

Associations between ERAP1 polymorphisms and susceptibility to ankylosing spondylitis

A meta-analysis of East Asian Population

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Abstract

Background: The genetic factor is importantly enrolled in the pathogenesis of ankylosing spondylitis (AS) and haplotype leukocyte antigen (HLA)-B27 is the most well-known. However, only 1% to 5% of B27-positive individuals will develop AS, and it confers only 20% to 30% of the overall genetic risks, indicating more genes other than HLA-B27 may play important roles in AS pathologies. The present study aims to investigate whether the polymorphisms of endoplasmic reticulum aminopeptidase 1 (ERAP1) is associated with increased risk of AS susceptibility.

Methods: The Cochrane library, Pubmed, and Embase databases were carefully searched for potential researches published before May 30, 2018. The title, abstract, and full text were assessed to determine whether the paper was suitable for inclusion. The pooled odds ratios (ORs) with 95% confidence intervals (CIs) were presented to assess the associations between ERAP1 polymorphisms and AS susceptibility.

Results: The study finally enrolled 10 papers, 4 matched single nucleotide polymorphisms (SNPs) of ERAP1 (rs27044, rs27434, rs30187, and rs27037), and a total of 30552 patients (12492 with AS and 18060 for control). No significant difference was found between the AS susceptibility and polymorphisms of rs27044 and rs27434. However, there was a significant association between ERAP1 polymorphisms rs30187 and rs27037 (T vs C, OR, 1.322, 95% CI = 1.240–10410, $P < .05$; T vs G, OR, 1.247, 95% CI = 1.149–1.353; $P < .05$; respectively) and AS susceptibility.

Conclusion: There was a significant association between ERAP1 polymorphisms (rs30187 and rs27037) and increased risk of AS susceptibility.

Abbreviations: AS = Ankylosing spondylitis, ERAP1 = endoplasmic reticulum aminopeptidase 1, HLA = haplotype leukocyte antigen, MHC = major histocompatibility complex, NOS = Newcastle-Ottawa Scale, TNF = tumor necrosis factor receptor.

Keywords: ankylosing spondylitis, ERAP1, meta-analysis, SNP

1. Introduction

Ankylosing spondylitis (AS) is an obscure, systemic, and progressive chronic autoimmune disease, which affects predomi-

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nantly the axial skeleton where ligaments and tendons insert into the bone. Clinically, the disease is characterized by inflammatory lower back pain, sometimes accompanied by peripheral arthritis, enthesitis and iritis, and even spinal deformity and ankylosis.^[1] The approximate prevalence of AS is 5 out of 1000 adults of European descent and 2.4 per 1000 in the Chinese population.^[2] The AS patients have a high prevalence of work-related disabilities, ranging from 4% at 5 years after disease diagnosis to 50% at 45 years after diagnosis.^[3] And unfortunately, there is no effective treatment against AS till now.

Complex interactions between environmental factors and host immune responses are the origins for AS development.^[4] The genetic factor is importantly enrolled in the pathogenesis of AS, as shown in a twin study that reported the estimated genetic heritability was more than 90%.^[5] For example, as known to us all, the famous human major histocompatibility complex (MHC) haplotype leukocyte antigen (HLA)-B27 is strongly associated with AS susceptibility.^[6] The HLA-B27 is positive in over 89% of the AS patients, while it is less than 10% among healthy individuals.^[7] However, as shown in other studies, only 1% to 5% of B27-positive individuals will develop AS, and it confers only 20% to 30% of the overall genetic risks, indicating more genes other than HLA-B27 may play important roles in AS pathologies.^[8–10]

Recently, accumulating evidences have provided many non-MHC genes that associated with AS, including endoplasmic reticulum aminopeptidase 1 (ERAP1), Interleukin 23R, Interleukin 1R2, anthrax toxin receptor 2, kinesin family member 21B,

and et al.^[11–13] ERAP1 is an aminopeptidase with ubiquitous tissue distribution involved in peptide processing within the endoplasmic reticulum for class MHC II presentation. ERAP1 is located at 5q15 and has 2 major functions, “molecular ruler” for antigen peptides and shedding enzyme.^[14] The association with ERAP1 may help to explain the mechanism by which HLA-B27 contributes to AS.

Burton et al.^[11] first found ERAP1 had the second strongest association with a population attributable risk of 26% in AS and reported 2 new loci at a high significance level (rs27044 and rs30187) with AS in a European population, and the rs17482078, rs10050860, and rs2287987 polymorphisms of ERAP1 also trended toward association with AS. Another study depended on the North American Caucasian with 992 AS cases and 1437 controls confirmed the strongly association between ERAP1 haplotype rs27044 and increased risk of AS.^[15] Similarly, the ERAP1 polymorphism rs27980 was also found correlated with AS susceptibility in southern Han Chinese.^[16,17] However, many well-designed case–control studies failed to draw the same conclusions mentioned above, which depended on different SNPs and different populations.

It suggests that ancestry-based heterogeneity in AS susceptibility between populations. Meta-analysis provides a powerful means of summarizing the results produced by different studies, and in the present study, we performed a meta-analysis to investigate whether ERAP1 polymorphisms were associated with susceptibility to AS in East Asian population.

2. Methods

The Cochrane library, Pubmed, and Embase databases were carefully searched independently by JYQ and RY to detect relevant studies published before May 30, 2018. The search criteria “ERAP1 or endoplasmic reticulum aminopeptidase 1” and “ankylosing spondylitis or AS” were used for text word searches. The “related articles” function was used for potentially additional articles. The reference lists of the selected articles were also manually examined to find relevant studies that were not discovered during the above-mentioned database searches. The language was restricted to only English.

Any study explored the relationship between ERAP1 polymorphisms and AS susceptibility of east Asian population with a case–control design was potentially enrolled in the present research. All the papers were assessed carefully for eligibility with the titles, abstracts and finally full papers. When several papers from the same study were published, only the most recent or informative 1 was included.

2.1. Data extraction

The data extraction of all outcomes and variables of interest was performed independently by JYQ and RY. Disagreements were resolved through discussion and consensus. Data on author affiliation, number of participants, patients’ data and genotyping information were extracted. If insufficient data were reported, we contacted corresponding authors for additional information and the paper was excluded if there was no response.

2.2. Quality assessment

The quality assessments of the included studies were performed independently by the 2 reviewers JYQ and RY using the

Newcastle-Ottawa Scale (NOS).^[18] The NOS employs a star rating system to assess quality from 3 broad perspectives of the study:

- (1) selection of the study groups,
- (2) comparability of the groups, and
- (3) identification of the exposure (for case-control studies) or outcome of interest (for cohort studies).

Scores ranged from 0 to 9 stars, and studies with no less than 7 stars were considered to be of high quality. Additionally, Egger test was performed to assess the publication bias of studies included in this meta-analysis.

2.3. Statistical analysis

The statistical analysis was performed with the software named “Comprehensive Meta Analysis (Version 2.2)”. The association strength between the gene polymorphisms of ERAP1 and AS susceptibility risk was calculated by the Z test, presented with the OR (respective 95% CIs). And the significance of the pooled OR was determined with *P* value (less than 0.05 was considered significant). *I*² statistics, with the value ranges from 0% to 100% (complete consistency to complete inconsistency), was used to determine the statistical heterogeneity among studies. If the *I*²-value was more than 50%, the random-effects model was chosen to calculate the pooled OR; otherwise, the fixed-effects model was used. All of the results were presented as forest plots.

3. Results

The meta-analysis was reported according to the preferred reporting items for systematic reviews and meta-analyses guidelines. All analyses were based on previous published studies; thus, no ethical approval or patient consent was required.

3.1. Literature search

The initial literature search retrieved 109 relevant articles (duplicates were discarded). Among these, 9 articles were excluded as no primary data was reported (review and meta-analysis), and another 65 articles were excluded for not investigating the topic (ERAP1 or AS) after carefully screening the titles and abstracts. Then, full text review of the remaining 35 paper was performed. 21 studies were performed outside the East Asian, 2 studies with incomplete outcomes, and another 2 articles with no SNP of interest were further excluded. Finally, a total of 10 studies were included in the present study.^[16,19–27] The patients of all included studies were diagnosed according to the modified New York criteria. Only 4 SNPs of ERAP1 (rs27044, rs27434, rs30187, and rs27037) were matched across the studies and finally selected, as shown in Table 1. All of the 10 included studies were assessed as high quality (≥ 7 stars). The flowchart describing the study selection is shown in Figure 1. A review of the information and data extraction revealed 100% agreement between the 2 reviewers.

3.2. Main analysis

A total of 30552 patients (12492 with AS and 18060 for control) were enrolled in this study. The Table 2 listed the genotype information of the included studies. The meta-analysis for the relationship between gene ERAP1 polymorphisms and AS susceptibility was shown in Table 3.

Table 1

The matched polymorphisms of ERAP1 between the researches included.

C. Chen 2014	Chan-Bum Choi 2015	CHAO LI 2011	Chin-Man Wang 2012	Jian Wang 2015	SO-YOUNG BANG 2011	Wenliang Wu 2011	Ya-Feng Wen 2014	zhang2014	Zhiming Lin 2011
rs27044	rs27044		rs27044			rs27044			
rs27434		rs27434		rs27434	rs27434		rs27434	rs27434	rs27434
rs30187			rs30187 rs27037		rs27037			rs27037	rs30187

ERAP1 = endoplasmic reticulum aminopeptidase 1.

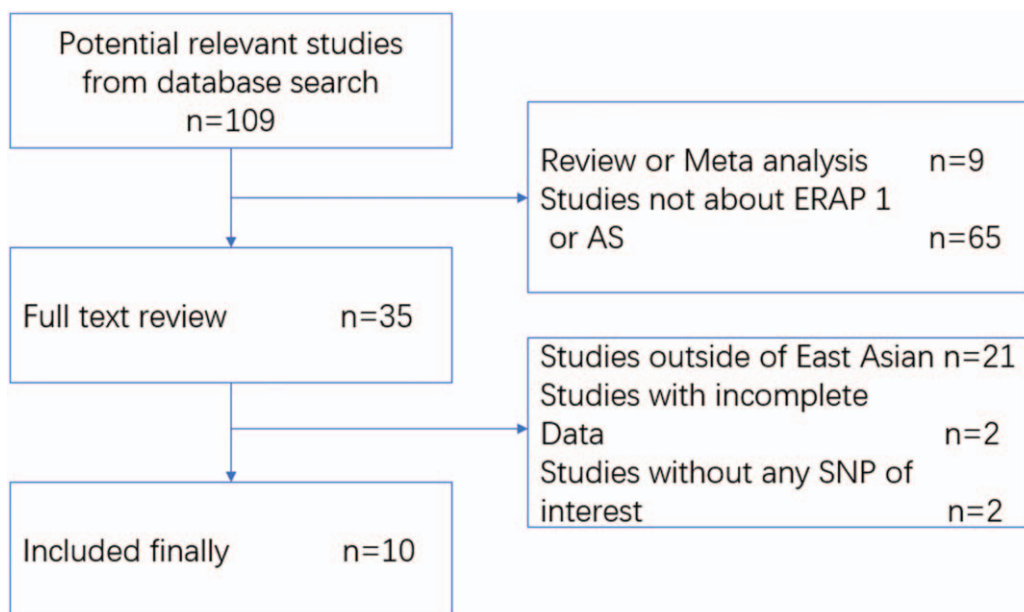


Figure 1. Search strategy flow diagram.

Table 2

Characteristics of the individual studies included in the meta-analysis.

Author	Year	Country	Groups		ERAP1 rs27044									
			AS	Control	AS					Control				
					CC	CG	GG	C	G	CC	CG	GG	C	G
Chan-Bum Choi	2015	Korea	872	403	/	/	/	802	942	/	/	/	458	348
C. Chen	2014	China	368	460	/	/	/	375	361	/	/	/	489	431
Chin-Man Wan	2012	China	796	1149	140	404	252	684	908	270	589	290	1129	1169
Wenliang Wu	2012	China	382	627	178	156	48	512	252	90	252	285	432	822

Author	Year	Country	AS	Control	ERAP1 rs27434									
					AS					Control				
					AA	AG	GG	A	G	AA	AG	GG	A	G
Jian Wang	2015	China	100	100	29	49	22	107	93	21	42	37	84	116
C. Chen	2014	China	368	460	/	/	/	506	230	/	/	/	444	476
SO-YOUNG BANG	2014	Korea	1119	752	295	626	198	1216	1022	167	336	216	670	768
Ya-Feng Wen	2014	China	475	527	/	/	/	513	437	/	/	/	790	264
Z. Zhang	2014	China	602	619	/	/	/	566	638	/	/	/	632	606
Zhiming Lin	2011	China	1837	4231	/	/	/	2021	1653	/	/	/	4485	3977
CHAO LI	2011	China	50	50	/	/	/	51	49	/	/	/	43	57

Author	Year	Country	AS	Control	ERAP1 rs30187									
					AS					Control				
					TT	TC	CC	T	C	TT	TC	CC	T	C
C. Chen	2014	China	368	460	/	/	/	412	324	/	/	/	446	474
Chin-Man Wan	2012	China	797	1150	262	400	135	924	670	319	578	253	1216	1087
Zhiming Lin	2011	China	1837	4231	/	/	/	1470	2204	/	/	/	2792	5670

Author	Year	Country	AS	Control	ERAP1 rs27037									
					With					Without				
					GG	GT	TT	G	T	GG	GT	TT	G	T
SO-YOUNG BANG	2014	Korea	1123	712	403	578	142	1384	862	343	280	89	966	458
Z. Zhang	2014	China	602	619	/	/	/	711	493	/	/	/	755	483
Chin-Man Wan	2012	China	796	1150	205	417	174	827	765	392	561	197	1345	955

ERAP1 = endoplasmic reticulum aminopeptidase 1.

Table 3
Meta-analysis of associations between ERAP1 polymorphisms and AS.

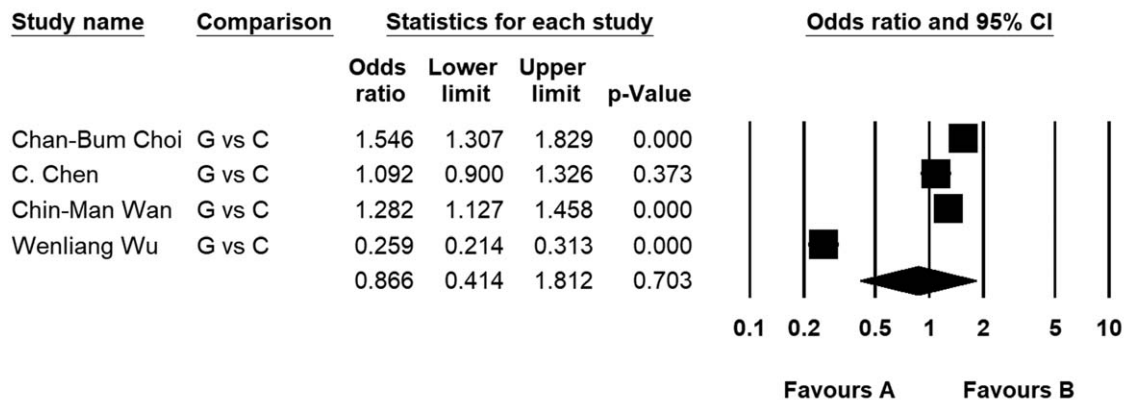
Polymorphisms	Study count	Cases/controls	Effect model	a vs A	
				OR (95% CI)	P* values
rs27044	4	2418/2639	Random	0.866 (0.414, 1.812)	.703
rs27434	7	4551/6739	Random	1.143 (0.788, 1.656)	.481
rs30187	3	3002/5841	Fixed	1.322 (1.240, 10410)	0
rs27037	3	2521/2481	Fixed	1.247 (1.149, 1.353)	0

For convenience, we considered the major allele in the variants as "A" and the minor as "a". AS= Ankylosing spondylitis, CI= confidence interval, ERAP1 = endoplasmic reticulum aminopeptidase 1, OR=odds ratio. * P<.05 was considered as statistical significant.

For rs27044 polymorphism, quantitative synthesis from 4 studies showed no significant difference in the gene allele comparison of G versus C (OR, 0.866; 95% CI, 0.414, 1.812; P=.703) (Fig. 2). Similarly, no significant difference was found

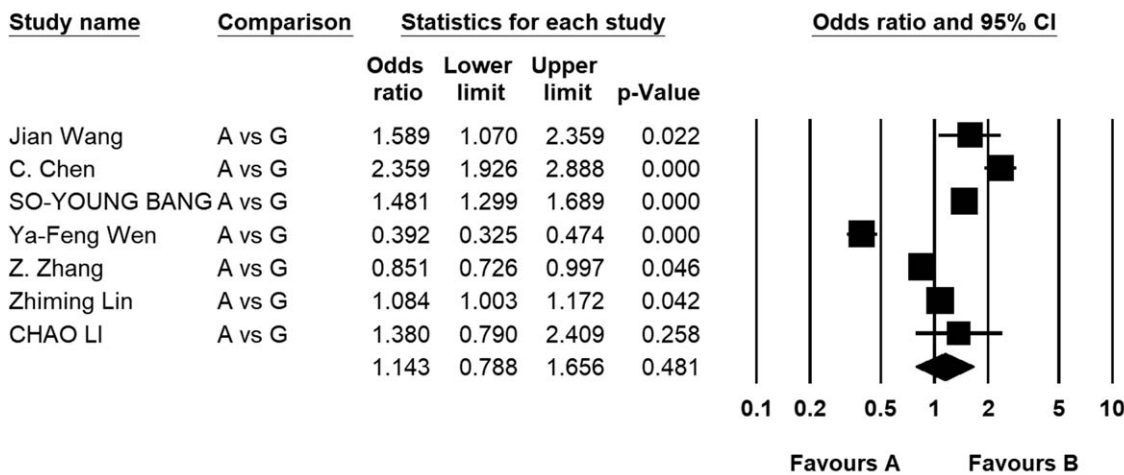
when comparing the allele frequency between A versus G of rs27434 (OR, 1.143; 95% CI, 0.788, 1.656; P=.481) (Fig. 3).

However, for SNPs rs30187 and rs27037 of ERAP1, quantitative synthesis showed significant differences in the



Meta Analysis

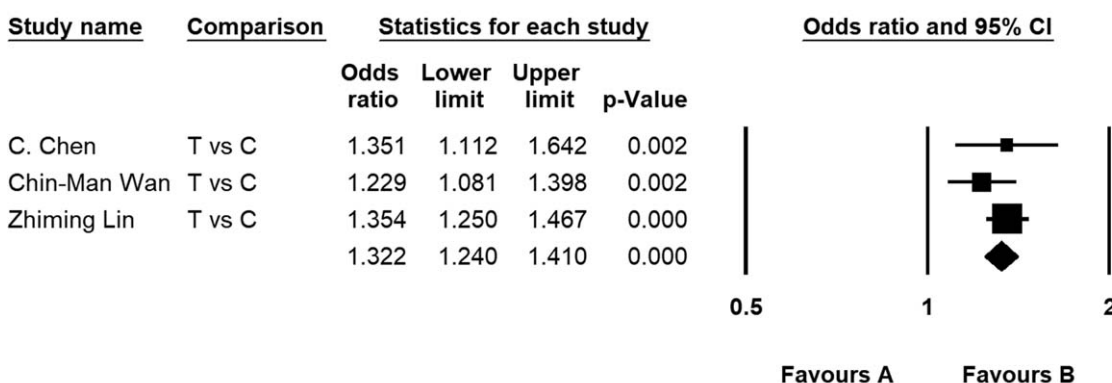
Figure 2. The forest plots present the association between polymorphism of rs27044 and AS susceptibility. Number of included studies: n=4; OR, 0.866; 95% CI, 0.414, 1.812; P=.703). CI=confidence interval, OR=odds ratio.



Meta Analysis

Figure 3. The forest plots present the association between polymorphism of rs27434 and AS susceptibility. Number of included studies: n=7; OR, 1.143; 95% CI, 0.788, 1.656; P=.481). CI=confidence interval, OR=odds ratio.

Meta Analysis



Meta Analysis

Figure 4. The forest plots present the association between polymorphism of rs30187 and AS susceptibility. Number of included studies: n=3; OR, 1.322, 95% CI= 1.240–1.410, *P*<.05). CI=confidence interval, OR=odds ratio.

comparisons of allele frequencies (T vs C, OR, 1.322, 95% CI= 1.240–1.410, *P*<.05, Fig. 4; T vs G, OR, 1.247, 95% CI= 1.149–1.353; *P*<.05, Fig. 5; respectively)

3.3. Publication bias

The Egger test demonstrated no evidence of publication bias for all the 4 SNPs.

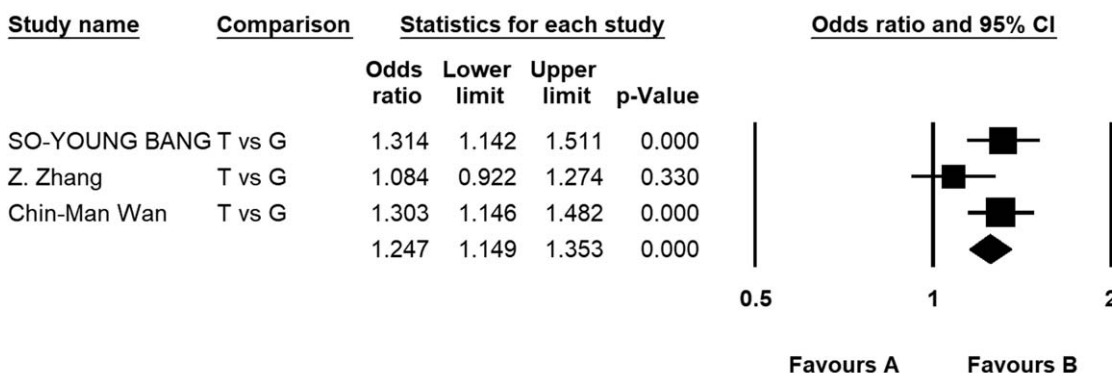
4. Discussion

Controversy results regarding the relationship between SNPs of ERAP1 and AS susceptibility have been reported so far. For example, a previous study analyzing 38 SNPs of ERAP1 demonstrated rs27037 was significantly associated with AS, but rs27434 was not.^[17] However, in another study, the SNP

rs27434 was found significantly associated with increased risk of AS.^[23] The present study aimed to detect whether ERAP1 polymorphisms were associated with AS susceptibility with the method of meta-analysis. The study enrolled 10 papers, 4 matched SNPs of ERAP1 (rs27044, rs27434, rs30187, and rs27037), and a total of 30552 patients (12492 with AS and 18060 for control). Unlike the results found with the European population, no significant difference was found between the AS susceptibility and polymorphisms of rs27044 and rs27434. However, there was a significant association between ERAP1 polymorphisms (rs30187 and rs27037) and AS susceptibility.

ERAP1, also known as aminopeptidase regulator of tumor necrosis factor receptor (TNF) shedding 1 or ERAP1, is thought to be an important part involved in immune response and to be an important non-MHC gene associated with AS.^[11,12] In humans, over-expression of ERAP1 was observed in dendritic cells of AS

Meta Analysis



Meta Analysis

Figure 5. The forest plots present the association between polymorphism of rs27037 and AS susceptibility. Number of included studies: n=3; OR, 1.247, 95% CI= 1.149–1.353; *P*<.05). CI=confidence interval, OR=odds ratio.

patients.^[28] ERAP1 played a central role in processing and trimming of peptides in the endoplasmic reticulum before HLA Class I presentation. It broke down protein antigen precursors and facilitated trimming the peptides fragments into suitable length for peptide/MHC I complex formation.^[29–33] In addition, ERAP1 involved the shedding of pro-inflammatory cytokine receptors for TNF α , IL-1, and IL-6,^[18–20] which might be another way that ERAP1 participated in the pathologies of AS.^[34] Moreover, ERAP1 was found able to enhance the phagocytic activity of macrophages through generating active peptides.^[35]

With regard to the fact that HLA-B27 was not positive in all AS patients and not all HLA-B27 positive subjects developed AS, the function of ERAP1 could not be ignored. More and more evidences suggested the ERAP1 might have synergistic action with HLA-B27. A previous study demonstrated ERAP1 variants was able to affect the stability and processing of HLA-B27.^[31] It was also reported to be able to affect the balance of HLA-B27 between destruction and epitope generation.^[36]

Though the present study explored the relationship between ERAP1 polymorphisms and AS susceptibility in East Asian population successfully, it still had some limitations that could not be ignored. First, the inconsistency of the base line characteristics and the publication bias between the case and control groups might have distorted the meta-analysis. Similarly, a significant heterogeneity was found during the statistical analysis between the studies, and thus a random effect model was applied. However, unlike the previous meta-analyses that included both the Asian and then European, the bias because of the ethnicity was much smaller and was more useful for clinical implication. Second, the possibility of synergistic action to AS susceptibility by ERAP1 haplotypes could not be ignored, but the present meta-analysis was not able to explore it. Third, as mentioned above, the relationship between ERAP1 polymorphisms and HLA-B27 status was also important for investigating, but no available data was provided till now.

In conclusion, the meta-analysis suggested that no significant difference was found between the AS susceptibility and polymorphisms of rs27044 and rs27434. However, there was a significant association between ERAP1 polymorphisms (rs30187 and rs27037) and AS susceptibility.

Author contributions

YQJ and RY performed the study; DZ searched the literatures and performed partial statistical analysis; YJX provided the idea and support the funding.

Data curation: Yi Ren, Dong Zhou, Youjia Xu.

Formal analysis: Yuqing Jiang, Yi Ren, Dong Zhou.

Funding acquisition: Youjia Xu.

Investigation: Yi Ren, Youjia Xu.

Methodology: Yuqing Jiang, Yi Ren, Dong Zhou, Youjia Xu.

Software: Yuqing Jiang, Dong Zhou.

Writing – original draft: Yuqing Jiang, Yi Ren, Youjia Xu.

Writing – review & editing: Yuqing Jiang, Yi Ren, Youjia Xu.

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