SNP was significantly associated with the risk of AIS in the Caucasian population, which runs counter to the results of the present study. After studying the article carefully, it was observed that the author did not exclude the repeated published literature and there may be the phenomenon of repeated statistical data. For example, related articles published by Nikolova *et al* (29,45) in 2015 and 2016 involve the phenomenon of repetition of statistical data. The author also included data from degenerative lumbar scoliosis that was not relevant to this study, which led to discrepancies in the data. Based on this, it is assumed that the data and conclusions are not reliable.

After screening, newly published articles were selected for inclusion in the present study. Notably, significant heterogeneity was also detected and it mainly emerged from the study conducted by Mórocz *et al* (31); is hypothesized that this heterogeneity may be caused by ethnic differences and the weight of the number of cases. This leads to differences in the analytical results, and thus the data need to be confirmed by further study. Statistical analysis in the present study showed that there was no significant correlation between IL-6 rs1800795 locus gene polymorphism and the pathogenesis of AIS.

In the current study, the association between MMP-3 rs3025058SNP and AIS was analyzed by meta-analysis. The results showed that allele model (5A vs. 6A), the codominant model (5A5A vs. 6A6A) and the recessive model (5A5A vs. 5A6A + 6A6A) were related to the susceptibility to AIS. Results of the subgroup analysis demonstrated that the codominant model (5A5A vs. 6A6A) and the recessive model (5A5A vs. 5A6A + 6A6A) were associated with the susceptibility to AIS in Asian population. In Caucasian population, the allele model (5A vs. 6A), codominant model (5A5A vs. 6A6A) and recessive model (5A5A vs. 5A6A + 6A6A) are associated with AIS susceptibility, and the combined OR value of the codominant model (5A5A vs. 6A6A) in the Caucasian population was statistically significant, which is consistent with the overall population, suggesting that this association is more common in Caucasian population. Further study is required to clarify the correlation of other populations. On the whole, there is an association between allele 5A at this locus and susceptibility to AIS. It is considered that although the sample size has increased, it is still less overall, and the reliability of the conclusion still needs more research for verification. In this case, a false negative may be obtained. In the analysis of the association between MMP-3 rs3025058SNP and AIS, the overall allele model (5A vs. 6A) OR=1.18; 95% CI: 1.04-1.33, the codominant model (5A5A vs. 6A6A) OR=1.65, 95% CI: 1.23-2.21 and the recessive model (5A5A vs 5A6A + 6A6A) OR=1.54; 95% CI: 1.19-1.99, indicated an association between the two. In addition, in the overall and subgroup analyses of the relationship between MMP-3 rs3025058SNP and AIS, the heterogeneity was small, suggesting that the results are more reliable. At the same time, the results of subgroup analysis showed that the proportion of risk gene (5A) was similar in Asian and Caucasian population. It is possible to detect the MMP-3 rs3025058 gene early in children and provide long-term prevention guidance for children who may have AIS, by including the following methods: i) Bone nutrition strengthening (high-protein, high-carbohydrate, high-vitamin, high-fiber food consumption); ii) correct sitting and standing posture, which may delay the deterioration of symptoms; and iii) health education, strengthening physical exercise, reasonable nutrition, reasonable regulation of body weight and psychological adjustment. Concurrently, it is recommended to use traditional methods such as Baduanjin, Tai Chi and schroth exercises as interventions (46-48). In addition, regular follow-up and review of children and adolescents' body posture test index, low back pain score, spinal positive position and lateral X-ray Cobb angle is important.

The main advantages of the present meta-analysis include the following: i) Most of the studies included in the present meta-analysis are high quality case-control studies; and ii) most were based on relatively large samples, and specific gene results were extracted and analyzed. However, the current meta-analysis also has numerous limitations: i) Although the meta-analysis contains a relatively large sample size (1,601 patients with AIS and 1,899 controls) so the conclusion should be relatively accurate, the results could still be an overestimation that could be overturned with the addition of more data; ii) the subjects only included East Asian and Caucasian races, and thus the study does not reflect the overall population. In the subgroup analysis, the sample size of each subgroup was smaller, which may also cause the results of the analysis to deviate from the actual situation; and iii) when informed patient consent is required in clinical research, when it comes to medical ethical issues, it may also lead to the loss of a significant number of reluctant patients, which will affect the reliability of meta-analysis conclusions. Therefore, the conclusion needs to be further verified by larger sample randomized controlled trials.

In conclusion, the present meta-analysis revealed that there was no significant association between the gene polymorphism of IL-6 rs1800795 locus and the pathogenesis of AIS, but the 5A allele of the MMP-3 rs3025058 locus was associated with the susceptibility to AIS, especially in the Caucasian population. The 5A5A genotype of the MMP-3 rs3025058 locus is associated with susceptibility to AIS, both in Asians and Caucasians. Based on the synthesis of the relevant case-control studies regarding the association between IL-6 rs1800795/MMP-3 rs3025058 and AIS, the present study obtained more reliable and credible results, although, further research is still required to better understand its specific pathogenesis and confirm the conclusions of the previous studies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YPW and JPH confirm the authenticity of all the raw data. YPW and SLQ designed and performed the research, collected and analyzed the data, wrote the article and performed the statistical analysis. KDH and JPH conceived the present study. SY, PFH and AHL collected the data. YFX, KDH and JPH reviewed the articles and interpreted the data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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