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Association of HLA-B27 with ankylosing spondylitis and clinical features of the HLA-B27-associated ankylosing spondylitis: a meta-analysis

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Abstract Many studies have estimated the correlation between HLA-B27 polymorphisms and ankylosing spondylitis (AS). However, the results were controversial. Therefore, we performed this meta-analysis to determine the association of HLA-B*27 polymorphisms with AS and investigate the impacts of HLA-B27 on the clinical symptoms of AS patients. A comprehensive search was performed in PubMed, Web of Science and Embase databases to retrieve the eligible studies, which addressed the association between HLA-B27 polymorphisms and AS susceptibility. The correlation in fixed-effect model was estimated using the relative risk (RR) and 95% confidence intervals (CI). Finally, 41 studies were included in this meta-analysis, among which 35 studies were used to analyze the correlation between HLA-B27 and AS. And 11 studies were applied to estimate the effects of HLA-B27 on the clinical characteristics of AS patients. Besides, our meta-analysis was composed of 8993 AS patients and 19,254 healthy controls. The results suggested that HLA-B27, HLA-B27*02 and HLA-B27*04 were positively in relation to AS ($RR_{HLA\text{-}B27}$ (95% CI) 16.02 (13.85, 18.54), $P < 0.001$; $RR_{HLA\text{-}B*2702}$ (95% CI) 1.28 (1.08, 1.53), $P = 0.005$; $RR_{HLA\text{-}B27*04}$ (95% CI) 1.14 (1.01, 1.29), $P = 0.041$). Moreover, positive association was observed between HLA-B27 and sex (male) [RR (95% CI) 1.10 (1.05, 1.15), $P < 0.001$], family history [RR (95% CI) 1.10 (1.06, 1.140), $P < 0.001$], uveitis [RR (95% CI) 1.07 (1.03, 1.11), $P < 0001$], peripheral joint involvement [RR (95% CI) 1.04 (1.01,1.07), $P = 0.013$] and hip joints involvement [RR (95% CI) 1.06 (1.02, 1.10), $P = 0.003$]. In addition, we also found that HLA-B27*04 showed association with peripheral joint involvement [RR (95% CI) 1.13 (1.05–1.23), $P = 0.002$]. In conclusion, the current meta-analysis indicates that HLA-B27, especially, its subtypes (HLA-B27*02 and HLA-B27*04) may be potential risk factors for AS.

Keywords Ankylosing spondylitis · HLA-B27 · Meta-analysis · Relative risk · 95% confidence intervals

Introduction

Ankylosing spondylitis (AS), a chronic and immune-mediated disorder, is characterized by new bone formation and inflammation in the axial skeleton, which can induce irretrievable structural damage, deterioration of function, disability, spinal and pelvic joint dysfunction [1–4]. Whereas effective treatments are mainly used to control symptom, it has not verified that any treatment could decrease the occurrence of AS. Meanwhile, the therapy of AS mainly depends on the use of drugs including nonsteroidal anti-inflammatory drugs (NSAIDs), conventional disease-modifying antirheumatic drugs (DMARDs), which are often insufficient to suppress inflammation and improve symptoms [5]. In addition, although anti-tumor necrosis factor (TNF) therapy is widely recognized as the effective method for patients with disease activity, its application often causes unacceptable side effects and fails to control disease [6–10].

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Accumulating evidence has demonstrated that human leukocyte antigen (HLA) class I molecule B27 (HLA-B27) is strongly related to the progression of AS via restricting immune responses and inducing autophagy responses [11]. And over 100 different allelic variants of B27 have been recognized (HLA-B2701 to HLA-B27106) in AS patients, among which B27*05 and B27*02 are widely prevalent in European populations, and B27*04 is predominate in Asian populations [11]. The articles reported by Kim et al. [12] and Al-Qadi et al. [13] found that the incidence of HLA-B27 was higher in AS cases versus controls. Akassou et al. also [14] concluded the RR and 95% CI to show that high frequency of HLA-B27 was related to high risk of AS (RR: 16.8, 95% CI 5.83–51.03; $P < 0.001$). In contrast, the study reported by Diyarbakir et al. showed no difference of the frequency of HLA-B27 and its subtypes (HLA-B2702, HLA-B2704 and HLA-B2705) between AS patients and the controls [15]. In addition, Qi et al. [16] discovered the different expression of HLA-B27 alleles in AS patients and healthy control patients, and found that HLA-B2704 expression was equal in both groups and the frequency of HLA-B2705 was higher in AS patients than control patients. However, another study reported that HLA-B2704 and HLA-B2705 were both more likely to appear in AS patients compared with healthy controls [17]. Additionally, Al-Qadi et al. also discovered that the presence of HLA-B27 are prone to affect the function of combined axial and peripheral joint involvement of the AS patients and cause inflammatory back pain and buttock pain [13]. Qi et al. [16] also found that compared to HLA-2705-positive patients, HLA-2704-positive patients were more likely to get the risk of AS at a younger age, and HLA-B2705-positive patients had a higher risk of dactylitis and uveitis compared with HLA-B2704-positive patients. To the opposite, another study reported that AS patients with uveitis were observed more in HLA-B2704+ patients than HLA-B2705+ patients [18]. Thus, the association between HLA-B27 and its subtypes with AS and clinical features of AS patients are controversial.

Meta-analysis has the potential roles to detect an association with overcoming the problems of small sample studies and inadequate statistics in complex traits. In the current study, a meta-analysis was performed to investigate the risk of AS with HLA-B27/HLA-B27 subtypes and the association between HLA-B27/HAL-B27 subtypes and clinical features in AS patients.

Materials and methods

Identification of eligible studies

PubMed, Web of science and Embase databases were applied to retrieve cross-sectional and cohorts studies linking HLA-B27 polymorphisms to AS with updating to November, 2016. The query for searching was as follows: "HLA-B27" or "HLA-B*27" or "human leukocyte antigen B27" (Mesh) and "ankylosing spondylitis" or "AS" (Mesh). Review articles and references from included articles were manually searched to check for other relevant researches. Two independent reviewers (HL and YZG) first read the title and abstract of the candidate papers. Full text would be retrieved when articles could not be decided from title and abstract. Any disparity in quality assessment and data collection was reached a final agreement via discussion.

Studies were included for the meta-analysis with meeting the following inclusion criteria: (1) the diagnosis of AS was based on the modified New York criteria; (2) studies evaluated the frequency of HLA-B27 in cases of AS patients and control groups; (3) relative risk (RR) and 95% confidence interval (95% CI) were available; (4) articles written in English; (5) cross-sectional or cohorts studies.

Data extraction

The available data were extracted by two independent reviewers (Hai Lin and Yi-Zhen Gong), and the following information was included: first author, country, publication time, sample size, the frequency of HLA-B27(+)in both cases and controls, the clinical features of AS patients. Inconsistencies in the data extraction were resolved through debates and consultations.

Statistical analysis

RR and 95% CI were performed to estimate the impact of HLA-B27 on risk of AS in the current meta-analysis. By convention, it implies a high risk for the group with more frequency of HLA-B27 when RR > 1. The influence of HLA-B27 expression on the risk of AS was regarded as statistically significant when the 95% CI for the HR did not overlap 1 and $P < 0.05$. Stata version 11.0 was applied to perform the [15] data analysis, while Q tests and I squared test were conducted to evaluate the heterogeneity. A fixed effects model was used when no heterogeneity was present and the results were similar with the random effects model. It was considered that there existed no statistically significant heterogeneity when $P \geq 0.05$ or $I^2 \leq 50\%$. Subgroup analysis was performed on the basis of region. In addition, the sensitivity analysis was conducted to find the sources of heterogeneity. The Begg's funnel plot and Egger's test were used to evaluate the publication bias when more than ten articles were included in the meta-analysis.

Results

Characteristics of studies

The flow chart for the search strategy was summarized in Fig. 1. We first reviewed 1760 articles and excluded 1691 articles after reviewing the title and abstract. Finally, we included 41 articles after excluding 1 article without full text, 2 meta-analyses, 1 review and 24 articles without available data. The main features of the eligible studies were presented in Tables 1 and 2. Finally, 41 articles were included in our current study, including 35 studies (described the relationship of HLA-B27 and AS) and 11 studies (identified the association between HLA-B27 frequency and clinical features of AS patients). The total numbers of AS patients and healthy controls were, respectively, 8993 and 19,254. Among the 35 studies mentioned above, 17 studies reported the expression of HLA-B27 in case–control groups (cases: 3983; controls: 17,856) and the influence of most common HLA-B27 subtypes (HLA-B27*02, HLA-B27*04, HLA-B27*05) were, respectively, demonstrated in 19 articles (cases:2958; controls:14,258), 19 articles (cases:4656; controls:7569) and 23 articles (cases:5162; controls:8358). In the 11 studies related to the clinical characteristics of AS, HLA-B27-positive patients accounted for 80% (3711 out of 4384). The clinical features included in the meta-analysis mainly as follows: sex (male), family history, uveitis, peripheral joint involvement, hip joints involvement, low back pain (LBP) or buttock pain, dactylitis, enthesitis.

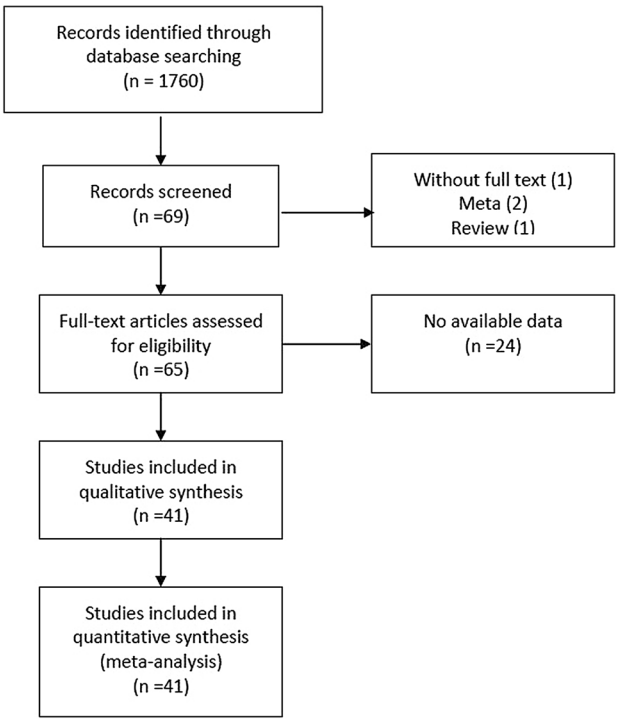


Fig. 1 Flow chart of study selection

Analysis for the association between HLA-B27 expression and AS

The results of this meta-analysis showed there existed positive association between HLA-B27, HLA-B27*02, HLA-B27*04, HLA-B27*05 and susceptibility to AS [$RR_{HLA\text{-}B27}$ (95% CI) 8.24 (7.75–8.76), $P < 0.001$; $RR_{HLA\text{-}B*2702}$ (95% CI) 1.49 (1.31, 1.70), $P < 0.001$; $RR_{HLA\text{-}B27*04}$ (95% CI) 58 (4.25, 4.94), $P < 0.001$; $RR_{HLA\text{-}B*2705}$ (95% CI) 1.53 (1.46, 1.61), $P < 0.001$]. However, there was heterogeneity in our current study ($P_{HLA\text{-}B27} < 0.001$, $I^2 = 99.4\%$; $P_{HLA\text{-}B27*02} < 0.001$, $I^2 = 80\%$; $P_{HLA\text{-}B27*04} < 0.001$, $I^2 = 99.5\%$; $P_{HLA\text{-}27*05} < 0.001$, $I^2 = 96.1\%$). The subgroup analysis was performed according to the distribute region of the patients. As a result, the heterogeneity was mainly induced by the samples from East Asia ($P_{HLA\text{-}B27} = 0.004$, $I^2 = 70.7\%$; $P_{HLA\text{-}B27*02} < 0.001$, $I^2 = 80\%$; $P_{HLA\text{-}B27*04} < 0.001$, $I^2 = 99.8\%$; $P_{HLA\text{-}27*05} < 0.001$, $I^2 = 94.9\%$), Southwest Asia ($P_{HLA\text{-}B27} = 0.030$, $I^2 = 62.7\%$; $P_{HLA\text{-}B27*02} < 0.001$, $I^2 = 91\%$; $P_{HLA\text{-}27*05} < 0.001$, $I^2 = 97.9\%$), South Europe ($P_{HLA\text{-}B27*02} = 0.003$, $I^2 = 82.8\%$; $P_{HLA\text{-}27*05} < 0.001$, $I^2 = 97.5\%$) and Africa ($P_{HLA\text{-}B27*02} < 0.001$, $I^2 = 94.5\%$; $P_{HLA\text{-}27*05} < 0.001$, $I^2 = 92.3\%$). After removal of the studies contributed to the heterogeneity analyzed by the sensitivity analysis, the prevalence of HLA-B27, HLA-B27*02 and HLA-B27*04 were still positively related to the susceptibility of patients to AS ($RR_{HLA\text{-}B27}$ (95% CI) 16.02 (13.85, 18.54), $P < 0.001$; $RR_{HLA\text{-}B*2702}$ (95% CI) 1.28 (1.08, 1.53), $P = 0.005$; $RR_{HLA\text{-}B27*04}$ (95% CI) 1.14 (1.01, 1.29), $P = 0.041$) (Fig. 2). While no association was observed between HLA-B27*05 and susceptibility to AS ($RR_{HLA\text{-}B*2705}$ (95% CI) 1.04 (0.97, 1.12), $P = 0.256$).

Analysis for the association between HLA-B27 expression and the clinical parameters of AS patients

The results showed that there was a positive relation between HLA-B27 and family history [RR (95% CI) 1.10 (1.07, 1.14), $P < 0.001$), uveitis [RR (95% CI) 1.05 (1.02, 1.09), $P = 0.006$), peripheral joint involvement [RR (95% CI) 1.04 (1.01, 1.07), $P = 0.013$] and hip joints involvement [RR (95% CI) 1.04 (1.01, 1.08), $P = 0.011$]. Moreover, HLA-B27 could increase the susceptibility of male populations to AS [RR (95% CI) 1.06 (1.01, 1.11) $P = 0.013$]. However, we observed heterogeneity in the present meta-analysis: sex ($I^2 = 87.70\%$, $P < 0.001$), family history ($I^2 = 73.5\%$, $P = 0.005$), uveitis ($I^2 = 59.9\%$, $P = 0.008$), and hip joints involvement ($I^2 = 88.45\%$, $P < 0.001$). There was no statistically significant heterogeneity after removal of the

Table 1 Characteristics of studies included in the meta-analysis

Study	Type of study	Year	Country	Population	No. patients/controls	B27+ patients (n/N)	B27+ controls (n/N)	B27*02+ patients (n/N)	B27*02+ controls (n/N)	B27*04+ patients (n/N)	B27*04+ controls (n/N)	B27*05+ patients (n/N)	B27*05+ controls (n/N)
Diaz-Pena et al. [19]	Cohorts	2016	Spain	Southern Europe	867/1378	318/367	549/1011	22/367	19/1011	1/367	0/1011	293/367	531/1011
Kim et al. [12]	Cross-sectional	2015	Korea	East Asia	718/3220	576/754	142/3166						
Wei et al. [20]	Cross-sectional	2015	Taiwan	East Asia	474/1028	431/471	43/557						
Akassou et al. [14]	Cross-sectional	2015	Morocco	Africa	30/181	24/53	6/128						
AL-Qadi et al. [13]	Cross-sectional	2015	Kurd	Southwest Asia	35/250	27/41	8/209						
Videm et al. [21]	Cohorts	2014	Norway	Northern Europe	162/1027	50/103	112/924						
Qi et al. [16].	Cross-sectional	2013	China	East Asia	780/1805	741/846	39/959	4/846	0/959	652/846	36/959	75/846	0/959
Yi et al. [17]	Cross-sectional	2013	China	East Asia	362/710	336/360	26/350			245/846	16/959	80/846	9/959
Gaalen et al. [22]	Cross-sectional	2012	Netherlands	Western Europe	536/5738	133/154	403/5584						
Acar et al. [23]	Cross-sectional	2012	Turkey	Southwest Asia	89/999	46/51	43/948	12/51	11/948	3/51	1/948	30/51	19/948
al Attia et al. [24]	Cohorts	1998	Arab	Southwest Asia	41/575	9/16	32/559						
al Attia et al. [24]	Cohorts	1998	Arab	Southwest Asia	22/187	9/11	13/176						
Liu et al. [25]	Cross-sectional	2009	China	East Asia	191/1698	130/153	61/1545			105/153	38/1545	24/153	21/1545
Mou et al. [26]	Cross-sectional	2010	China	East Asia	527/1837	453/505	74/1368			395/505	47/1368	49/505	22/1368
Harfouch et al. [27]	Cross-sectional	2011	Syria	Southwest Asia	33/267	30/50	3/217	6/50	0/217			20/50	3/217
Cipriani et al. [28]	Cross-sectional	2003	Venezuela	South America	52/103	48/48	4/55	15/48	1/55			33/48	0/55
Kchir et al. [29]	Cross-sectional	2010	Tunisia	Africa	65/200	62/100	3/100	32/100	0/1001			24/100	1/100
Diyarbakir et al. [15]	Cross-sectional	2012	Turkey	Southwest Asia	43/39			21/43	18/39	1/43	0/39	17/43	16/39
Chavan et al. [30]	Cross-sectional	2011	India	South Asia	81/29			1/81	0/29	23/81	3/29	55/81	18/29
Pazár et al. [31]	Cross-sectional	2010	Hungary	Central Europe	231/70			65/231	14/70	0/231	2/70	166/231	32/70
Ben Radhia et al. [32]	Cross-sectional	2008	Tunisia	Africa	121/39			57/121	16/39	1/121	0/39	57/121	16/39
Liu et al [33]	Cross-sectional	2010	China	East Asia	172/145			1/172	2/145	119/172	78/145	41/172	48/145
Alaez et al. [34]	Cross-sectional	2007	Israeli	Southwest Asia	24/51			15/24	21/51			9/24	26/51

Table 1 continued

Study	Type of study	Year	Country	Population	No. patients/controls	B27+ patients (n/N)	B27+ controls (n/N)	B27*02+ patients (n/N)	B27*02+ controls (n/N)	B27*04+ patients (n/N)	B27*04+ controls (n/N)	B27*05+ patients (n/N)	B27*05+ controls (n/N)
Birinci et al. [35]	Cross-sectional	2006	Turkey	Southwest Asia	38/47			10/38	15/47			27/38	32/47
Gonzalez et al. [36]	Cross-sectional	2002	Spain	Southern Europe	89/97			3/89	7/97			86/89	88/97
López-Larrea et al. [37]	Cross-sectional	2006	Spain	Southern Europe	71/105			3/71	9/105			68/71	94/105
López-Larrea et al. [37]	Cross-sectional	2006	Azorian	Southwest Asia	55/57			7/55	2/57			45/55	52/57
Varnavidou-Nicolaidou et al. [38]	Cross-sectional	2004	Greek Cypriot	Europe	31/60			25/31	31/60			6/31	19/60
López-Larrea et al. [39]	Cross-sectional	1995	Mexico	North America	64/9			3/64	2/9	1/64	0/9	60/64	6/9
Gonzalez-Roces et al. [40]	Cross-sectional	1997	Worldwide	Worldwide	476/235			65/476	32/235	93/476	40/235	232/476	147/235
Ren et al. [41]	Cross-sectional	1997	Singapore	Southeast Asia	50/45					48/50	40/45	2/50	1/45
Hou et al. [42]	Cross-sectional	2007	China	East Asia	314/71					309/314	65/71	3/314	3/71
Ma et al. [43]	Cross-sectional	2006	China	East Asia	111/18					98/111	14/18	12/111	1/18
Chou et al. [44]	Cross-sectional	2003	China	East Asia	82/47					77/82	40/47	5/82	7/47
Park et al. [45]	Cross-sectional	2009	Korea	East Asia	143/32					11/143	11/32	130/143	19/32

Table 2 Correlation of HLA-B27 with clinical features of AS patients

Author	Year	Country	Region	Sex		Family history		Uveitis		Peripheral joint involvement	
				B27+cases (n/N)	B27+controls (n/N)	B27+cases (n/N)	B27+controls (n/N)	B27+cases (n/N)	B27+controls (n/N)	B27+cases (n/N)	B27+controls (n/N)
Akassou et al. [14]	2015	Morocco	Africa	18/32	6/21						
AL-Qadi et al. [13]	2015	Kurd	Southwest Asia	23/33	4/8	13/15	14/26	4/5	23/36	15/17	12/24
AL-Qadi et al. [6]	2015	Kurd	Southwest Asia								
Qi et al. [16]	2013	China	East Asia	620/719	103/127	171/182	570/664	52/56	689/790	260/289	481/557
Yang et al. [46]	2013	China	East Asia	1349/1684	332/460	378/450	1258/1639	159/191	1522/1953	717/900	964/1244
Wu et al. [47]	2009	China	East Asia	68/83	13/15	24/25	69/73			43/44	49/54
Wu et al. [47]	2009	China	East Asia	10/83	2/15						
Park et al. [45]	2009	Korea	East Asia	10/124	1/19			1/29	10/114	6/69	5/74
Park et al. [36]	2009	Korea	East Asia	11/124	18/19			28/29	102/114	63/69	67/74
Cipriani et al. [28]	2003	Venezuela	South America	8/34	7/14						
Cipriani et al. [28]	2003	Venezuela	South America	26/34	7/14						
Kim et al. [12]	2009	Korea	East Asia	402/432	52/58			148/151	306/339	229/246	225/243
Sun et al. [48]	2016	China	East Asia					32/38	338/352		
Chavan et al. [30]	2011	India	South Asia					9/18	46/63	32/48	23/33
Chavan et al. [30]	2011	India	South Asia					8/18	15/63	15/48	8/33
Harfouch et al. [27]	2011	Syria	Southwest Asia		8/8	22/42	5/5	25/45	6/6	24/44	

Author	Year	Country	Region	Hip joints involvement		LBP or buttock pain		Dactylitis		Enthesitis	
				B27+cases (n/N)	B27+controls (n/N)	B27+cases (n/N)	B27+controls (n/N)	B27+cases (n/N)	B27+controls (n/N)	B27+cases (n/N)	B27+controls (n/N)
Akassou et al. [14]	2015	Morocco	Africa								
AL-Qadi et al. [13]	2015	Kurd	Southwest Asia			25/37	2/4				
AL-Qadi et al. [6]	2015	Kurd	Southwest Asia		11/13	16/28					
Qi et al. [16]	2013	China	East Asia	177/197	546/649	670/788	51/58	32/35	709/811		
Yang et al. [46]	2013	China	East Asia	620/764	1061/1380			99/120	1582/2024	603/767	1078/1377
Wu et al. [47]	2009	China	East Asia								
Wu et al. [47]	2009	China	East Asia								
Park et al. [45]	2009	Korea	East Asia								
Park et al. [36]	2009	Korea	East Asia								
Cipriani et al. [28]	2003	Venezuela	South America								
Cipriani et al. [28]	2003	Venezuela	South America								
Kim et al. [12]	2009	Korea	East Asia	334/352	120/121	216/234	238/252				
Sun et al. [48]	2016	China	East Asia								
Chavan et al. [30]	2011	India	South Asia	21/32	34/49	51/76	4/5			13/21	42/60

Table 2 continued

Author	Year	Country	Region	Hip joints involvement		LBP or buttock pain		Dactylitis		Enthesitis	
				B27+cases (n/N)	B27+controls (n/N)	B27+cases (n/N)	B27+controls (n/N)	B27+cases (n/N)	B27+controls (n/N)	B27+cases (n/N)	B27+controls (n/N)
Chavan et al. [30]	2011	India	South Asia	10/32	13/49	23/76	0/5			8/21	15/60
Harfouch et al. [27]	2011	Syria	Southwest Asia								

studies induced the heterogeneity based on the sensitivity analysis, and the results were in favor of the findings mentioned above: sex (male) [RR (95% CI) 1.10 (1.05, 1.15), $P < 0.001$]; family history [RR (95% CI) 1.10 (1.06, 1.140), $P < 0.001$], uveitis [RR (95% CI) 1.07 (1.03, 1.11), $P < 0.001$], and hip joints involvement [RR (95% CI) 1.06 (1.02, 1.10), $P = 0.003$]. In addition, we also found HLA-B27*04 was remarkably in relation to peripheral joint involvement in AS patients without heterogeneity [RR (95% CI) 1.13 (1.05–1.23), $P = 0.002$; $I^2 = 0.0\%$, $P_{heterogeneity} = 0.972$]. And association was observed between HLA-B27*05 and uveitis [RR (95% CI) 1.31 (1.07–1.61), $P = 0.009$; $I^2 = 93.1\%$, $P < 0.001$]. It also showed that HLA-B27*05 might decrease the risk of male to AS [RR (95% CI) 0.48 (0.344–0.655), $P < 0.001$; $I^2 = 95.9\%$, $P < 0.001$]. As was shown, there existed heterogeneity in the analysis of HLA-B27*05 and sex/uveitis in AS patients. Interestingly, no association was found between HLA-B27*05 and sex/uveitis after eliminating the heterogeneity [sex: RR (95% CI) 1.37 (0.81–2.32), $P = 0.241$; uveitis: RR (95% CI) 0.90 (0.61–1.31), $P = 0.578$]. The statistically significant results were shown in Fig. 3.

Publication bias

Publication bias was evaluated by Begg's funnel plot and Egger's test. The combined results of Begg's funnel plots and *P* values of the Egger's test suggested no obvious publication bias (Tables 3 and 4 and Fig. 4).

Discussion

Summary of the results

Previously, two meta-analyses reported by Yang et al. [49] and Zhang et al. [50] have demonstrated the association between HLA-B27 genetic polymorphisms and susceptibility to AS. In comparison with the previous meta-analysis, the present meta-analysis was the first one to identify the effects of HLA-B27 and its subtypes (HLA-B27*04 and HLA-B27*05) on the clinical features of AS patients including 11 articles (4384 AS patients). Furthermore, 35 studies have been included in our meta-analysis with 3983 AS patients and 17,856 controls, which was more than those of the article reported by Yang et al. [49] (31 studies involved with 3140 AS patients and 1735 controls) and the report of Zhang et al. [50] (14 studies consisted of 1900 AS patients and 831 healthy controls). In consideration of these, our current study gains advantages over the studies published by Yang et al. and Zhang et al. Therefore, our meta-analysis could provide more powerful evidence to

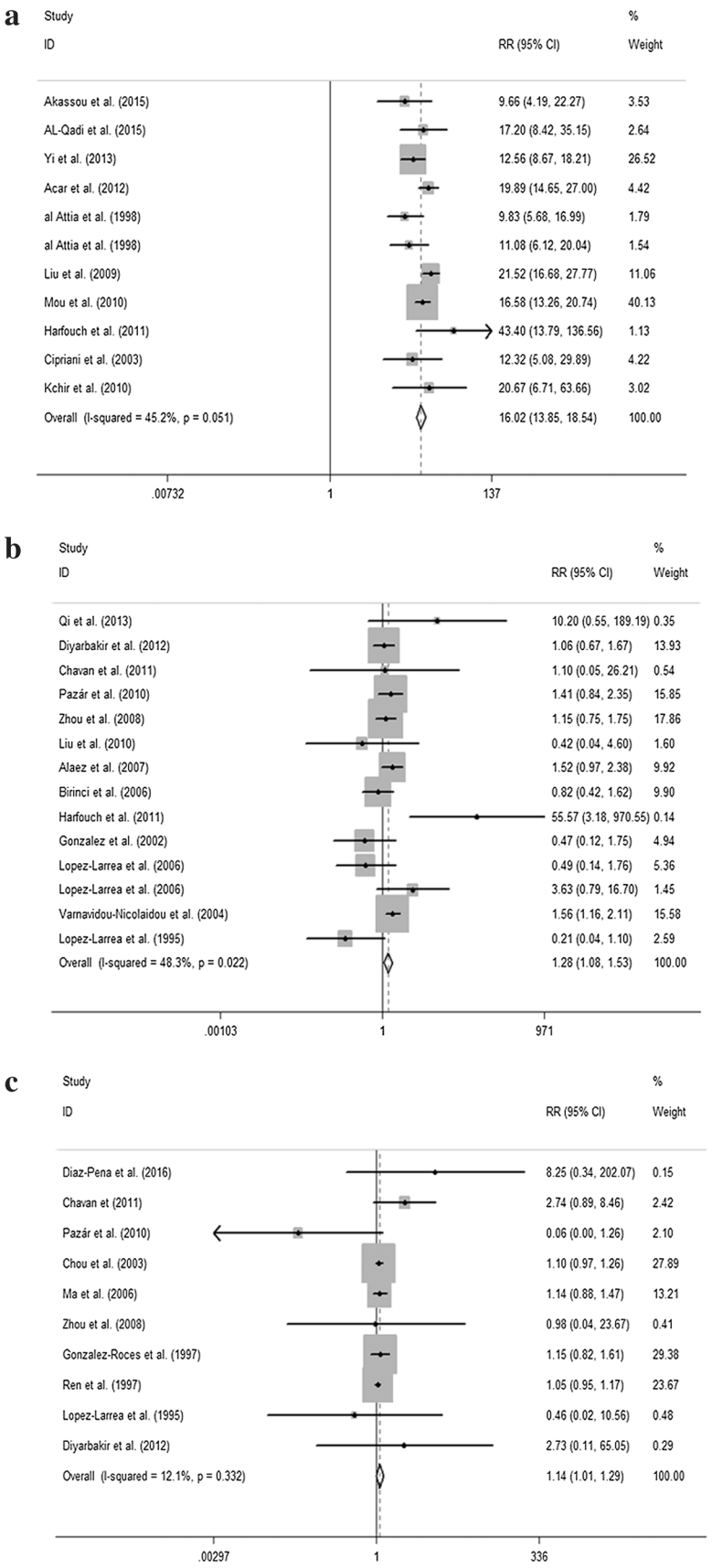


Fig. 2 Forest plots showing the association between B27/B27*02/B27*04 and AS. **a** HLA-B27; **b** HLA-B27*02; **c** HLA-B27*04

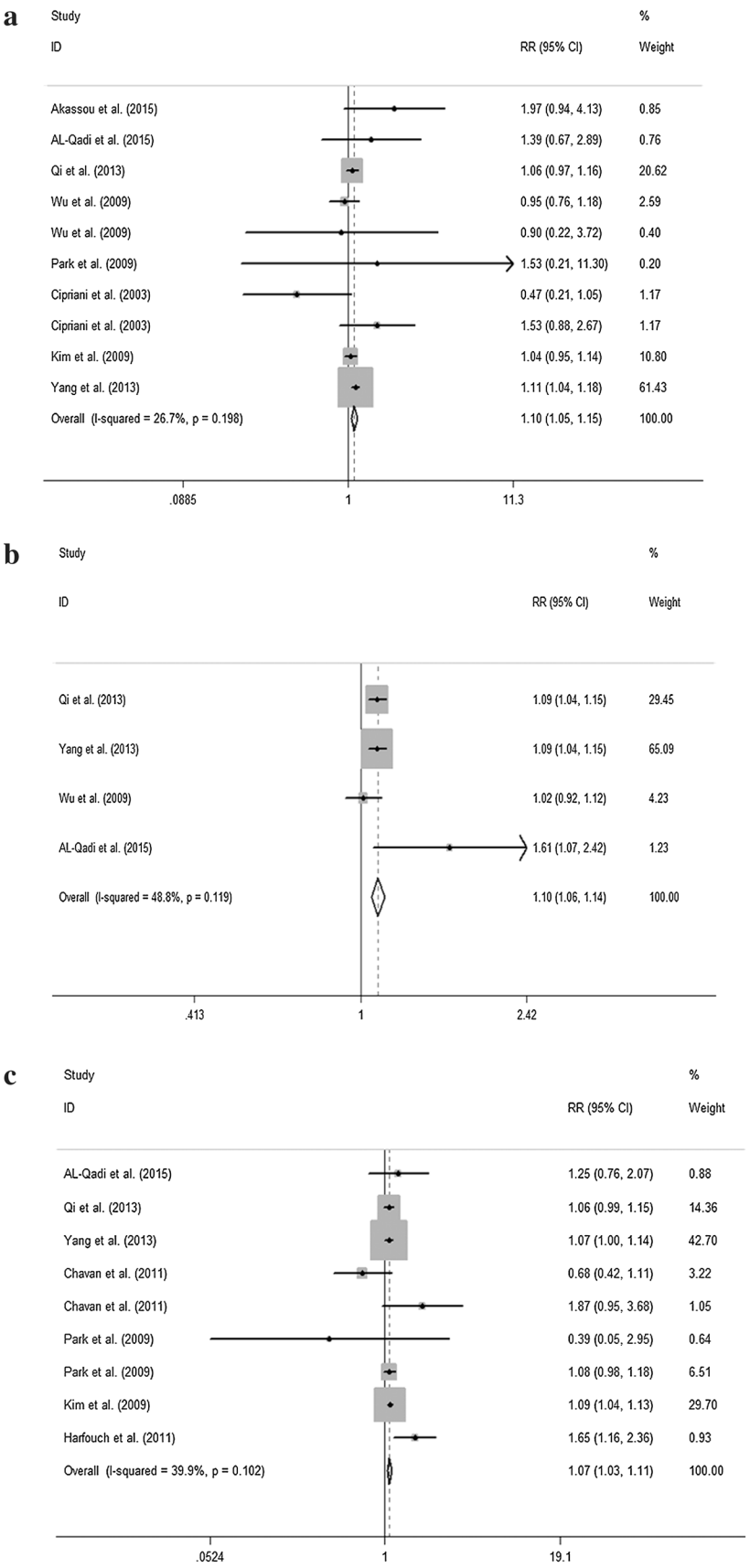
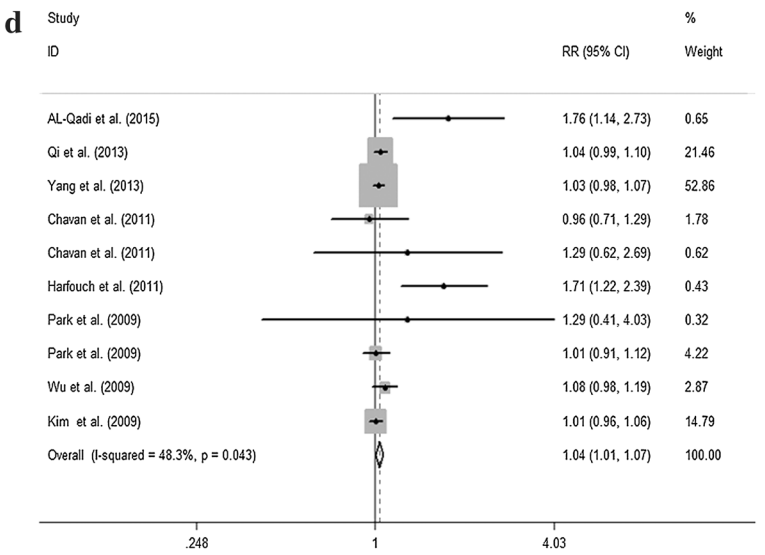
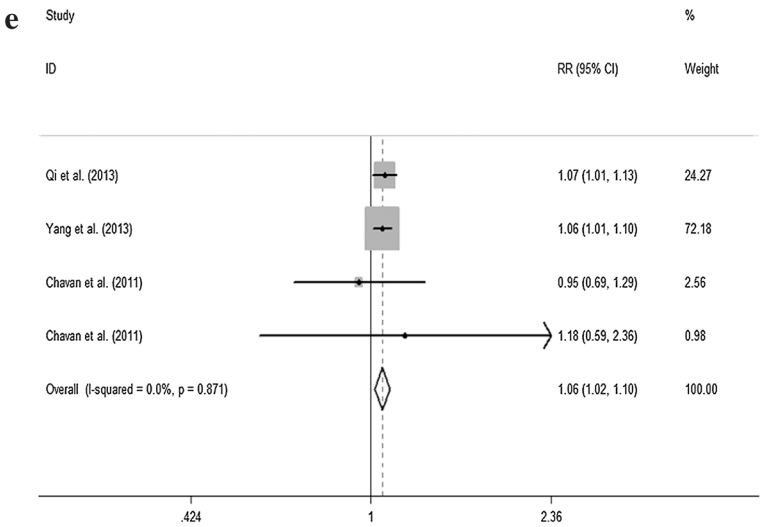


Fig. 3 Forest plots showing the relationship of HLA-B27/HLA-B27*04 with the clinical features of AS patients. HLA-B27: **a** sex (male); **b** family history; **c** uveitis; **d** peripheral joint involvement; **e** hip joints involvement. HLA-B27*04: **f** peripheral joint involvement

Fig. 3 continued





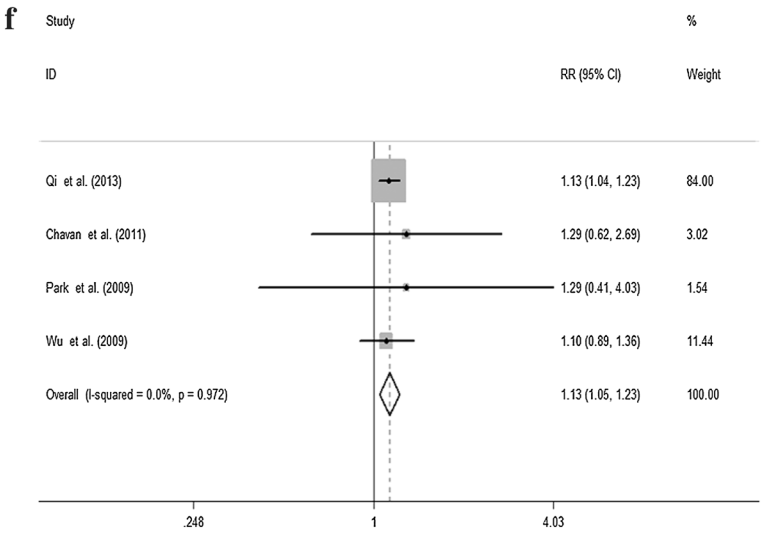


Table 3 Association between the risk of AS and HLA-B27/HLA-B27 subtypes

Polymorphisms and characteristics	RR (95% CI)	Heterogeneity				Publication bias			
		I^2 (%)	*P*	Z	*P*	Begg's test	*P*	Egger's test	*P*
B27	8.24 (7.75, 8.76)	99.40	<0.001	67.37	<0.001	1.94	0.053	2.67	0.018
	16.02 (13.85, 8.54)	45.20	0.051	37.29	<0.001	0.47	0.64	−0.86	0.411
B2704	4.58 (4.25, 4.94)	99.50	<0.001	39.82	<0.001	1.21	0.225	1.69	0.111
	1.14 (1.01, 1.29)	12.10	0.332	2.04	0.041	0.89	0.371	0.51	0.622
B2705	1.53 (1.46, 1.61)	96.10	<0.001	16.8	<0.001	1.58	0.113	1.94	0.063
	1.04 (0.97, 1.12)	40	0.055	1.14	0.256	0.79	0.428	−0.7	0.498
B2702	1.49 (1.31, 1.70)	80.00	<0.001	6.07	<0.001	0.47	0.637	0.75	0.462
	1.28 (1.08, 1.53)	48.30	0.022	2.79	0.005	0.33	0.743	−0.32	0.753

Table 4 The relationship of clinical features with HLA-B27 in AS patients

Polymorphisms and characteristics	RR (95% CI)	Heterogeneity				Publication bias			
		I^2 (%)	*P*	Z	*P*	Begg's test	*P*	Egger's test	*P*
Uveitis	1.05 (1.02, 1.09)	59.90	0.008	2.76	0.006	0	1	−0.12	0.911
	1.07 (1.03, 1.11)	39.90	0.102	3.54	<0.001	−0.1	1	0.39	0.710
Sex	1.06 (1.01, 1.11)	87.70	<0.001	2.48	0.013	0.47	0.64	−0.96	0.363
	1.10 (1.05, 1.15)	26.70	0.198	3.84	<0.001	0.18	0.858	0.08	0.942
Family history	1.10 (1.07, 1.14)	73.50	0.005	5.54	<0.001	0.24	0.806	1.69	0.189
	1.10 (1.06, 1.140)	48.80	0.119	5.18	<0.001	−0.34	1	0.64	0.589
Peripheral joint involvement	1.04 (1.01, 1.07)	48.30	0.043	2.43	0.013	0.89	0.371	2.23	0.056
Hip joints involvement	1.04 (1.01, 1.08)	88.45	<0.001	2.55	0.011	−0.24	1	0.66	0.559
	1.06 (1.02, 1.10)	0.00	0.871	2.95	0.003	−0.34	1	−0.36	0.75

identify the association between HLA-B27 and AS susceptibility. Notably, it could also offer some indications on the influence of HLA-B27 on the clinical characteristics in AS patients.

In our current study, we found HLA-B27 was positively associated with AS susceptibility [RR (95% CI) 16.02 (13.85, 18.54), $P < 0.001$] without identifying the subtypes of HLA-B27, which has not been reported in other articles. Moreover, no matter there was heterogeneity or not, the prevalence of HLA-B27*04 could increase the risk of AS, which was inconsistent with the results concluded by Yang et al. [49] and Zhang et al. [50]. The same to HLA-B27*04, we also found positive association between HLA-B27*02 and susceptibility to AS. In contrast, Yang et al. [49] and Zhang et al. [50] have suggested that HLA-B27*02 showed no relation to AS. In addition, it was observed that HLA-B27*05 was positively in relation to AS with the existence of heterogeneity, and no association was found when the heterogeneity was not statistically significant, which was in line with the study reported by Yang et al. [49]. To the opposite, Zhang et al. have found there was negative association between HLA-B27*05 and AS susceptibility [50].

Importantly, we are the first to explore the relationship of HLA-B27 and the clinical features in AS patients. The results suggested that male populations and patients with AS family history were more susceptible to AS, which were in consistent with previous studies [13, 14, 27]. While another study reported by Wu et al. showed no association between family history and the susceptibility to AS [47]. In addition, we also found that HLA-B27 positive AS patients were more likely accompanied with uveitis, peripheral joint involvement and hip joints involvement. Three previous studies showed the same results that the incidence of uveitis was positively related to HLA-B27 expression in AS patients [16, 45, 51]. In contrast, another three studies demonstrated that HLA-B27 had no relationship with the risk of AS [13, 30, 46]. The researches studied by Al-Qadi et al. and Kim et al. identified that HLA-B27+ patients are more likely to suffer the functional disability of peripheral join and hip joints, respectively [13, 51]. However, Chavan et al. testified that no significant difference was observed between the distribution of HLA-B27 and peripheral join involvement and hip joints involvement [30]. In addition, we

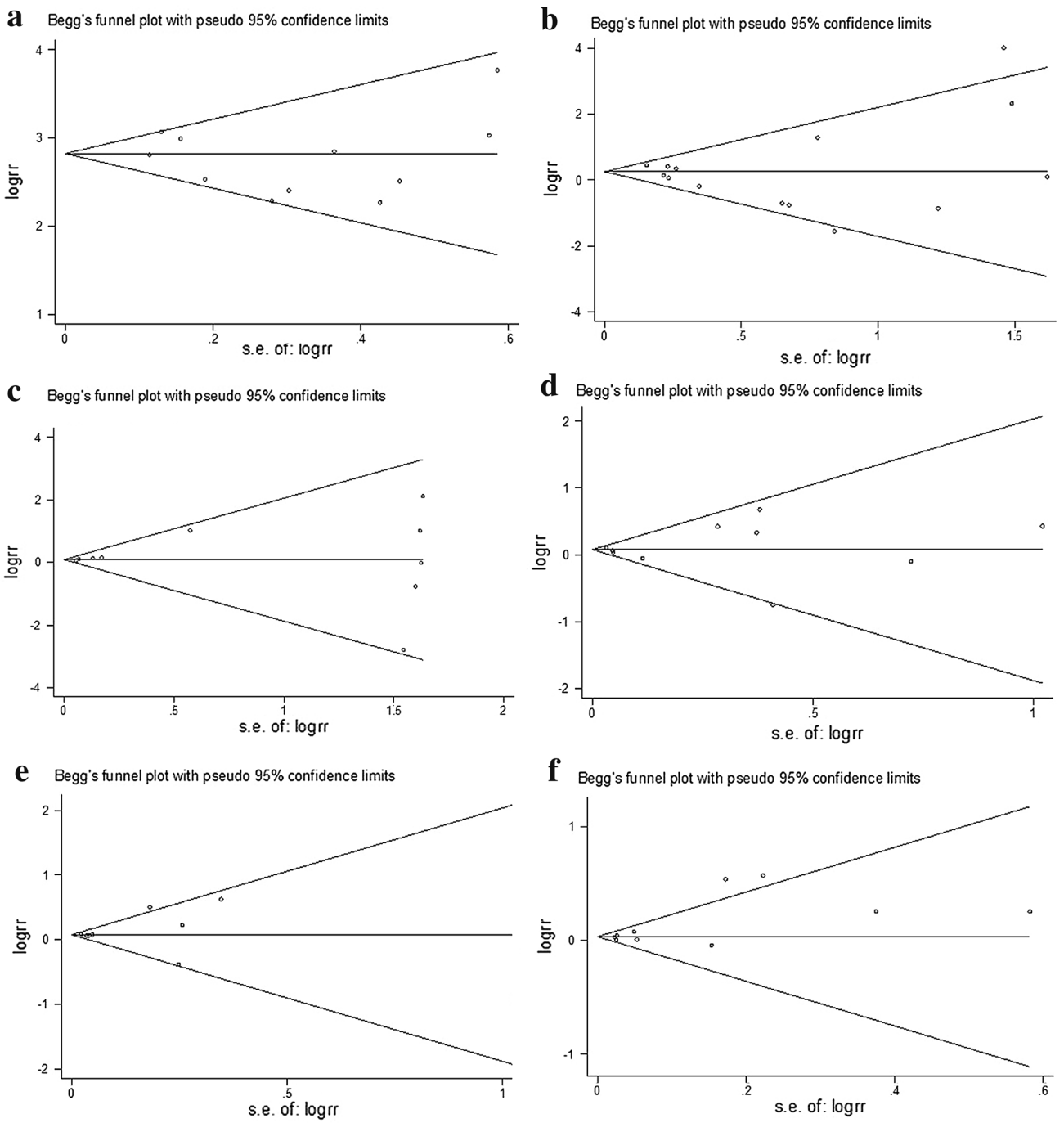


Fig. 4 Begg's funnel plots for publication bias test on studies assessing the association between HLA-B27/HAL-B27*02/HLA-27*04 and AS/clinical features. The relationship of HLA-B27/B27*02/B27*04 with AS: **a** HLA-B27 ($I^2 = 26.7$, $P = 0.198$); **b** HLA-B27*02; **c** HLA-B27*04. Positive association between HLA-B27 and clinical features of AS patients: **d** sex (male); **e** uveitis; **f** peripheral joint involvement

also investigated that AS patients with HLA-B27*04 tended to peripheral joint involvement, which was in contrast with previous studies [16, 47]. Although we found HLA-B27*05 was associated with sex and uveitis in AS patients, there existed heterogeneity. Therefore, further investigation was needed to be conducted.

The limitation

We attempted to make a comprehensive analysis via extensive strategy. However, as we did not involve the articles not published in English, some relevant articles might be missed. Besides, the samples were collected from different region in the worldwide and the sample size differed in different studies, which contribute to the heterogeneity. As we excluded the literatures in related to other subtypes of HLA-27 studied in less than three articles, which might make it unavailable to understand the effects of other HLA-B27 subtypes on AS. In addition, the studies demonstrated the clinical features of AS patients were limited, so it was needed to make further investigation for exploring the association between HLA-B27 and clinical parameters in AS patients.

Conclusion

In conclusion, our current meta-analysis not only demonstrated that HLA-B27, HLA-B27*02 and HLA-B27*04 showed association with AS, but also indicated the prevalence of HLA-B27 might influence the clinical symptoms of AS patients. While considering the existence of limitation in our meta-analysis, further studies should be performed to explore the relationship of HLA-B27 with AS and the symptoms in AS patients.

Compliance with ethical standard

Conflict of interest The authors declare that they have no conflict of interests.

Ethical approval No procedure in this study has involved human participants.

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