Association between HLA-B*27 polymorphisms and ankylosing spondylitis in Han populations: a meta-analysis

L. Zhang[1*], J.L. Liu[2*], Y.J. Zhang[3], H. Wang[1]

[1]*Department of Orthopaedic Surgery, Shengjing Affiliated Hospital, China Medical University, Shenyang, China;* [2]*Department of Oncology, the Fourth Affiliated Hospital, China Medical University, Shenyang, China;* [3]*Department of General Surgery, the First Affiliated Hospital, China Medical University, Shenyang, China.*

Abstract

Objective

*The aim of this study was to determine whether the HLA-B*27 polymorphisms confer susceptibility to ankylosing spondylitis (AS) in Han populations by conducting a meta-analysis.*

Methods

*Publications addressing the association between the HLA-B*27 polymorphisms and susceptibility to AS in Han populations were selected from the MEDLINE, EMBASE and CBMdisc databases. Data was extracted from the studies by 2 independent reviewers. The meta-analyses were performed by Review Manager Version 5.0.24 and STATA Version 9.2 software. From these data, the odds ratio (OR) with 95% confidence interval (95%CI) was calculated.*

Results

*Fourteen studies with a total of 1900 AS cases and 831 healthy controls were retrieved. Meta-analysis results showed a positive association between B*2704 and susceptibility to AS in Han population (OR=2.20, 95%CI=1.60-3.02, p<0.00001). However, B*2705, B*2706 and B*2707 showed negative associations with susceptibility to AS in Han populations (OR=0.59, 95%CI=0.43–0.81, p=0.001; OR=0.13, 95%CI=0.05–0.37, p=0.0001; OR=0.23, 95%CI=0.11–0.46, p<0.0001; respectively). In subgroup analysis, there was a positive association between B*2704 and susceptibility to AS in the southerners of China, but not in the northerners. Negative associations between B*2705, B*2706 and susceptibility to AS were determined in the southerners of China, but also not in the northerners. Results showed obviously negative associations between B*2707 and susceptibility to AS both in the southerners and northerners of China.*

Conclusion

*This meta-analysis confirms that B*2704 might be a potential risk factor and B*2705, B*2706, B*2707 might be potential protective factors for AS in Han populations, especially in the southerners of China.*

Key words

human leukocyte antigen-B27, polymorphism, ankylosing spondylitis, meta-analysis

Lei Zhang, MMed
Jia-Li Liu, MMed
Yi-Jie Zhang, MMed
Huan Wang, MD, Professor

**L. Zhang and J.L. Liu contributed equally to the manuscript and are co-first authors.*

Please address correspondence and reprint requests to:
Prof. Huan Wang, MD,
Department of Orthopaedic Surgery,
Shengjing Affiliated Hospital,
China Medical University,
Shenyang 110004, China.
E-mail: spinewh@sj-hospital.org

Received on September 25, 2010; accepted in revised form on December 15, 2010.

Competing interests: none declared.

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that can affect the axial skeleton, causing characteristic inflammatory back pain due to sacroiliitis and spondylitis, which can also lead to structural and functional impairments and a decrease in quality of life (1). AS is a complex kind of spondyloarthropathies, which is the product of an interaction between environmental triggers, susceptibility and severity genes, gender, age and ethnic background (2). However, the cause of AS is still unknown. Ongoing studies have produced evidence supporting HLA-B*27 has a strong association with AS and related spondyloarthropathies, which plays an important role in disease pathogenesis (3). The HLA-B*27 shows remarkable polymorphisms, with a gradually increasing number of alleles. Up to now, there are 62 subtypes of HLA-B*27 based on amino acid sequence differences according to data published in the international ImMunoGeneTics (IMGT) database (4). There are considerable racial and ethnic differences in the prevalence of HLA-B*27 worldwide. HLA-B*2705 is the most common subtype in Eurasian, Amerindians and Africans, while B*2704 is the predominant subtype in Asian populations, particularly in China (5-7). Liu *et al*. (8) and Mou *et al*. (9) have confirmed that HLA-B*2704 has a stronger association to AS than HLA-B*2705 in Han populations. The variety and distinctness of ethnic groups can show not only new subtypes, subtype frequencies, and disease associations, as illustrated in the two reports in this issue, but also a host of presumably distinct genetic features whose relationship to AS remains to be explored (7). In addition, the confluence of genetic population analyses and molecular studies on the HLA-B*27 subtypes prevalent in Asian populations especially in Han populations has much potential to significantly improve our understanding of the pathogenetic role of HLA–B27 (7, 10).

Meta-analysis can be a resourceful tool in detecting an association that could otherwise remain masked in the sample size studies, especially in those evaluating rare allele frequency polymorphisms (11). The use of the meta-analysis has recently become an important part of genetic research mainly to reconcile previously conducted studies that gave inconsistent results. The aim of this meta-analysis was to investigate the association between HLA-B*27 polymorphisms and susceptibility to AS in Han populations by conducting a meta-analysis from all eligible case-control studies published to date.

Materials and methods

Identification of eligible studies and data extraction

MEDLINE, EMBASE and CBMdisc databases searches were performed to retrieve papers linking HLA-B*27 polymorphisms and susceptibility to AS in Han populations available by September 2010 without language restrictions, using the following query: ["HLA-B*27 antigen" or "HLA-B*27" or "antigen, HLA-B*27" or "human leukocyte antigen B*27" (Mesh)] and ["polymorphism, single nucleotide" or "polymorphism, genetic" (Mesh)] and ["spondylitis, ankylosing" or "ankylosing spondylarthritis" (Mesh)]. The reference lists of major textbooks, review articles, and included articles were identified through manual searches to find other potentially eligible studies. To be eligible for inclusion in this meta-analysis, the following criteria were established: case-control study that addressed B*27-positive AS cases and healthy controls; patients with clinically diagnosed ankylosing spondylitis according to the modified New York criteria (13); case-control study which evaluated the association of HLA-B*27 polymorphisms and susceptibility to AS in Han populations; the study must have included sufficient genotype data for extraction; and healthy controls were in Hardy-Weinberg equilibrium (HWE). Studies were excluded when they were: not case-control studies about HLA-B*27 polymorphisms and susceptibility to AS in Han populations; based on incomplete raw data and no usable data were reported; the study contained overlapping data; the study was a family-based design; and healthy controls

were not in HWE. Using a standardised form, data from published studies were extracted independently by two reviewers (*Y.J. Zhang* and *H. Wang*) to populate the necessary information. From each of the included articles the following information was extracted: first author, year of publication, race, region, language, study design, sample, source of cases and controls, number of cases and controls, histopathological confirmations, detection methods, polymorphisms of gene and frequency and evidence of HWE in controls.

Quality assessment of included studies

The quality of papers was also independently assessed by two reviewers (*L. Zhang* and *J.L. Liu*) based on the STROBE quality score systems (13). 40 items relevant to the quality appraisal were used for assessment in this meta-analysis, scores ranged from 0 to 40 (Table I). Any discrepancies between the two reviewers were resolved by discussion and consultation with a third reviewer (*H. Wang*).

Evaluation of publication bias

Funnel plots are often used to detect publication bias. However, due to the limitations of funnel plotting, which requires a range of studies with varying sizes and subjective judgments, we evaluated publication bias using Egger's linear regression test (14), which measures funnel plot asymmetry using a natural logarithm scale of odds ratio (OR). Publication bias was considered significant when the *p*-value was less than 0.1.

Evaluation of statistical associations

Individual and pooled odds ratio (OR) and 95% confidence interval (95%CI) were calculated for each study using *Review Manager Version 5.0.24* (provided by *The Cochrane Collaboration*, available at: http://www.cc–ims.net/revman) and *STATA Version 9.2* software. Between-study variations and heterogeneities were estimated using Cochran's Q-statistic (15, 16). We also quantified the effect of heterogeneity by using a recently developed measure, *i.e.* $I^2=100\%\times(Q-df)/Q$. I^2 ranges between 0 and 100% and represents the

Table I. Scale for quality assessment based on the STROBE quality score systems.

Criteria items	Score 0 to 40
Title and Abstract	
Title and Abstract: Indicate the study's design (case-control or cohort study) in the title or the abstract	☐ 0 ☐ 1
Abstract: Provide an informative and balanced summary of the study	☐ 0 ☐ 1
Introduction: Explain the scientific background and rationale for the investigation	☐ 0 ☐ 1
Introduction: State specific objectives, including any prespecified hypotheses	☐ 0 ☐ 1
Methods	
Study Design: Present key elements of study design	☐ 0 ☐ 1
Setting: Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	☐ 0 ☐ 1
Participants: Give the eligibility criteria of case	☐ 0 ☐ 1
Participants: Give the sources and methods of case ascertainment and control selection	☐ 0 ☐ 1
Participants: Give matching criteria and the number of controls	☐ 0 ☐ 1
Variables: Clearly define all outcomes, exposures, predictors, potential confounders, effect modifiers	☐ 0 ☐ 1
Data sources/ Measurement: Give sources of data and details of methods of assessment	☐ 0 ☐ 1
Data sources/ Measurement: Describe comparability of assessment methods	☐ 0 ☐ 1
Bias: Describe any efforts to address potential sources of bias	☐ 0 ☐ 1
Study size: Explain and describe the estimation of the study size	☐ 0 ☐ 1
Quantitative variables: Explain how quantitative variables were handled in the analyses	☐ 0 ☐ 1
Quantitative variables: Give group included criteria in the analyses	☐ 0 ☐ 1
Statistical methods: Describe all statistical methods, including those used to control for confounding	☐ 0 ☐ 1
Statistical methods: Describe any methods used to examine subgroups and interactions	☐ 0 ☐ 1
Statistical methods: Explain how missing data were addressed	☐ 0 ☐ 1
Statistical methods: Explain how matching of cases and controls was addressed	☐ 0 ☐ 1
Statistical methods: Describe any sensitivity analyses	☐ 0 ☐ 1
Hardy-Weinberg equilibrium: HWE was assessed	☐ 0 ☐ 1
Hardy-Weinberg equilibrium: HWE of control group was assessed	☐ 0 ☐ 1
Results	
Participants: Report the numbers of individuals at each stage of the study, such as numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up and analysed	☐ 0 ☐ 1
Participants: Give reasons for non-participation at each stage	☐ 0 ☐ 1
Participants: Give a flow diagram	☐ 0 ☐ 1
Descriptive data: Give characteristics of study participants (*e.g.* demographic, clinical diagnosis, race)	☐ 0 ☐ 1
Descriptive data: Indicate the number of participants with missing data	☐ 0 ☐ 1
Outcome data: Report numbers in each exposure category, or summary measures of exposure	☐ 0 ☐ 1
Main results: Give unadjusted estimates and confounder-adjusted estimates and their 95% confidence intervals	☐ 0 ☐ 1
Main results: Make clear which confounders were adjusted for and why they were included	☐ 0 ☐ 1
Main results: If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	☐ 0 ☐ 1
Other analyses: Report other analyses such subgroups, interactions, and sensitivity analyses	☐ 0 ☐ 1
Discussion	
Key results: Summarise key results with reference to study objectives	☐ 0 ☐ 1
Main results: Report category boundaries when continuous variables were categorised	☐ 0 ☐ 1
Limitations: Discuss both direction and magnitude of any potential bias	☐ 0 ☐ 1
Interpretation: Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	☐ 0 ☐ 1
Generalisability: Discuss the generalisability (external validity) of the study results	☐ 0 ☐ 1
Other	
Funding: Give the source of funding and the role of the funders for the present study	☐ 0 ☐ 1

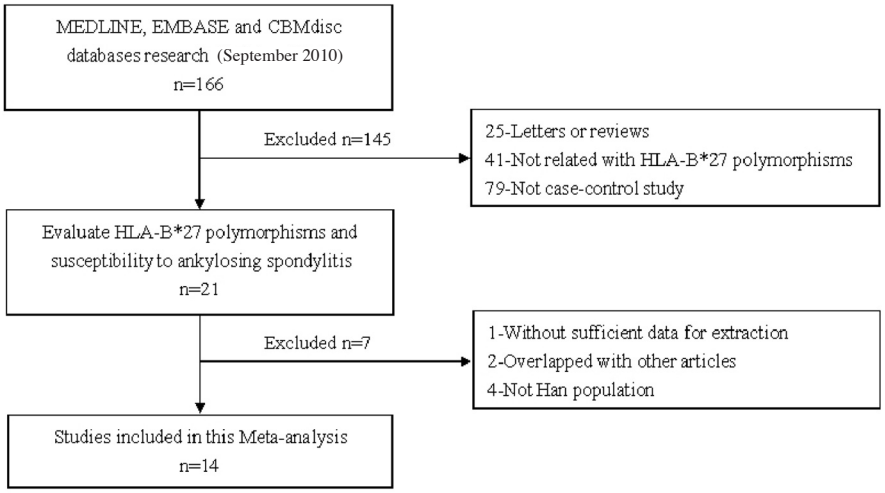

Fig. 1. Flow chart showing study selection procedure. Fourteen case-control studies were included in this meta-analysis.

proportion of inter–study variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50 and 75% were defined as low, moderate and high estimates, respectively. When a significant Q-test ($p<0.10$) or $I^2>50\%$ indicated heterogeneity across studies, the random effects model was used for meta-analysis, or else the fixed effects model was used. We tested whether genotype frequencies of controls were in HWE using the chi–square test. Subgroup analysis was used to explore and to explain the diversity among the results of different studies. Sensitivity analysis was mainly performed by sequential omission of individual studies. All the *p*-values were two-sided. To ensure the reliability and the accuracy of the results, two reviewers (*L. Zhang* and *J.L. Liu*) inputted the data in the statistic software programs independently and obtained the same results.

Results

Studies included in the meta-analysis

The search strategy retrieved 166 potentially relevant studies (106 in MEDLINE, 30 in EMBASE, 30 in CBMdisc). According to the inclusion criteria, 14 studies were included in this meta-analysis (8-9, 17-28) (including 6 in English and 8 in Chinese) and 152 studies were excluded. The flow chart of study selection is summarised in Figure 1. These 14 case-control studies selected included a total of 1900 AS cases and 831 healthy controls. All studies were case-control studies which evaluated the association of HLA-B*27 polymorphisms and susceptibility to AS in Han populations. The publishing year of the included studies ranged from 2002 to 2010. All patients fulfilled the 1984 modified New York criteria for the diagnosis of AS. The family histories of all controls were negative for AS and related diseases. The source of controls in two studies were hospital-based and twelve studies were population-based. Fourteen HLA-B*27 polymorphisms were addressed in 14 studies: HLA-B*2702~B*2708, B*2710~B*2713, B*2715, B*2720 and B*2724. The most common polymorphisms were B*2704 and B*2705. HWE test was performed on genotype distribution of the controls in all included studies, all of them showed in HWE ($p>0.05$). The characteristics and methodological quality of the included studies are summarised in Table Π.

Main results, subgroup and sensitivity analysis

A summary of the meta-analysis findings of the association between HLA-B*27 polymorphisms and susceptibility to AS in Han populations is provided in Table Ш. Meta-analysis results iden-

Table Π. Characteristics of individual studies included in meta-analysis.

Author (Ref.)	Year	Region	Language	Source of cases	Source of controls	Detection methods	Number of patients AS cases	Number of patients Controls	HLA-B*27 polymorphisms	Quality score
Chou *et al*. (15)	2002	Taiwan	English	HB	HB	PCR-SSP	82	47	B*2704, B*2705	27
Cui *et al*. (16)	2003	Hebei	Chinese	HB	PB	PCR-SSP	58	16	B*2703~B*2708, B*2712, B*2713	24
Sun *et al*. (17)	2006	Liaoning	Chinese	HB	PB	PCR-SSP	28	12	B*2702, B*2704, B*2705, B*2710	19
Ma *et al*. (18)	2006	Hunan	English	HB	PB	PCR-SSP	111	18	B*2704~B*2707, B*2724	23
Xu *et al*. (19)	2007	Beijing	Chinese	HB	PB	PCR-SSP	118	150	B*2704~B*2707	27
Chen-1 *et al*. (20)	2007	Guangxi	Chinese	HB	PB	PCR-SSP	59	24	B*2704, B*2705	24
Chen-2 *et al*. (21)	2007	Fujian	Chinese	HB	PB	PCR-SSP	108	132	B*2703~B*2707, B*2711, B*2720	24
Hou *et al*. (22)	2007	Taiwan	English	HB	HB	PCR-SSP	314	71	B*2704~B*2707	28
Yu *et al*. (23)	2006	Jiangsu	Chinese	HB	PB	PCR-SSP	160	50	B*2702~B*2707, B*2711	24
Yu *et al*. (24)	2007	Shandong	Chinese	HB	PB	PCR-SSP	59	1	B*2704, B*2705, B*2711	17
Liu *et al*. (25)	2009	Shanghai	English	HB	PB	PCR-SSP	130	61	B*2704, B*2705, B*2710	30
Zhou *et al*. (26)	2009	Jiangsu	Chinese	HB	PB	PCR-SSP	48	30	B*2702, B*2704, B*2705, B*2707	17
Mou *et al*. (27)	2010	Guangdong	English	HB	PB	PCR-SSP	453	74	B*2702~B*2707, B*2715	30
Liu *et al*. (28)	2010	Hubei	English	HB	HB	PCR-SSP	172	145	B*2702~B*2706, B*2713	30

Ref: references; AS: ankylosing spondylitis; HLA-B*27: human leukocyte antigen B*27; HB: hospital-based; PB: population-based; PCR-SSP: polymerase chain reaction-sequence specific primer.

Table III. Meta-analysis of the associaton between HLA–B*27 polymorphisms and AS.

Polymorphisms	Eligible studies	AS cases n/N	Controls n/N	OR (95%CI)	*p*-value	Heterogeneity test	Effect model
B*2702	5	10/861	4/311	0.93 (0.32-2.76)	0.90	p=0.94, I^2=0%	Fixed
Southerner	4	8/833	4/299	0.78 (0.24-2.55)	0.69	p=0.95, I^2=0%	
Northerner	1	2/28	0/12	2.36 (0.11-52.88)	0.59	–	
B*2703	4	12/893	17/401	0.55 (0.27–1.13)	0.10	p=0.29, I^2=21%	Fixed
B*2704	14	1523/1900	503/831	2.20 (1.60–3.02)	<0.00001	p=0.02, I^2=49%	Random
Southerner	10	1374/1637	433/652	2.25 (1.66–3.04)	<0.00001	p=0.13, I^2=35%	
Northerner	4	149/263	70/179	1.99 (0.44–8.99)	0.37	p=0.008, I^2=74%	
B*2705	14	331/1900	242/831	0.59 (0.43–0.81)	0.001	p=0.05, I^2=43%	Random
Southerner	10	222/1637	156/652	0.57 (0.38–0.85)	0.006	p=0.02, I^2=54%	
Northerner	4	109/263	86/179	0.67 (0.44–1.03)	0.07	p=0.52, I^2=0%	
B*2706	7	3/1436	18/640	0.13 (0.05–0.37)	0.0001	p=0.87, I^2=0%	Fixed
Southerner	6	2/1318	15/490	0.10 (0.03–0.31)	<0.0001	p=0.93, I^2=0%	
Northerner	1	1/118	3/150	0.42 (0.04–4.08)	0.45	–	
B*2707	8	9/1370	31/541	0.23 (0.11–0.46)	<0.0001	p=0.21, I^2=28%	Fixed
Southerner	6	8/1194	18/375	0.30 (0.14–0.65)	0.002	p=0.19, I^2=32%	
Northerner	2	1/176	13/166	0.09 (0.02–0.55)	0.009	p=0.15, I^2=52%	
B*2708	1	4/58	0/16	2.72 (0.14–53.28)	0.51	–	Fixed
B*2710	2	2/158	2/73	0.45 (0.08–2.68)	0.38	p=0.39, I^2=0%	Fixed
Southerner	1	1/130	2/61	0.23 (0.02–2.57)	0.23	–	
Northerner	1	1/28	0/12	1.36 (0.05–35.87)	0.85	–	
B*2711	3	5/324	3/181	0.76 (0.18–3.18)	0.70	p=0.40, I^2=0%	Fixed
Southerner	2	4/265	3/180	0.96 (0.20–4.51)	0.95	p=0.66, I^2=0%	
Northerner	1	1/59	0/1	0.08 (0.00–2.78)	0.16	–	
B*2712	1	0/58	1/16	0.09 (0.00–2.28)	0.14	–	Fixed
B*2713	2	7/230	0/161	3.41 (0.39–29.47)	0.26	p=0.83, I^2=0%	Fixed
Southerner	1	1/172	0/145	2.55 (0.10–62.96)	0.57	–	
Northerner	1	6/58	0/16	4.09 (0.22–76.45)	0.35	–	
B*2715	2	7/561	0/206	2.69 (0.30–23.91)	0.37	p=0.81, I^2=0%	Fixed
B*2720	1	0/108	1/132	0.40 (0.02–10.02)	0.58	–	Fixed
B*2724	1	1/111	0/18	0.50 (0.02–12.80)	0.68	–	Fixed

AS: ankylosing spondylitis; OR: odds ratios; 95%CI: 95% confidence interval.

tified a positive association between B*2704 and susceptibility to AS in Han populations (OR_{B*2704} = 2.20, 95%CI = 1.60-3.02, p<0.00001). There were negative associations of B*2705, B*2706 and B*2707 with susceptibility to AS in Han populations (OR_{B*2705} = 0.59, 95%CI = 0.43–0.81, p=0.001; OR_{B*2706} = 0.13, 95%CI = 0.05–0.37, p<0.0001; OR_{B*2707} = 0.23, 95%CI = 0.11–0.46, p<0.0001; respectively) (Fig. 2). Nevertheless, B*2702, B*2703, B*2708, B*2710, B*2711, B*2712, B*2713, B*2715, B*2720 and B*2724 showed no association with susceptibility to AS in Han populations (OR_{B*2702} = 0.93, 95%CI = 0.32–2.76, p=0.90; OR_{B*2703} = 0.55, 95%CI = 0.27–1.13, p=0.10; OR_{B*2708} = 2.72, 95%CI = 0.14–53.28, p=0.51; OR_{B*2710} = 0.45, 95%CI = 0.08–2.68, p=0.38; OR_{B*2711} = 0.76, 95%CI = 0.18–3.18, p=0.70; OR_{B*2712} = 0.09, 95%CI = 0.00–2.28, p=0.14; OR_{B*2713} = 3.14, 95%CI = 0.39–29.47, p=0.26; OR_{B*2715} = 2.69, 95%CI = 0.30–23.91, p=0.37; OR_{B*2720} = 0.40, 95%CI = 0.02–10.02, p=0.58; OR_{B*2724} = 0.50, 95%CI = 0.02–12.80, p=0.68; respectively).

In the subgroup analysis based on geographic distribution, subjects of all included studies were divided into the southerners and northerners of China due to significantly geographic variation in Han populations. Results of subgroup analysis showed that there was a positive association between B*2704 and susceptibility to AS in the southerners of China (OR=2.25, 95%CI=1.66–3.04, p<0.00001), but not in the northerners (OR = 1.99, 95%CI = 0.44–8.99, p=0.37). Negative associations between B*2705, B*2706 and susceptibility to AS were determined in the southerners of China (OR = 0.57, 95%CI = 0.38–0.85, p=0.006; OR = 0.10, 95%CI = 0.03–0.31, p<0.0001; respectively) but also not in the northerners (OR = 0.67, 95%CI = 0.44–1.03, p=0.07; OR = 0.42, 95%CI = 0.04–4.08, p=0.45; respectively). In addition, results showed obviously negative associations between B*2707 and susceptibility to AS both in the southerners and northerners of China (OR = 0.30, 95%CI = 0.14-0.66, p=0.003; OR = 0.09, 95%CI = 0.03–0.55, p=0.009; respectively). Similarly, no association has been found between B*2702, B*2703, B*2708, B*2710, B*2711, B*2712, B*2713, B*2715, B*2720, B*2724 and susceptibility to AS both in the southerners and northerners of China.

Sensitivity analysis was performed by sequential omission of individual studies. The significance of pooled OR in all individuals analyses and subgroup analyses was not influenced excessively by omitting any single study.

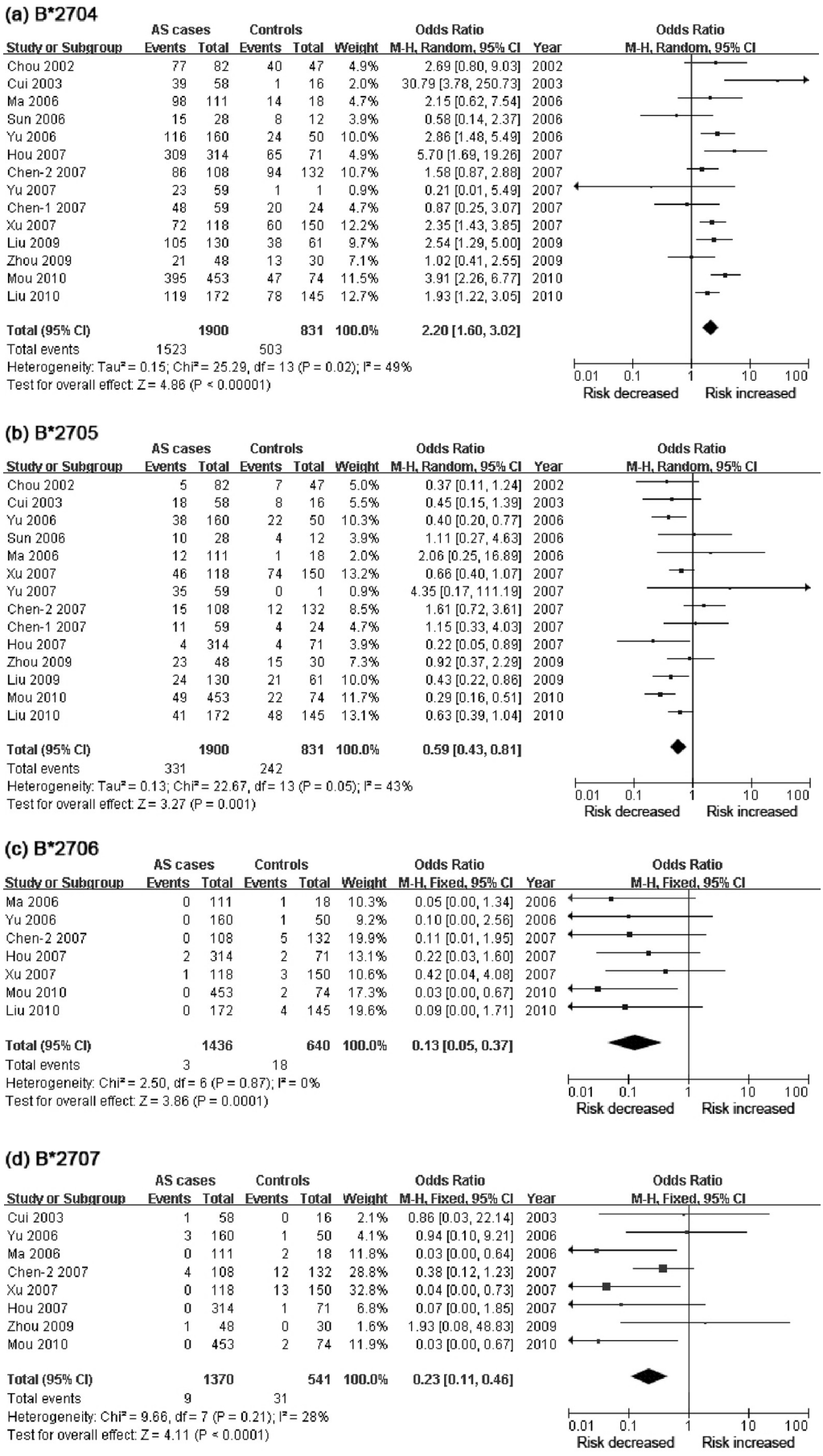

Fig. 2. Association of B*2704 (**a**), B*2705 (**b**), B*2706 (**c**) and B*2707 (**d**) with susceptibility to AS in Han population. The squares and horizontal lines correspond to the study-specific OR and 95%CI. The area of the squares reflects the study specific weight (inverse of the variance). The diamond represents the summary OR and 95%CI.

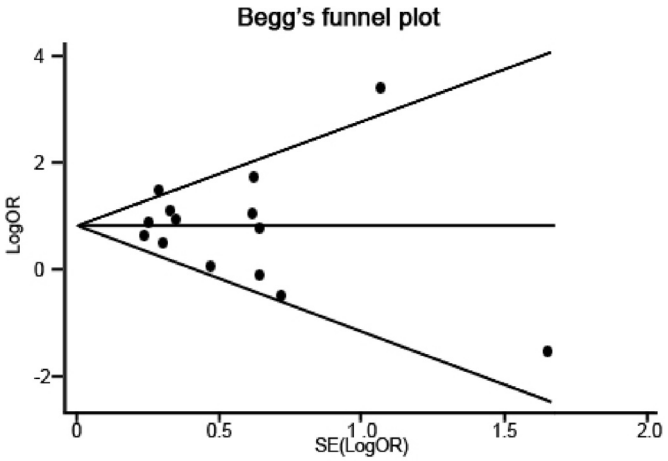

Fig. 3. Begg's funnel plot and Egger's test of publication bias for the association between B*2704 and susceptibility to AS (Egger's regression test: t=–0.39, p=0.70, 95%CI= –2.27–1.58).

Heterogeneity and publication bias

Significant heterogeneity ($P_{Heterogeneity}$<0.1 or I^2>50%) between studies was observed in B*2704 and B*2705, but no heterogeneity was found in other HLA-B*27 polymorphisms. Therefore, the random effects model was used to pool the result. Publication bias of the literatures was accessed by Begg's funnel plot and Egger's test. The publication bias of the meta-analysis on the association between HLA-B*27 polymorphisms and susceptibility to AS was detected by the funnel plot on B*2704. The graphical funnel plots of 14 studies appeared to be symmetrical, we found no evidence of publication bias (Egger's regression test: t = -0.39, p=0.70, 95%CI = -2.27-1.58) (Fig. 3).

Discussion

AS is the prototypic seronegative spondyloarthropathy, characterised by chronic inflammatory condition of the spine and sacroiliac joints (29). This has been supported by many studies which showed that susceptibility to AS is >90% hereditary (8-9, 17). In Han populations, the pooled prevalence of AS is not very different, and has been reported to be around 0.2~0.4% (30). Genetic factors are clearly attributed to the susceptibility of AS (24). The HLA-B*27 proved to be the very useful marker for diagnosing AS, which contributes about half of genetic risk (32, 33). With an ever-increasing number of HLA-B*27 alleles being discovered using DNA methodologies, it is becoming imperative to establish association of each individual allele with AS and its biological functions and characteristics in connection to the disease (31). Ever-increasing numbers of HLA-B*27 alleles were found, and these differences of the nucleotide affected the peptide-presenting specificity, which is now considered a factor in the pathogenesis of AS (24).

Although there are many research studies have evaluated the association of HLA-B*27 polymorphisms with AS risk in Han populations. However, the results are controversial. Our meta-analysis quantitatively assessed the association between HLA-B*27 polymorphisms with susceptibility to AS in Han populations. Finally, 14 case-control studies with a total of 1900 AS cases and 831 healthy controls were included and assessed. In this meta-analysis, 14 HLA-B*27 polymorphisms were addressed and evaluated: B*2702~B*2708, B*2710~B*2713, B*2715, B*2720 and B*2724. B*2704 and B*2705 were the most common polymorphisms, and next were B*2706 and B*2707. Meta-analysis results showed that there was a positive association between B*2704 and susceptibility to AS in Han populations, which indicated that B*2704 may be a potential risk factor for AS in Han populations. However, unlike what has been shown for previous association, B*2705, B*2706 and B*2707 showed negative associations with susceptibility to AS in Han populations. Therefore, B*2705, B*2706 and B*2707 might be potential protective factors for AS in Han populations. Unfortunately, no association has been found between B*2702, B*2703, B*2708, B*2710, B*2711, B*2712, B*2713, B*2715, B*2720, B*2724 and susceptibility to AS in Han populations. In the subgroup analysis by geographic distribution, results showed that B*2704 might be a potential risk factor for AS in the southerners of China but not in the northerners. In addition, results also demonstrated that B*2705 and B*2706 might be potential protective factors for AS in the southerners but not in the northerners. However, results showed that B*2707 might be a potential protective factor for AS both in the southerners and northerners of China. Obvious heterogeneity between studies were found, suggesting a possible role of geographic differences in genetic backgrounds and the environment they lived in. No evidence showed publication bias in this meta-analysis.

There were some limitations in our meta-analysis. First, because of incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Secondly, we were not able to address the sources of heterogeneity existed among studies for each polymorphism. However, we could not to perform further subgroup stratifications analysis for the limited number of published studies. Thirdly, the lack of genotype frequency information provided by some published studies did not allow the estimation of the best genetic model of inheritance to follow. Although we actively contacted with the authors, they did not provide a comprehensive set of data. In addition, the small sample size available was not ideal for detecting small genetic effects. Finally, our systematic review was based on unadjusted data, as the genotype information stratified for the main confounding variables was not available in the original papers and also the confounding factors addressed across the different studies were variable.

In conclusion, our meta-analysis of 14 case–control studies demonstrated that B*2704 might be a potential risk factor and B*2705, B*2706, B*2707 might be potential protective factors for AS in Han populations, especially in the southerners of China. As few studies are available in this field and current

evidence remains limited. Therefore, it should be emphasised the necessity to conduct large studies with an adequate methodological quality, properly controlling for possible confounds in order to obtain valid results.

Acknowledgments

We would like to thank Yan Wu (Department of Dermatology, the First Affiliated Hospital, China Medical University) for her valuable contribution and for kindly revising the manuscript.

References

1. BRAUN J, SIEPER J: Ankylosing spondylitis. *Lancet* 2007; 369: 1379-190.
2. CALIN A: Ankylosing Spondylitis. *Medicine* 2002; 30: 54-7.
3. KHAN MA, MATHIEU A, SORRENTINO R, AKKOC N: The pathogenetic role of HLA-B27 and its subtypes. *Autoimmun Rev* 2007; 6: 183-9.
4. KAAS Q, RUIZ M, LEFRANC MP: IMGT/3Dstructure-DB and IMGT/StructuralQuery, a database and a tool for immunoglobulin, T cell receptor and MHC structural data. *Nucleic Acids Res* 2004; 32: D208-10.
5. BLANCO-GELAZ MA, LÓPEZ–VÁZQUEZ A, GARCÍA–FERNÁNDEZ S, MARTÍNEZ–BORRA J, GONZÁLEZ S, LÓPEZ–LARREA C: Genetic variability, molecular evolution, and geographic diversity of HLA-B*27. *Hum Immuno* 2001; 62: 1042-50.
6. FELTKAMP TE, MARDJUADI A, HUANG F, CHOU CT: Spondyloarthropathies in eastern Asia. *Curr Opin Rheumatol* 2001; 13: 285-90.
7. DE CASTRO JA: HLA–B27 and ankylosing spondylitis: tales from China. *Tissue Antigens* 2010; 75: 9-11.
8. LIU Y, JIANG L, CAI Q *et al*.: Predominant association of HLA-B*2704 with ankylosing spondylitis in Chinese Han patients. *Tissue Antigens* 2009; 75: 61-4.
9. MOU Y, WU Z, GU J *et al*.: HLA-B27 polymorphism in patients with juvenile and adult-onset ankylosing spondylitis in Southern China. *Tissue Antigens* 2010; 75: 56-60.
10. BROWN MA: Genomewide screens in ankylosing spondylitis. *Adv Exp Med Biol* 2009; 649: 148-58.
11. ATTIA J, THAKKINSTIAN A, D'ESTE C: Meta-analysis of molecular association studies: methodologic lessons for genetic epidemiology. *J Clin Epidemiol* 2003; 56: 297-303.
12. VAN DER LINDEN S, VALKENBURG HA, CATS A: Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27: 361-8.
13. VANDENBROUCKE JP, VON ELM E, ALTMAN DG *et al*.: STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology* 2007; 18: 805-35.
14. PETERS JL, SUTTON AJ, JONES DR, ABRAMS KR, RUSHTON L: Comparison of two methods to detect publication bias in meta-analysis. *JAMA* 2006; 295: 676-80.
15. ZINTZARAS E, IOANNIDIS JP: Heterogeneity testing in meta-analysis of genome searches. *Genet Epidemiol* 2005; 28: 123-37.
16. HIGGINS JP, THOMPSON SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539-58.
17. CHOU CT, CHEN JM, HSU CM, CHEN SJ: HLA-B27 and its subtypes in 4 Taiwanese Aborigine tribes: a comparison to Han Chinese patients with ankylosing spondylitis. *J Rheumatol* 2003; 30: 321-5.
18. CUI LF, SONG HT, LI HF, SHEN ZX: Association analysis on HLA-B*27 alleles and ankylosing spondy. *Clin J Rheumatol* 2003; 7: 55-6.
19. SUN GH, LI YL, XIAO XG: Clinical implication of HLA-B*27 subtypes by polymerase chain reaction with sequence specific primers. *Journal of Dalian Medical University* 2006; 28: 410-3.
20. MA HJ, HU F: Diversity of human leukocyte antigen–B*27 alleles in Han population of Hunan province, southern China. *Tissue Antigens 2006*; 68: 163-6.
21. XU N, SUN H, SAN XY *et al*.: A study on the association of HLA-B*27 subtype with ankylosing spondylitis in Chinese Northern Han population. *Bei Jing Yi Xue* 2007; 29: 241-3.
22. CHEN ZJ, LI S: Analysis of HLA-B*27 subtypes in Guangxi Zhuang nationality patients with ankylosing spondylitis. *Journal of Guangxi Medical University* 2007; 24: 738-9.
23. CHEN CR, ZHANG ZY, NI HY *et al*.: A study of HLA-B*27 subtypes and their association with ankylosing spondylitis. *Chin J Blood Transfusion* 2007; 20: 13-4.
24. HOU TY, CHEN HC, CHEN CH, CHANG DM, LIU FC, LAI JH: Usefulness of human leucocyte antigen-B27 subtypes in predicting ankylosing spondylitis: Taiwan experience. *Intern Med J* 2007; 37: 749-52.
25. YU HC, LI ZN, LIU S, LI HH, QIAN DM, WANG B: The study on the correlation between HLA-B*27 subtype and Ankylosing spondylitis. *World Journal of infection* 2007; 7: 51-2.
26. YU XY, GU GH, GAO C *et al*.: Association analysis on heterogenity of HLA-B*27 and ankylosing spondy. *Suzhou University Journal of Medical Science* 2006; 26: 605-8.
27. ZHOU F, YU C, ZHANG K: Distribution of HLA-B*27 subtypes in Nantong and their association with ankylosing spondylitis. *J Mod Lab Med* 2009; 24: 135-6.
28. LIU X, HU LH, LI YR, CHEN FH, NING Y, YAO QF: The association of HLA-B*27 subtypes with ankylosing spondylitis in Wuhan population of China. *Rheumatol Int* 2010; 30: 587-90.
29. MANSOUR M, CHEEMA GS, NAGUWA SM *et al*.: Ankylosing spondylitis: a contemporary perspective on diagnosis and treatment. *Semin Arthritis Rheum* 2007; 36: 210-23.
30. GU J, HUANG J, LI C *et al*.: Association of chromosome 2q36.1-36.3 and autosomal dominant transmission in ankylosing spondylitis: results of genetic studies across generations of Han Chinese families. *J Med Genet* 2009; 46: 657-62.
31. YANG KL, CHEN IH, HSIAO CK *et al*.: Polymorphism of HLA-B27 in Taiwanese Chinese. *Tissue Antigens* 2004; 63: 476-9.
32. KIM TJ, NA KS, LEE HJ, LEE B, KIM TH: HLA-B27 homozygosity has no influence on clinical manifestations and functional disability in ankylosing spondylitis. *Clin Exp Rheumatol* 2009; 27: 574-9.
33. DOMÍNGUEZ-LÓPEZ ML, ORTEGA-ORTEGA Y, MANRÍQUEZ-RAYA JC, BURGOS-VARGAS R, VEGA-LÓPEZ A, GARCÍA-LATORRE E: Antibodies against recombinant heat shock proteins of 60 kDa from enterobacteria in the sera and synovial fluid of HLA-B27 positive ankylosing spondylitis patients. *Clin Exp Rheumatol* 2009; 27: 626-32.