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The LMP2 CfoI polymorphism is associated with ankylosing spondylitis (AS) risk but not with acute anterior uveitis (AAU)

A meta-analysis

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Abstract

Background: Ankylosing spondylitis (AS) is one of the most common chronic inflammatory disorders affecting the sacroiliac joints, spine, and peripheral joints. Apart from HLA-B27, the LMP2 gene has been shown to play a role in the pathogenesis of AS as well as AAU in AS. However, genetic associations between LMP2 CfoI polymorphism and AS and AAU were inconclusive. We aimed to investigate the correlation of LMP2 CfoI polymorphism and AS and AAU using meta-analysis.

Methods: An exhaustive search was conducted using the PubMed, Embase, Cochrane Library, and Chinese National Knowledge Infrastructure (CNKI) electronic databases. The strength association was assessed by crude ORs with 95% CI.

Results: Eight eligible records with 449 AS patients and 317 healthy controls were included in the present study. The allelic model of the LMP2 CfoI polymorphism is associated with AS risk (OR = 0.60, 95%CI = [0.32, 1.11], $P = .003$). A stratified analysis based on ethnicity has shown that the allelic model of LMP2 CfoI was associated with AS in the Caucasian population (OR = 0.72, 95%CI = [0.55, 0.93], $P = .01$) but not in the Asian population ($P > .05$). Furthermore, no association was detected between LMP2 CfoI polymorphism and AS complication (AAU).

Conclusion: Our combined results revealed that the allelic model of LMP2 CfoI might be a protective factor for AS in the Caucasian population. Nevertheless, future studies on different ethnicities with larger sample sizes are needed to obtain a more convincing result.

Abbreviations: AAU = acute anterior uveitis, AS = Ankylosing spondylitis, CIs = confidence intervals, CNKI = Chinese National Knowledge Infrastructure, HLA = human leukocyte antigen, LMP = large molecular weight protein, NOS = Newcastle-Ottawa Scale, ORs = odds ratios, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus.

Keywords: acute anterior uveitis, ankylosing spondylitis, LMP2, meta-analysis, single nucleotide polymorphism

1. Introduction

Ankylosing spondylitis (AS), an inflammatory rheumatologic disease, is characterized by inflammation and progressive structural damage to the affected joints, leading to pain and disability.[1–3] A large number of studies have suggested that AS has similar pathogenesis to systemic lupus erythematosus (SLE)[4,5] and rheumatoid arthritis (RA).[6,7] The strong association between AS and human leukocyte antigen (HLA)-B27 has generally been accepted, although it is also clear that only a minority of B27-positive individuals (2%) develop the disease.[8,9] Apart from HLA-B27, a number of other genes, including protein tyrosine phosphatase type 22 (PTPN22),[10] cytotoxic T lymphocyte antigen-4 (CTLA-4),[11] endoplasmic reticulum aminopeptidase 1 (ERAP1),[12] and anthrax toxin receptor 2 (ANTXR2),[13] were identified as susceptible factors for AS. Subsequent work has implicated an important role of polymorphism of the HLA linked proteasomal subunit large molecular weight protein (LMP) 2 and LMP7 in AS.[14–16] LMP genes are polymorphic, and their products constitute two subunits of the proteasome complex involved in the degradation of cytosolic proteins and the generation of antigenic peptides.[17,18] Several studies have attempted to demonstrate the relationship between the polymorphism of LMP genes and the occurrence of AS in various populations[19–21] in both HLA-B27-positive and HLA-B27-negative subjects. Only the study by Maksymowych et al.[22] reported a significant association between LMP2 CfoI polymorphism (rs17587(G > A), Arg60His) and AS susceptibility. Other publications have shown no relationship between the LMP2 CfoI polymorphism and AS risk.[16,19]

Acute anterior uveitis (AAU), which presents unilaterally with sudden onset, is self-limiting and recurrent and represents the specific uveitis phenotype associated with AS.[23,24] Recurrent AAU may lead to glaucoma, cataract development, and significant

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visual loss. AAU occurs in 30% to 40% of patients with AS, suggesting a shared etiology. HLA–B27 is the major risk factor for AAU.[25] However, HLA–B27 could not account for the pathogenesis of AAU cases. Even in HLA-B27-associated AAU, other genetic factors are involved.[26,27] Robinson et al. suggested that ERAP1, interleukin-receptor 23 (IL23R), IL6R, and ANTXR2 may be associated with the development of AAU.[28] Population studies in Caucasian and Mexican individuals with AS suggest that LMP2 gene polymorphism influences the development of AAU.[16,19] However, discrepant findings have been found in one population of Caucasians from England.[22]

Considering the relatively small sample size and contradictory conclusions in individual studies, we attempted to perform a meta-analysis of existing studies to clarify whether the LMP2 CfoI polymorphism was associated with AS risk as well as AAU in AS.

2. Methods

2.1. Patient and public involvement

There was no patient or public involvement in the present meta-analysis. Ethical approval is not required for a meta-analysis.

2.2. Literature search

An exhaustive literature search for studies on the association of LMP2 CfoI polymorphism and AS, as well as AAU in AS, was performed through the PubMed, Embase, Cochrane Library, and Chinese National Knowledge Infrastructure (CNKI) databases. The search keywords were as follows: "low molecular weight polypeptide 2" or "LMP2" and "polymorphism" or "variation" or "single nucleotide polymorphisms" or "SNP" and "ankylosing spondylitis" or "AS" and "acute anterior uveitis" or "AAU". No language was restricted. The last search date was March 1, 2019. All available publications from the database were screened first. Then, the abstracts were checked to verify the titles fulfilled our criteria. Additional potentially relevant literature was identified by searching cross-references within available studies.

2.3. Inclusion and exclusion criteria

Inclusion criteria: Studies were included if they

(1) were case-control designed;
(2) concerned LMP2 CfoI polymorphism and the risk of AS or AAU in AS;
(3) and had enough data for the calculation of odds ratios (ORs) and 95% confidence intervals (CIs).

Exclusion criteria: Studies were included if they

(1) were duplicated;
(2) were not original articles;
(3) were not case-control designed studies;
(4) and if their genotype frequencies were unavailable.

2.4. Data extraction and quality assessment

Two authors (Chen BQ and Sheng XW) independently selected the relevant articles according to the inclusion and exclusion criteria and performed the data extraction process. Information including the first author, published year, ethnicity, age, gender, genotyping methods, number of cases and controls, and frequencies of genotypes were extracted and summarized in Table 1. All discrepancies were settled by discussion. The Newcastle–Ottawa Scale (NOS) was used to evaluate the study quality.[29] The total score ranged from 0 (lowest quality) to 8 (highest quality). A study with a score of 6 or higher was classified as high quality and included in the present study.

2.5. Statistical analysis

The strength of the relationships between the allelic, dominant and recessive models of LMP2 CfoI polymorphism and AS, as well as AAU in AS, were evaluated using crude ORs with 95% CI. Stratified analyses by ethnicity were also performed. A Chi-square-based Cochran Q test and Higgins I-squared statistic were used to assess the between-study heterogeneity of the studies. A P value $> .05$ for the Q test indicated a lack of heterogeneity among studies, so the pooled OR estimate of each study was produced by the fixed-effects model. Otherwise, the random effects model was used. The stability of the results was assessed using sensitivity analysis, which omitted a single study each time to evaluate the influence of each study on the pooled OR. Funnel plots were used to evaluate publication bias by Begg test and Egger test. A t test was performed to determine the significance of the asymmetry. An asymmetric plot suggested possible publication bias ($P \geq .05$ suggests no bias). Statistical analyses were performed with STATA 12.0 software (StataCorp, College Station, TX) and Revman 5 (Cochrane Collaboration, London, UK).

3. Results

3.1. Description of studies

A total of 378 articles were first retrieved from databases. After screening the titles and abstracts, 264 were excluded for being duplications. Thirty-six were excluded for review, letters, or short

Table 1

Characteristics of eligible studies included in the meta-analysis.

Author (year)	Ethnicity	Genotyping methods	Number (case/control)	Gender (M/F)	Age (mean ± SD)	NOS scores
Maksymowych-1 et al 1995	Caucasian/Chinese	PCR-RFLP	193/163	152/41: NA	41.5 ± 11.8/NA	8
Maksymowych-2 et al 1995	Alberta	PCR-RFLP	38/48	NA	44.8 ± 23.5/NA	7
Maksymowych-1 et al 1997	Guadalajara	PCR-RFLP	68/22	68/22:NA	34.4 ± 19.1/NA	8
Maksymowych-2 et al 1997	Mexican	PCR-RFLP	70/10	70/10:NA	24.1 ± 13.4/NA	8
Maksymowych-3 et al 1997	Caucasian	PCR-RFLP	55/45	79/21/NA		7
Maksymowych et al 1999	Caucasian	NA	NA	NA	NA	6
Ding et al 1999	Chinese	PCR-RFLP	87/45	NA	NA	6
Bumey et al 1994	Caucasian	PCR-RFLP	85/55	NA	NA	6

F = female, M = male, NA = not available, NOS = Newcastle-Ottawa Scale, PCR = Polymerase Chain Reaction -restriction fragment length polymorphism, SD = standard deviation.

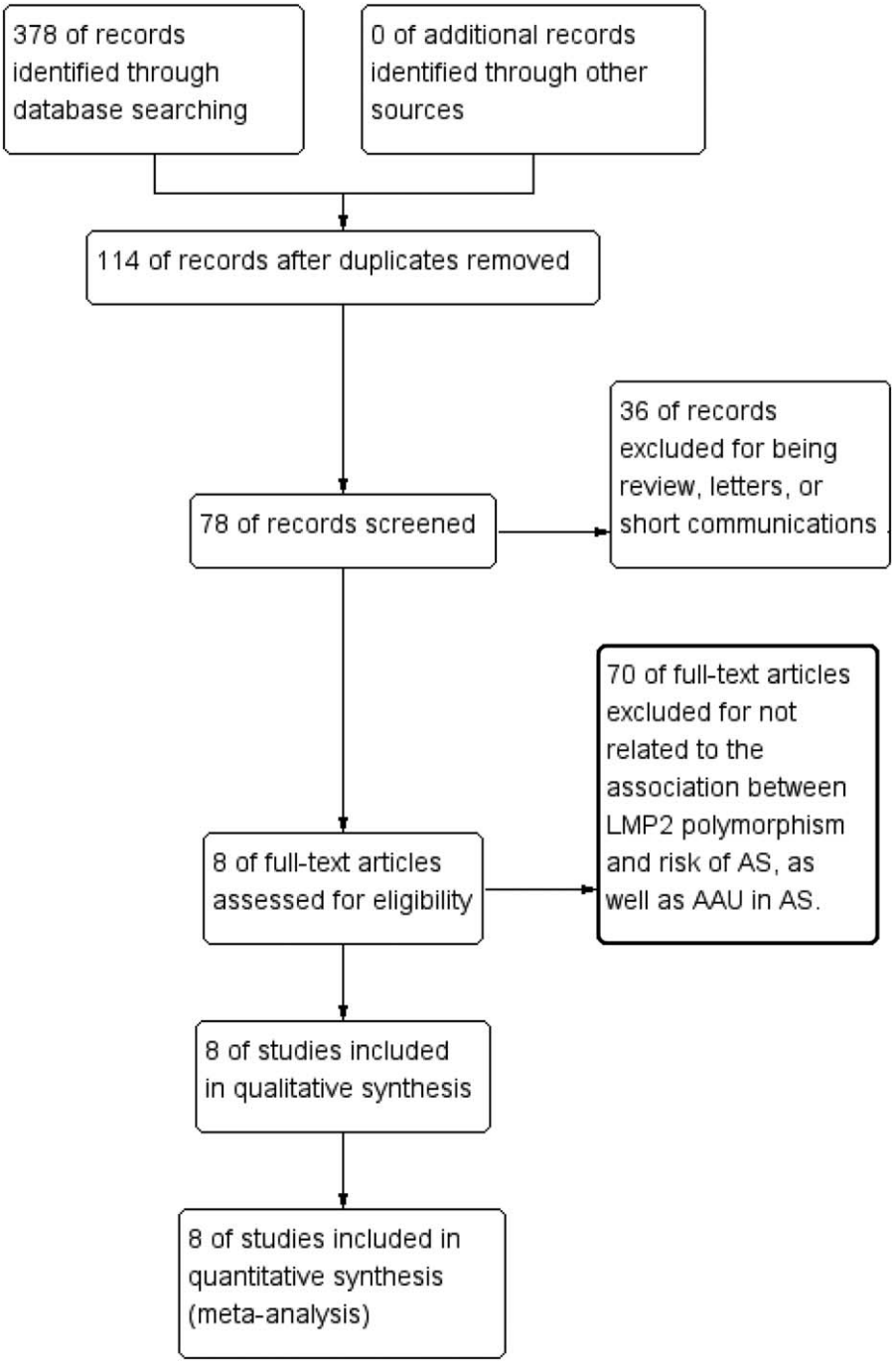


Figure 1. PRISMA flow chart of studies inclusion and exclusion.

communications. In addition, 70 were excluded due to lack of an association between LMP2 polymorphism and the risk of AS and AAU in AS. Finally, 8 eligible records were selected for data extraction and quality assessment[16,19–22,30–32] (Fig. 1). Among these studies, four studies with 449 AS patients and 317 healthy controls referred to the association between LMP2 CfoI polymorphism and AS risk. Seven studies with 215 AS patients (AAU positive) and 405 AS patients (AAU negative) documented the association between LMP2 CfoI polymorphism and AAU in AS. The demographic characteristics of these selected studies enrolled in the present meta-analysis are summarized in Table 1.

3.2. Meta-analyses for LMP2 CfoI polymorphism and AS and AAU complication

A significant association was detected between the allelic model of LMP2 CfoI polymorphism and AS risk (OR = 0.60, 95%CI = [0.32, 1.11], $P = .003$). However, no association was found between dominant and recessive models of LMP2 CfoI and AS ($P > .05$). Furthermore, subgroup analysis stratified by ethnicity has shown that a significant association was detected between the allelic model of LMP2 CfoI and AS in the Caucasian population (OR = 0.72, 95%CI = [0.55, 0.93], $P = .01$). However, no

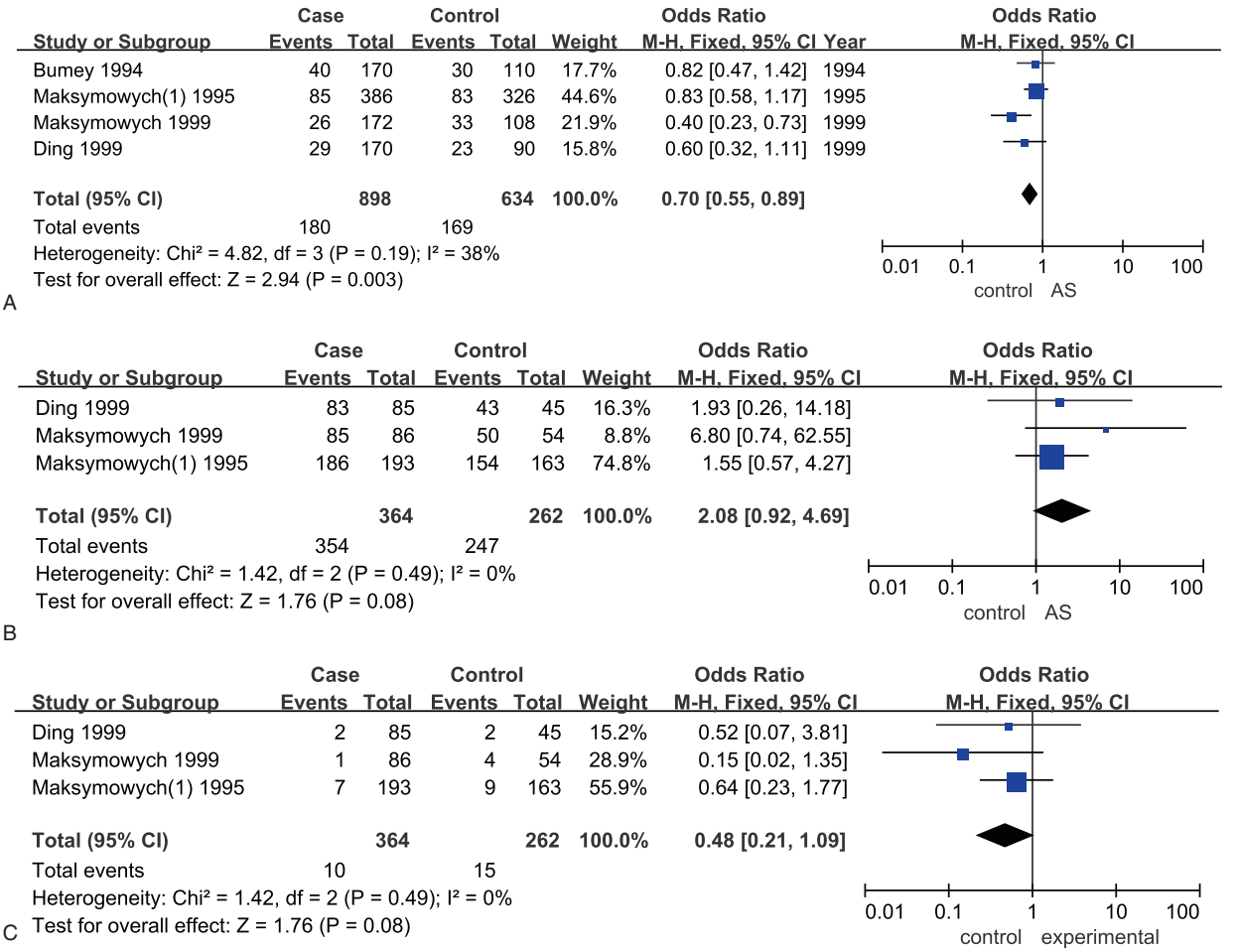


Figure 2. Forest plots of odds ratios for the association between LMP2 CfoI polymorphism and Ankylosing Spondylitis. A: Allelic model; B: Dominant model; C: Recessive model.

association was observed between dominant and recessive models of LMP2 CfoI and AS in Caucasian and Chinese populations ($P > .05$) (Fig. 2, Table 2).

The results on the association between the LMP2 CfoI polymorphism and AAU in AS have shown that none of the genetic models of the LMP2 CfoI polymorphism was associated with the AAU in AS ($P > .05$). Similar results were also detected in the subgroup analysis stratified by ethnicity ($P > .05$) (Fig. 3, Table 2).

3.3. Heterogeneity and publication bias

Significant between-study heterogeneity was detected in analyzing the allelic model of LMP2 CfoI polymorphism in Caucasian individuals ($I^2 = 56$). The significant heterogeneity in this genetic model was primarily documented in Maksymowych et al.[22] Removal of this study from meta-analysis gave 0% ($P > .05$) heterogeneity.

Significant heterogeneities were also detected in the genetic models of LMP2 CfoI polymorphism and AAU in AS (allelic model: $I^2 = 76$, dominant model: $I^2 = 70$, recessive model: $I^2 = 63$). The significant heterogeneities in these comparisons were contributed mainly by Maksymowych et al.[30] Removal of this study from meta-analysis showed 0% to 15% ($P > .05$) heterogeneities.

Sensitivity analysis on the overall risk estimate by excluding one study at a time was confirmed. The ORs were not significantly altered in the LMP2 CfoI allelic analysis (Fig. 4). Begg test and Egger test were used to evaluate publication bias. The p value for Egger linear regression test is shown in Figure 5. The results revealed that there was no obvious publication bias in the overall analysis ($P_{egger} > .05$).

4. Discussion

In the present study, we first investigated the association between LMP2 CfoI polymorphism and AS risk, as well as AAU in AS, using a meta-analysis. A significant association was found between the allelic model of LMP2 CfoI polymorphism and AS. The dominant and recessive models of the LMP2 CfoI polymorphism were not associated with AS. In addition, the LMP2 CfoI polymorphism was not associated with AAU in AS.

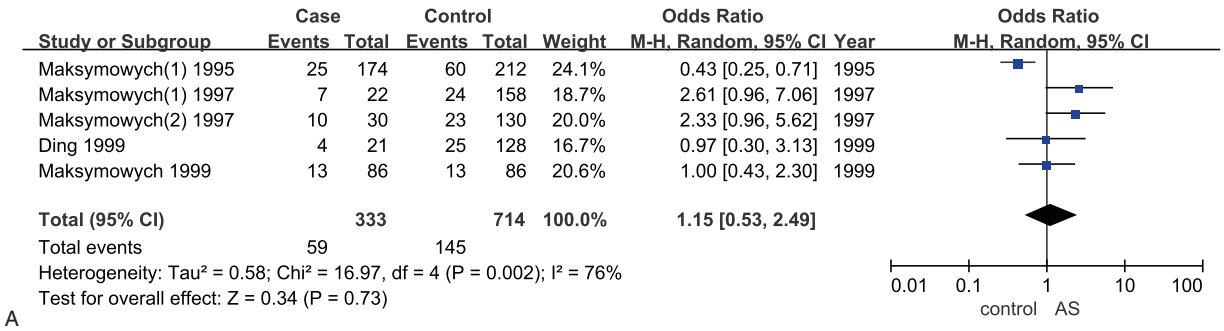
AS is a common inflammatory rheumatic disorder associated with characteristic inflammatory back pain, enthesitis, asymmetrical peripheral oligoarthritis, and specific organ attacks related to AAU.[32–35] In addition to the HLA genes, including HLA-B27, HLA-DR,[36] and HLA-B51,[37] the LMP genes (including LMP2 and LMP7) have been widely reported as genetic predisposing factors for AS.[38] How the polymorphisms of LMP genes could determine the susceptibility to AS and other autoimmune diseases

Table 2

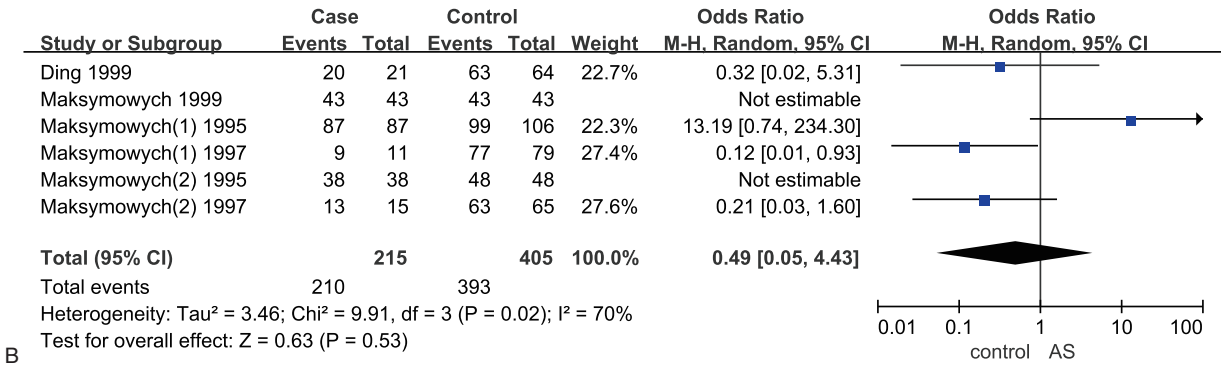
The combined result of the association between LMP2 CfoI polymorphism and AS, as well as AAU in AS.

Polymorphism (Disease)	Genotype	Subgroups	Number of studies	Test of association			Model	Test of heterogeneity	
				OR	95% CI	*P* value		*P* value	I^2 (%)
LMP2-AS	Allele	Total	4	0.70	[0.55, 0.89]	.003	F	.19	38
		Caucasian	3	0.72	[0.55, 0.93]	.01	R	.10	56
		Asian	1	0.60	[0.32, 1.11]	.11	-	-	-
	Dominant	Total	3	2.08	[0.92, 4.69]	.08	F	.49	0
		Caucasian	2	2.11	[0.86, 5.14]	.10	F	.23	30
		Asian	1	1.93	[0.26,14.18]	.52	-	-	-
	Recessive	Total	3	0.48	[0.21, 1.09]	.08	F	.49	0
		Caucasian	2	0.47	[0.19, 1.16]	.10	F	.23	30
		Asian	1	0.52	[0.07, 3.81]	.52	-	-	-
LMP2-AS (AAU)	Allele	Total	5	1.15	[0.53, 2.49]	.73	R	.002	76
		Caucasian	4	1.20	[0.47, 3.05]	.70	R	.0007	82
		Asian	1	0.97	[0.30, 3.13]	.96	-	-	-
	Dominant	Total	6	0.49	[0.05, 4.43]	.53	R	.02	70
		Caucasian	5	0.59	[0.03,11.43]	.73	R	.007	80
		Asian	1	0.32	[0.02, 5.31]	.42	-	-	-
	Recessive	Total	5	1.52	[0.23, 9.99]	.66	R	.03	63
		Caucasian	4	1.22	[0.12,12.92]	.87	R	.01	72
		Asian	1	3.15	[0.19,52.69]	.42	-	-	-

"-" = not available, AAU = acute anterior uveitis, AS = Ankylosing spondylitis, CI = confidence interval, F = fixed, LMP = large molecular weight protein, OR = odd ratio, R = random.



A



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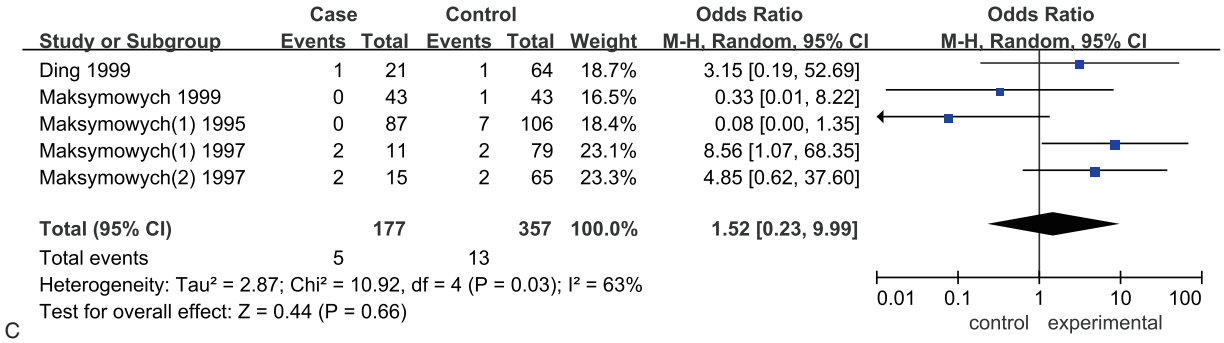


C

Figure 3. Forest plots of odds ratios for the association between LMP2 CfoI polymorphism and acute anterior uveitis. A: Allelic model; B: Dominant model; C: Recessive model.

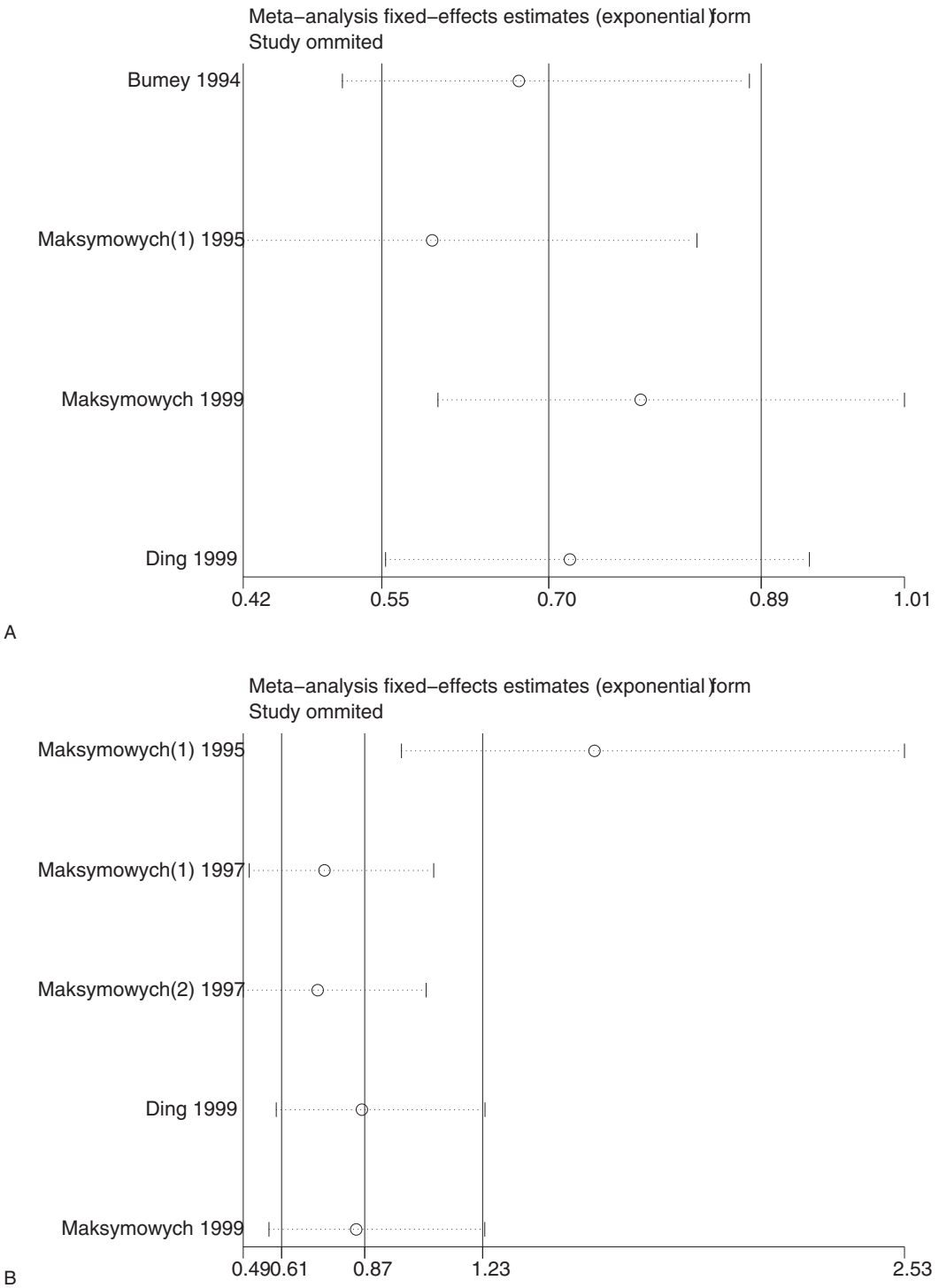
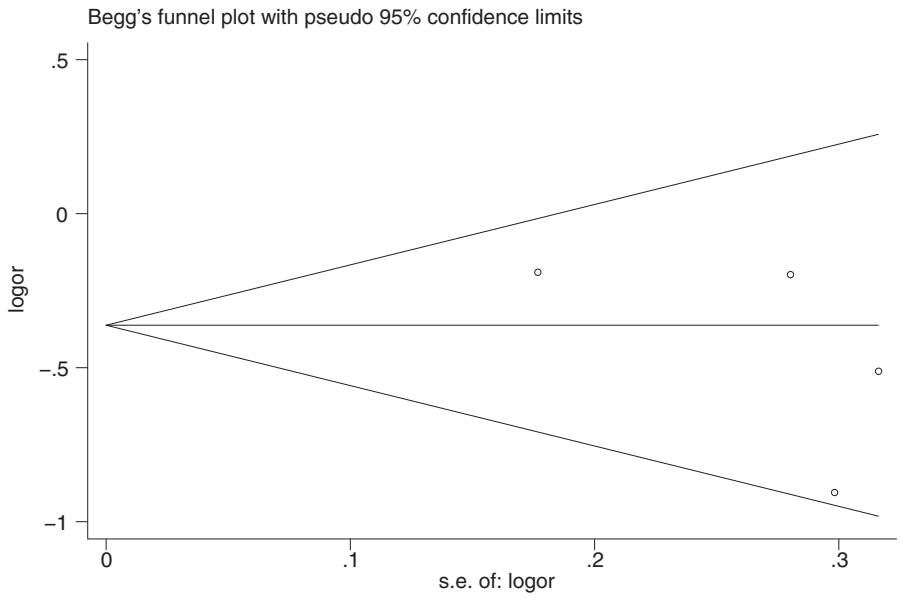


Figure 4. Sensitivity analyses between LMP2 Cfol and Ankylosing Spondylitis, as well as acute anterior uveitis Ankylosing Spondylitis. A: Ankylosing Spondylitis; B: acute anterior uveitis.

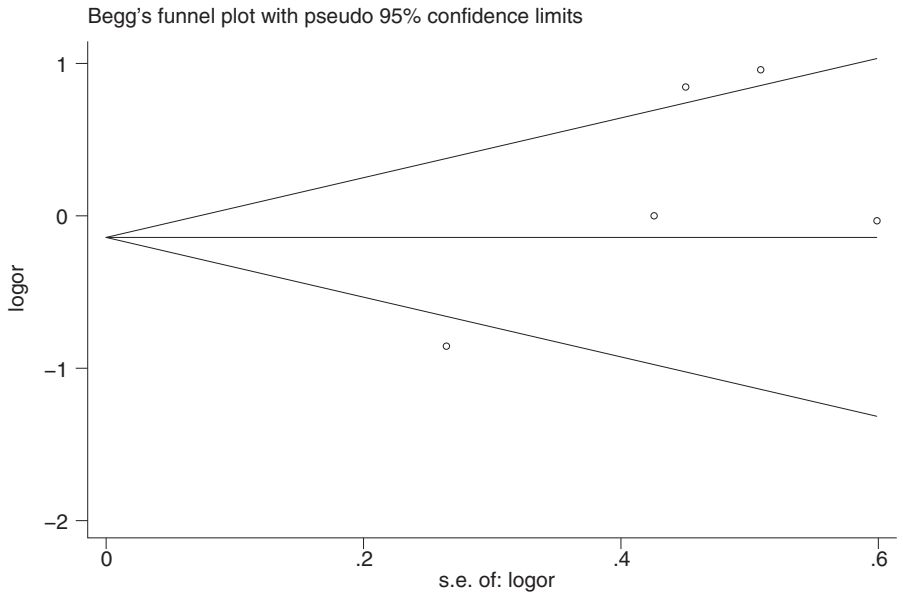
is largely unknown. However, LMP2 and LMP7 are involved in the cytosolic processing of antigens in the class I pathway of antigen presentation.[39] It is possible that polymorphisms in the LMP2 or LMP7 genes may affect the expression of disease in HLA-B27 individuals by influencing the spectrum of peptides available, first by binding to HLA-B27 and then by presenting to autoreactive cytotoxic T cells.[40]

Several variants, including rs1351383, rs17587, and rs2127675, have been associated with the risk of hepatitis C virus infection[41] and nonsmall cell lung cancer.[42] Sequent studies have focused on the association between the functional polymorphism rs17587 and AS risk. It is interesting to note that a substitution in mouse LMP2 (Arg/His40) is identical both in position and identity of the substituted residues observed in



A

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.4838575	.5432614	0.89	0.537	-6.418933	7.386648
bias	-3.872952	2.28868	-1.69	0.340	-32.95339	25.20748



B

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-2.096082	.850914	-2.46	0.091	-4.80407	.6119063
bias	5.119134	2.132304	2.40	0.096	-1.66681	11.90508

Figure 5. Publication bias of literatures for allelic model of LMP2 CfoI was tested by Begg funnel plot and Egger test. A: Ankylosing Spondylitis; B: acute anterior uveitis.

human LMP2 and that preliminary findings suggest that this structural polymorphism may have functional consequences.[43] Our meta-analysis found an association between the allele of LMP2 CofI and AS, which was consistent with a previous result found by Maksymowych.[22] However, other individual publications failed to find an association between LMP2 CofI and AS risk, which may be due to the limited sample size in each study. In addition, subgroup analysis has shown that the allele of LMP2 CofI was associated with AS risk in Caucasians but not in Asians, which may indicate the effect of genetic background in different populations. In addition, a relatively small number of studies and subjects in the Asian population may also influence the results.

Thus, further studies with larger numbers of patients are needed to confirm this.

AAU is the most common form of immune-mediated uveitis, which was suggested to be strongly associated with HLA-B27 and AS and other seronegative spondyloarthropathies (SpA).[44] Recent publications have shown that AAU has been associated with the early onset of SpA in HLA-B27-positive patients.[45] Maksymowych et al. suggested that the frequency of LMP2 gene polymorphism was significantly different in AS patients with and without a history of AAU.[31] At the same time, LMP2 gene polymorphism was correlated with the incidence of peripheral joints of AS. Studies have reported that there were significant differences between the normal population and patients with AS alone and those with AAU history ($P < .05$) but also between the normal population and patients with AS alone and those with AAU history ($P < .05$), and there was no significant difference between the latter two groups, indicating that there was a significant increase in LMP2 AA genotype in patients with AAU alone.[46] Therefore, the increased frequency of the AA genotype or allele A of the LMP2 gene is not only correlated with the occurrence of AS AAU but also correlated with the occurrence of pure AAU. Homozygous AA was associated with the incidence of AS +AAU or pure AAU, but the cause was not clear. According to previous data, the LMP2 AA genotype may have linkage imbalance with HLA-B27, which may independently play a role in the pathogenesis of AAU.[28] In our meta-analysis, no association was found between all the genetic models of LMP CofI polymorphism, which was in contrast with previous work conducted by Maksymowych et al.[16,19] Based on the larger sample size in the present meta-analysis, we may conclude that the LMP CofI polymorphism might not be a susceptible factor for AAU.

Arginine is the 40th amino acid on the peptide chain encoded by the LMP2 A allele, while histidine is the amino acid at the LMP2 G allele. This difference may change the hydrolysis site of the proteasome and the processing mode of the antigen, resulting in an iris peptide segment bound to HLA-B27, which induces the autoimmune response of T cells. Histidine on the peptide chain may be processed to produce a competitive high-affinity peptide that triggers the tolerance of the autoimmune T cells and thus does not produce an immune response.[47,48] This mechanism requires further study. In the present meta-analysis, no association was observed between the LMP2 polymorphism and AAU in AS, which suggests that this polymorphism was not the susceptible factor for AAU in AS. To confirm this result, a larger number of studies with more subjects is necessary in the future.

Limitations should be considered. First, the number of published studies was not enough for a comprehensive analysis. Therefore, our analysis should be interpreted with caution. Second, heterogeneity among studies existed, which may be derived from the study design, the source of controls, the differences in genetic background, and the environment presented among different countries. Third, only Asian and Caucasian populations were involved in the present study. Other ethnicities, such as African, were not included. Since gene variations might be different in different ethnicities, future studies on various ethnicities are needed.

Author contributions

Data curation: Bingqian Chen, Xiaowen Sheng.
Funding acquisition: Yuqin Peng.
Investigation: Yuqin Peng.
Methodology: Xiaowen Sheng.
Software: Bingqian Chen, Xiaowen Sheng.
Visualization: Bingqian Chen, Xiaowen Sheng.
Writing – original draft: Yufeng Qian.
Writing – review & editing: Yufeng Qian, Yuqin Peng.

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