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Review Article

Association between human leukocyte antigen-B and vitiligo risk: a meta-analysis

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Abstract: Objective: Previous studies have investigated the association between human leukocyte antigen-B (HLA-B) and vitiligo risk. However, the results of such studies remain conflicting. This meta-analysis was performed to systematically evaluate the association between HLA-B and vitiligo risk. Methods: We searched PubMed, Embase, Web of Science and China National Knowledge Infrastructure databases up to January 31, 2017 for relevant studies. Pooled odds ratios and corresponding 95% confidence intervals were calculated to assess the strength of the association. Results: Eighteen case-control studies involving 2967 vitiligo cases and 5599 controls were included, in which 61 HLA-B alleles were reported. Overall, 7 alleles (HLA-B*13, B*27, Bw*06, Bw*46, Bw*55, Bw*56 and Bw*60) were significantly associated with increased risk of vitiligo, 3 (HLA-B*18, B*35, and B*52) were associated with decreased risk, and the rest 51 were unassociated. In subgroup analyses stratified by ethnicity, clinical type and typing methods, the association of 8 (HLA-B*07, B*08, B*13, B*14, B*18, B*27, B*35 and B*37), 2 (HLA-B*07 and B*27) and 5 alleles (HLA-B*18, B*27, B*35, B*40 and B*50) with vitiligo risk was inconsistent in three populations, both types of vitiligo and both typing methods, respectively. Conclusion: This meta-analysis suggests that HLA-B*13, B*27, Bw*06, Bw*46, Bw*55, Bw*56 and Bw*60 are associated with increased risk of vitiligo, while HLA-B*18, B*35 and B*52 are associated with decreased risk of vitiligo. The association of some alleles varies in terms of ethnicity, clinical type and typing methods.

Keywords: Human leukocyte antigen-B, alleles, vitiligo, risk, meta-analysis

Introduction

Vitiligo is a common acquired depigmentation disorder of the skin characterized by white macules and patches [1]. It affects approximately 0.5-2% of the world population, involving both sexes and all age groups [2]. The exact pathogenesis of vitiligo is still unknown, but various theories have been proposed, including autoimmune, neural, genetic, melanocytorrhagy and reactive oxygen species model hypotheses [3]. Of these, the autoimmune hypothesis is currently most widely accepted because of the frequent occurrence of other concomitant autoimmune diseases [4, 5] and the presence of circulating autoantibodies against pigment cells [6, 7]. In addition, several genetic epidemiological studies have suggested that genetic factors play a key role in the pathogenesis of vitiligo [8, 9].

Human leukocyte antigen (HLA), the major histocompatibility complex (MHC) in humans, has been reported to be associated with a wide spectrum of human diseases, particularly the diseases with an immunological basis [10, 11]. It is the most gene-dense, polymorphic region of the human genome and has been divided into three regions: classes I (HLA-A, B and C), II and III [12]. The inherited nature of vitiligo and its frequent association with autoimmune diseases have prompted numerous studies on the association of vitiligo with HLA, especially HLA-B [11-28]. However, the results of these studies remain conflicting due to distinct ethnic populations, small sample sizes and different

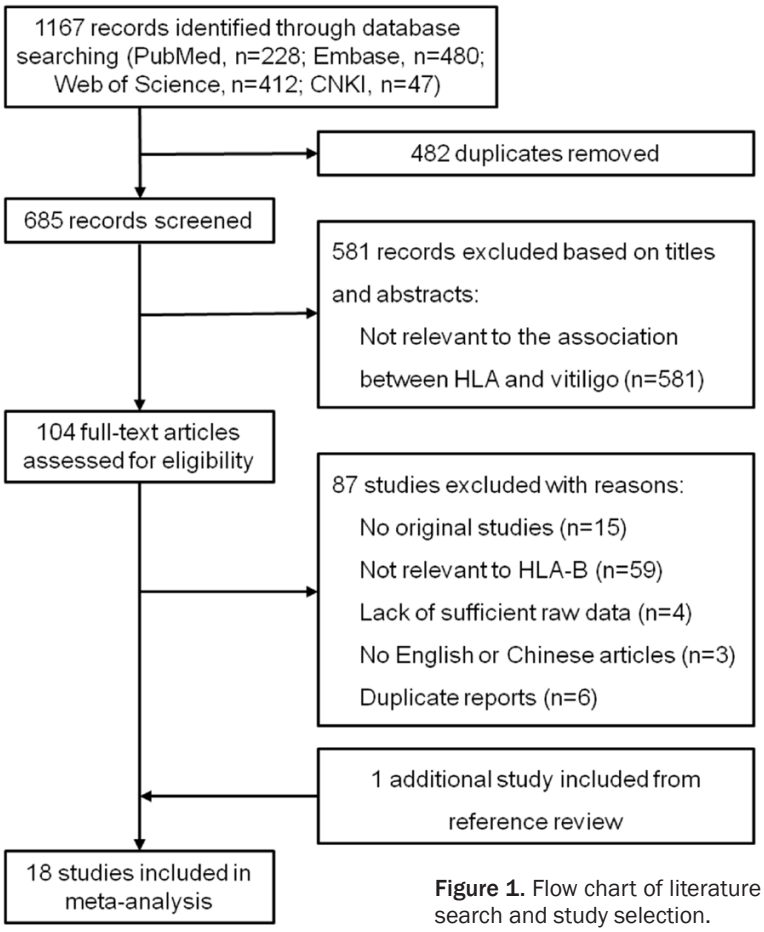

Figure 1. Flow chart of literature search and study selection.

research methods. Up to date, there is no published review on quantitative analysis of the association between HLA-B and vitiligo.

Therefore, in this study, we conducted a meta-analysis of case-control studies to systematically evaluate the association between HLA-B and vitiligo risk.

Materials and methods

Search strategy

We performed a comprehensive literature search of PubMed, Embase, Web of Science and China National Knowledge Infrastructure (CNKI) databases to identify the relevant studies on the association between HLA and vitiligo, using free text and Medical Subject Headings (MeSH) terms such as "human leukocyte antigen", "HLA", "major histocompatibility complex", "MHC" and "vitiligo". The search period was from inception to January 31, 2017, and the language was limited to either English or Chinese. Moreover, we reviewed the reference lists of retrieved articles to search for additional studies.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) primary studies exploring the association between HLA-B and vitiligo; (2) case-control design; (3) studies with full-text articles; (4) studies presenting sufficient data for calculating odds ratios (ORs) and corresponding 95% confidence intervals (CIs); (5) serological and molecular methods used for HLA-B typing. Exclusion criteria were as follows: (1) no original research (reviews, abstracts, editorials, case reports and nonresearch letters); (2) studies without control subjects; (3) incomplete raw data; (4) duplicate articles or reused data.

Data extraction and quality assessment

Two investigators (Li Z and Xu Q) independently extracted data using a standard form. Any discrepancy was resolved by discussion and consensus with a third investigator (Niu X). The following data were collected: first author, year of publication, study design, country, ethnicity, characteristics of the study population, numbers of cases and controls, clinical types of vitiligo, typing methods and frequencies of HLA-B alleles in cases and controls. The quality of all included studies was assessed using the criteria proposed by Chalmers et al. [29], which consist of three major aspects: selection of subjects, comparability between groups and outcome presented. The selected studies were rated on an ordinal star scoring scale from 1 to 9, with scores of 5 or more stars representing high quality [30].

Statistical analysis

The Chi-squared and Fisher's exact tests were applied to compare the frequencies of HLA-B

Table 1. Characteristics of studies included in the meta-analysis

Study	Country	Ethnicity	Cases		Controls		Typing methods	Significant association with HLA-B ($P < 0.05$)		Quality score
			Clinical types	Number	Types	Number		Positive	Negative	
Ramire et al., 2016 [13]	Brazil	American	27 localized, 78 generalized, 11 nonclassified	116	NCs	243	PCR-SSO	B18, 50	B07, 08, 13, 14, 15, 27, 35, 37, 38, 39, 40, 41, 42, 44, 45, 48, 49, 51, 52, 53, 55, 57, 58, 78, 81	8
Singh et al., 2012 [14]	India	Asian	412 localized, 1345 generalized	1757	NCs	1309	PCR-SSOP	B08, 37, 44, 51		7
Akay et al., 2010 [15]	Turkey	Asian	Unknown	52	NCs	100	LCT	B63	B07, 08, 14, 16, 17, 18, 27, 35, 38, 39, 44, 51, 52	9
Abanmi et al., 2006 [11]	Saudi Arabia	Asian	34 generalized, 6 universal	40	NCs	40	LCT	B05, 07, 15, 35, Bw06	B08, 10, 12, 13, 14, 16, 17, 21, 22, 41, 42, 46, 48, 53, 59, 70, 73, 78, Bw04	9
Zhang et al., 2004 [12]	China	Asian	93 localized, 94 generalized	187	NCs	252	PCR-SSP	B13, 27, 37	B07, 08, 15, 35, 38, 39, 40, 44, 46,47, 51, 52, 54, 57, 58, 67	9
Tastan et al., 2004 [16]	Turkey	Asian	Unknown	33	NCs	100	LCT		B05, 07, 08, 13, 14, 16, 18, 27, 35, 37, 38, 39, 41, 44, 45, 47, 49, 50, 51, 52, 53, 54, 56, 57, 58, 60, 61, 62, 63, 75	5
Wang et al., 2000 [17]	China	Asian	40 vulgaris, 22 focal, 8 acrofacial, 25 segmental	95	NCs	100	LCT	B13, 15, 40, 46, 51	B05, 07, 08, 12, 16, 17, 22, 27, 35, 37	9
Valsecchi et al., 1995 [19]	Italy	European	20 vulgaris, 3 focal, 7 acrofacial, 3 acral	33	NCs	443	LCT	B37	B07, 08, 13, 14, 15, 16, 17, 18, 21, 22, 27, 35, 40, 41, 44, 51	6
Venkataram et al., 1995 [18]	Oman	Asian	29 focal, 21 acrofacial	50	NCs	92	LCT	Bw06		7
al-Fouzan et al., 1995 [20]	Kuwait	Asian	40 nonsegmental	40	NCs	40	LCT	B21		9
Venneker et al., 1993 [21]	Dutch	European	48 generalized	48	NCs	703	LCT	B07, 14		6
Schallreuter et al., 1993 [22]	German	European	57 vulgaris, 13 focal, 22 acrofacial, 7 universal, 3 segmental	102	NCs	400	LCT		Bw60	9
Ando et al., 1993 [23]	Japan	Asian	39 nonsegmental	39	NCs	544	LCT	B52, Bw46, 55	B13, 27, 35, 39, 44, 51, Bw48, 54, 60, 61, 62	5
Orecchia et al., 1992 [24]	Italy	European	65 vulgaris, 13 focal, 7 acrofacial, 8 acral	93	NCs	388	LCT	B27, 35, Bw56	B21	6
Poloy et al., 1991 [25]	Hungary	European	Unknown	57	NCs	160	LCT	B08	B27	5
Dai et al., 1990 [26]	China	Asian	30 focal, 40 generalized, 30 segmental	100	NCs	116	LCT	B07, 15, Bw22	B05, 08, 12, 13, 16, 17, 27, 40, Bw35	6
Metzker et al., 1980 [27]	Israel	Mixed	Unknown	77	NCs	462	LCT		B05, 07, 08, 12, 13, 14, 15, 17, 18, 27, 37, 40, Bw16, 21, 22, 35	5
Kachru et al., 1978 [28]	America	American	Unknown	48	NCs	107	LCT		B05, 07, 08, 12, 13, 14, 15, 17, 18, 27, 40, Bw16, 21, 22, 35	7

HLA-B, human leukocyte antigen-B; Number, number of subjects; NCs, normal controls; LCT, lymphocytotoxicity test; PCR-SSP, polymerase chain reaction sequence-specific primers; PCR-SSO, polymerase chain reaction sequence-specific oligonucleotides; PCR-SSOP, polymerase chain reaction sequence-specific oligonucleotide probes.

Table 2. Association between 61 HLA-B alleles and vitiligo risk

Allele	Cases% (n/N)	Controls% (n/N)	OR (95% CI)/Article number	*P*	Effects model
B*05	19.85 (78/393)	19.57 (181/925)	0.77 (0.43, 1.38)/6	0.387	R
B*07	11.58 (96/829)	14.67 (391/2666)	1.12 (0.70, 1.78)/11	0.636	R
B*08	5.90 (153/2595)	9.50 (326/3432)	0.99 (0.60, 1.63)/12	0.969	R
B*10	0.00 (0/40)	2.50 (1/40)	0.33 (0.01, 8.22)/1	0.495	F
B*12	18.06 (65/360)	19.15 (158/825)	1.36 (0.96, 1.94)/5	0.086	F
B*13	25.26 (194/768)	9.72 (234/2407)	1.90 (1.30, 2.78)/10	0.001	R
B*14	4.70 (21/447)	7.05 (155/2198)	0.63 (0.27, 1.47)/8	0.288	R
B*15	17.39 (121/696)	10.49 (185/1763)	1.21 (0.59, 2.49)/8	0.606	R
B*16	4.53 (16/353)	6.23 (56/899)	0.96 (0.52, 1.78)/6	0.892	F
B*17	9.89 (44/445)	9.72 (133/1368)	0.84 (0.57, 1.24)/7	0.378	F
B*18	5.57 (20/359)	10.93 (159/1455)	0.55 (0.34, 0.90)/6	0.016	F
B*21	18.93 (39/206)	10.98 (100/911)	1.24 (0.31, 4.95)/4	0.760	R
B*22	5.95 (10/168)	3.43 (20/583)	1.10 (0.26, 4.75)/3	0.895	R
B*27	9.35 (87/930)	4.28 (129/3015)	1.72 (1.27, 2.32)/12	< 0.001	F
B*35	11.63 (80/688)	21.67 (479/2210)	0.66 (0.50, 0.87)/9	0.003	F
B*37	6.40 (147/2298)	3.85 (112/2909)	1.05 (0.43, 2.58)/7	0.918	R
B*38	6.96 (27/388)	7.63 (53/695)	0.91 (0.56, 1.49)/4	0.720	F
B*39	6.32 (27/427)	6.30 (78/1239)	1.23 (0.76, 2.01)/5	0.405	F
B*40	19.21 (126/656)	12.30 (212/1723)	0.90 (0.58, 1.41)/7	0.656	R
B*41	1.80 (4/222)	1.09 (9/826)	1.58 (0.48, 5.20)/4	0.448	F
B*42	5.77 (9/156)	5.30 (15/283)	1.19 (0.51, 2.77)/2	0.694	F
B*44	26.21 (581/2217)	13.51 (404/2991)	1.13 (0.56, 2.27)/7	0.727	R
B*45	1.34 (2/149)	2.62 (9/343)	0.58 (0.14, 2.35)/2	0.442	F
B*46	9.63 (31/322)	15.05 (59/392)	0.55 (0.15, 1.97)/3	0.358	R
B*47	6.82 (15/220)	6.53 (23/352)	0.93 (0.48, 1.83)/2	0.840	F
B*48	0.64 (1/156)	0.35 (1/283)	1.39 (0.21, 9.19)/2	0.732	F
B*49	5.37 (8/149)	5.25 (18/343)	1.05 (0.45, 2.45)/2	0.905	F
B*50	5.74 (14/244)	4.74 (21/443)	0.69 (0.06, 7.68)/3	0.760	R
B*51	11.86 (263/2217)	16.85 (504/2991)	1.03 (0.70, 1.52)/7	0.875	R
B*52	3.98 (17/427)	12.43 (154/1239)	0.48 (0.27, 0.83)/5	0.009	F
B*53	9.52 (18/189)	4.44 (17/383)	1.71 (0.83, 3.52)/3	0.147	F
B*54	10.91 (24/220)	11.65 (41/352)	0.79 (0.46, 1.35)/2	0.379	F
B*55	0.86 (1/116)	4.12 (10/243)	0.20 (0.03, 1.60)/1	0.130	F
B*56	9.09 (3/33)	5.00 (5/100)	1.90 (0.43, 8.42)/1	0.398	F
B*57	2.98 (10/336)	2.86 (17/595)	1.14 (0.52, 2.50)/3	0.753	F
B*58	5.06 (17/336)	4.20 (25/595)	1.21 (0.64, 2.26)/3	0.559	F
B*59	0.00 (0/40)	2.50 (1/40)	0.33 (0.01, 8.22)/1	0.495	F
B*60	0.00 (0/33)	5.00 (5/100)	0.26 (0.01, 4.81)/1	0.365	F
B*61	0.00 (0/33)	1.00 (1/100)	0.99 (0.04, 24.89)/1	0.995	F
B*62	3.03 (1/33)	2.00 (2/100)	1.53 (0.13, 17.45)/1	0.731	F
B*63	3.53 (3/85)	1.00 (2/200)	2.95 (0.13, 67.39)/2	0.498	R
B*67	2.67 (5/187)	1.59 (4/252)	1.70 (0.45, 6.43)/1	0.432	F
B*70	0.00 (0/40)	5.00 (2/40)	0.19 (0.01, 4.09)/1	0.289	F
B*73	5.00 (2/40)	0.00 (0/40)	5.26 (0.24, 113.11)/1	0.289	F
B*75	0.00 (0/33)	1.00 (1/100)	0.99 (0.04, 24.89)/1	0.995	F
B*78	0.00 (0/156)	0.71 (2/283)	0.47 (0.05, 4.58)/2	0.516	F
B*81	0.86 (1/117)	0.41 (1/243)	2.10 (0.13, 33.94)/1	0.600	F

Bw*04	50.00 (20/40)	60.00 (24/40)	0.67 (0.27, 1.62)/1	0.370	F
Bw*06	81.11 (73/90)	51.52 (68/132)	3.95 (2.10, 7.45)/2	< 0.001	F
Bw*16	11.20 (14/125)	12.30 (70/569)	1.17 (0.63, 2.20)/2	0.619	F
Bw*21	13.60 (17/125)	12.48 (71/569)	1.33 (0.75, 2.38)/2	0.330	F
Bw*22	7.11 (16/225)	7.15 (49/685)	0.73 (0.17, 3.18)/3	0.680	R
Bw*35	17.33 (39/225)	27.30 (187/685)	0.80 (0.53, 1.21)/3	0.287	F
Bw*46	7.69 (3/39)	0.55 (3/544)	15.03 (2.93, 77.12)/1	0.001	F
Bw*48	7.69 (3/39)	3.68 (20/544)	2.18 (0.62, 7.69)/1	0.224	F
Bw*54	17.95 (7/39)	17.83 (97/544)	1.01 (0.43, 2.35)/1	0.985	F
Bw*55	12.82 (5/39)	4.41 (24/544)	3.19 (1.14, 8.87)/1	0.027	F
Bw*56	3.23 (3/39)	0.26 (1/388)	12.90 (1.33, 125.46)/1	0.028	F
Bw*60	16.31 (23/141)	8.16 (77/944)	2.26 (1.34, 3.81)/2	0.002	F
Bw*61	25.64 (10/39)	25.92 (141/544)	0.99 (0.47, 2.07)/1	0.969	F
Bw*62	15.38 (6/39)	15.44 (84/544)	1.00 (0.40, 2.45)/1	0.992	F

HLA-B, human leukocyte antigen-B; N, total number of subjects; n, positive number of subjects; OR, odds ratio; CI, confidence interval; Article number, total number of the articles studied on HLA-B alleles; R, random effects model; F, fixed effects model.

alleles in patients with vitiligo and controls to identify the associated alleles, with significance set at $P < 0.05$. Meta-analysis of the association between HLA-B alleles and vitiligo risk was performed using two different approaches: a fixed effects model and a random effects model. Heterogeneity across studies was evaluated through the Chi-squared test and I^2 statistic, and $P < 0.10$ or $I^2 > 50\%$ was considered statistically significant. The pooled ORs and corresponding 95% CIs were calculated using either the random effects model when heterogeneity was confirmed or the fixed effects model when heterogeneity was absent. The test for overall effect was conducted using Z-scores, with significance set at $P < 0.05$. Subgroup analyses were conducted according to ethnicity, clinical type and typing methods. Sensitivity was analyzed by omitting each study at each step to assess whether any single study had a significant influence on the pooled OR. Finally, publication bias was assessed by Begg's funnel plots and Egger's test, and the significance level was set at $P < 0.05$. The statistical analyses were performed using SPSS version 19.0 (SPSS Institute, Chicago, USA) and Stata version 12.0 (Stata Corporation, College Station, TX, USA). All P values were two-sided.

Results

Literature search and study selection

As shown in **Figure 1**, a total of 1167 records were initially identified through database searches. After removing duplicates and screening titles and abstracts, 104 full-text articles were reviewed, and 17 studies [11-25, 27, 28] finally met the inclusion criteria. One additional study [26] was identified from a review of the reference lists. Altogether, 18 case-control studies were included in this meta-analysis, among which 16 [11-16, 18-25, 27, 28] and 2 studies [17, 26] were published in English and Chinese respectively.

Study characteristics and quality assessment

The main characteristics of the included studies are summarized in **Table 1**. These 18 studies comprised 2967 patients with vitiligo and 5599 controls. Ten studies [11, 12, 14-18, 20, 23, 26] were investigated in Asians, 5 [19, 21, 22, 24, 25] were conducted in Europeans, 2 [13, 28] were performed in Americans, and the remaining 1 [27] was carried out in mixed populations. HLA-B typing methods such as lymphocytotoxicity test (LCT) [11, 15-28], polymerase chain reaction sequence-specific primers (PCR-SSP) [12], PCR sequence-specific oligonucleotide probes (PCR-SSOP) [14] and PCR sequence-specific oligonucleotides (PCR-SSO) [13] were applied in these studies. In total, 61 HLA-B alleles were involved. The results of the Chi-squared and Fisher's exact tests indicated that 23 alleles were associated with vitiligo and 57 were unassociated. Nineteen alleles were disputed. According to the quality assessment criteria [29, 30], all the 18 studies [11-28] were of high quality with scores between 5 and 9 stars.

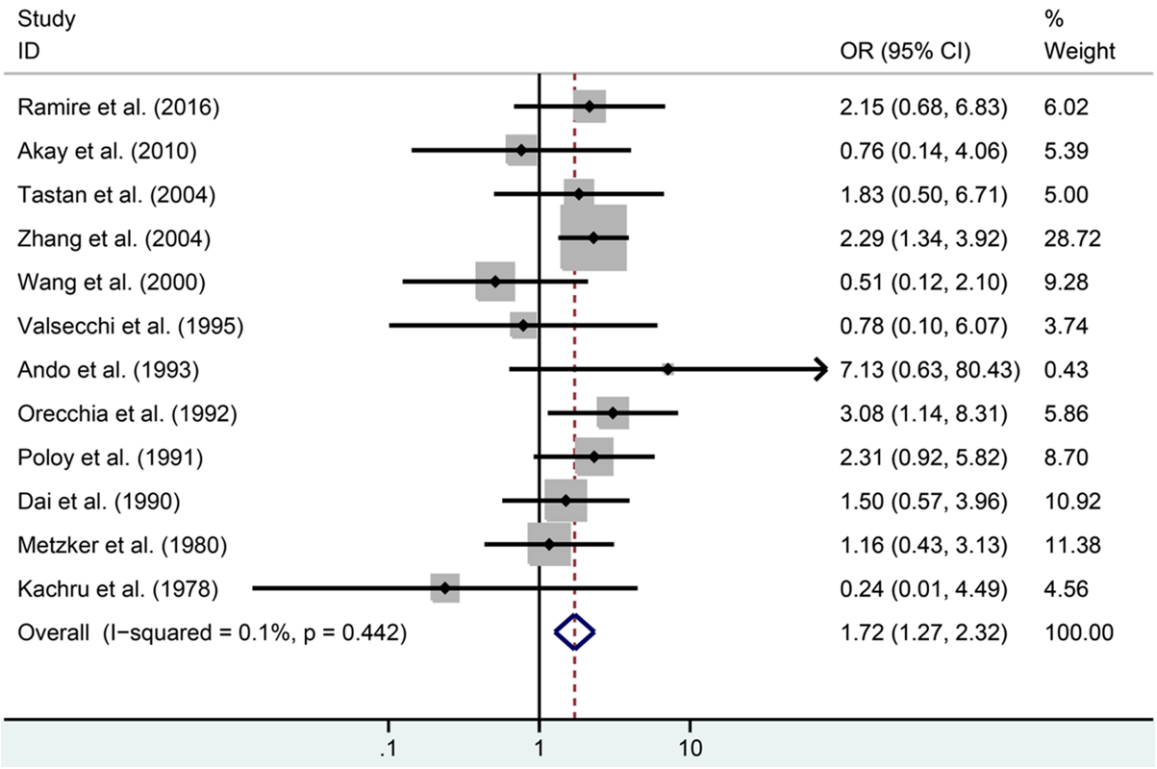

Figure 2. Forest plot of 12 included studies on the association between HLA-B*27 and vitiligo risk.

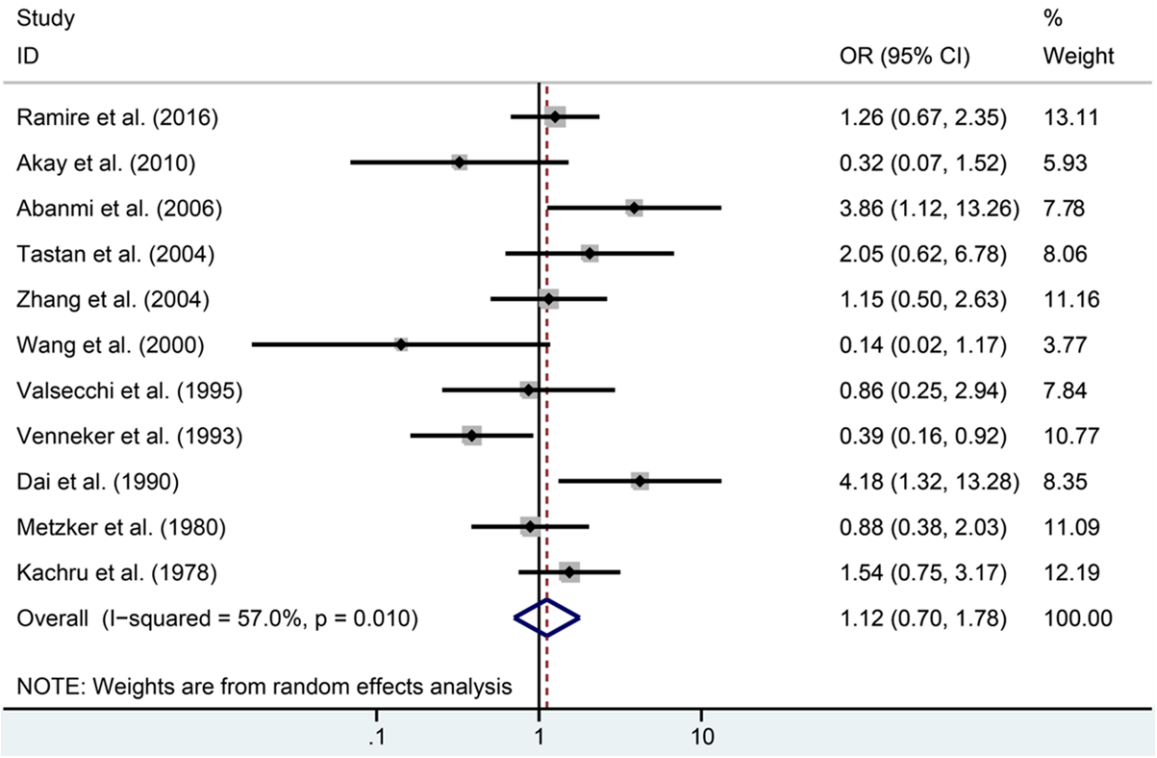

Figure 3. Forest plot of 11 included studies on the association between HLA-B*07 and vitiligo risk.

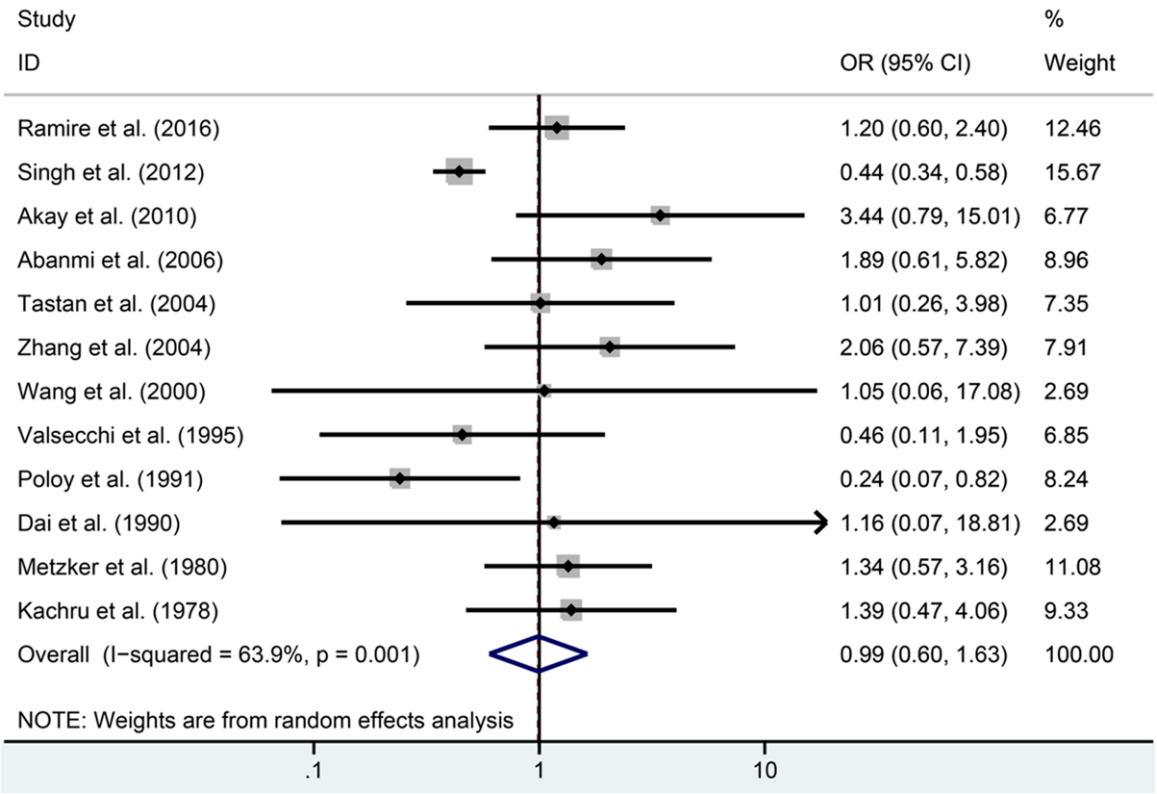

Figure 4. Forest plot of 12 included studies on the association between HLA-B*08 and vitiligo risk.

Meta-analysis of the association between HLA-B and vitiligo risk

The general information on the association of HLA-B with vitiligo risk is given in **Table 2**. Among the 61 HLA-B alleles included in the pooled analysis, 7 (HLA-B*13, B*27, Bw*06, Bw*46, Bw*55, Bw*56 and Bw*60) were significantly associated with increased risk of vitiligo, while 3 (HLA-B*18, B*35 and B*52) were associated with decreased risk. HLA-B*27 was reported in 12 studies. The pooled OR calculated with the fixed effects model was 1.72 (95% CI: 1.27-2.32, $P < 0.001$) (**Figure 2**), and no heterogeneity was detected ($P = 0.442$, $I^2 = 0.1\%$).

The rest 51 alleles were not associated with vitiligo, of which HLA-B*07 and B*08 were each involved in more than 10 studies. The pooled ORs calculated with the random effects model were 1.12 (95% CI: 0.70-1.78, $P = 0.636$) (**Figure 3**) and 0.99 (95% CI: 0.60-1.63, $P = 0.969$) (**Figure 4**), respectively. The heterogeneity was significant ($P = 0.010$, $I^2 = 57.0\%$, and $P = 0.001$, $I^2 = 63.9\%$, respectively).

Subgroup analysis according to ethnicity

Table 3 demonstrates the results of subgroup analysis based on ethnicity. Of the 54 HLA-B alleles studied in Asian patients with vitiligo, 4 (HLA-B*13, B*27, Bw*46 and Bw*55) were significantly associated with increased risk of vitiligo, and 2 (HLA-B*14 and B*35) were associated with decreased risk. The remaining 48 alleles were not associated with vitiligo. Among the 19 HLA-B alleles reported in European cases, 5 (HLA-B*14, B*27, B*37, Bw*56 and Bw*60) were significantly associated with increased risk of vitiligo, and 2 (HLA-B*07 and B*08) were associated with decreased risk. The rest 12 alleles were not associated. For American cases, 33 HLA-B alleles were studied. One allele (HLA-B*50) was significantly associated with increased risk of vitiligo, and 2 (HLA-B*14 and B*18) were associated with decreased risk. The other 30 alleles were not associated.

Fourteen alleles (HLA-B*07, B*08, B*13, B*14, B*15, B*17, B*18, B*27, B*35, B*37, B*40, B*41, B*44 and B*51) were common to

Table 3. Association between HLA-B alleles and vitiligo risk in terms of ethnicity

Ethnicity	Allele	Cases% (n/N)	Controls% (n/N)	OR (95% CI)/Article number	*P*	Effects model
Asian	B*05	21.27 (57/268)	19.10 (68/356)	0.77 (0.31, 1.89)/4	0.564	R
	B*07	8.68 (44/507)	6.21 (47/708)	1.33 (0.55, 3.21)/6	0.528	R
	B*08	5.34 (121/2264)	8.63 (174/2017)	1.23 (0.54, 2.79)/7	0.620	R
	B*10	0.00 (0/40)	2.50 (1/40)	0.33 (0.01, 8.22)/1	0.495	F
	B*12	12.77 (30/235)	7.81 (20/256)	1.75 (0.96, 3.19)/3	0.065	F
	B*13	34.21 (169/494)	12.41 (143/1152)	2.18 (1.22, 3.87)/6	0.008	R
	B*14	0.00 (0/125)	7.08 (17/240)	0.14 (0.03, 0.74)/3	0.021	F
	B*15	21.33 (90/422)	18.31 (93/508)	1.56 (0.45, 5.43)/4	0.484	R
	B*16	3.75 (12/320)	3.95 (18/456)	0.81 (0.39, 1.69)/5	0.575	F
	B*17	8.71 (25/287)	12.08 (43/356)	0.63 (0.37, 1.08)/4	0.091	F
	B*18	5.88 (5/85)	10.50 (21/200)	0.58 (0.21, 1.60)/2	0.293	F
	B*21	33.75 (27/80)	16.25 (13/80)	1.62 (0.04, 58.56)/2	0.794	R
	B*22	5.93 (8/135)	7.86 (11/140)	0.51 (0.05, 5.66)/2	0.582	R
	B*27	11.66 (59/506)	4.46 (54/1212)	1.73 (1.16, 2.57)/6	0.007	F
	B*35	7.40 (33/446)	16.46 (187/1136)	0.60 (0.40, 0.92)/6	0.018	F
	B*37	6.67 (138/2072)	4.83 (85/1761)	0.37 (0.06, 2.31)/4	0.286	R
	B*38	8.09 (22/272)	9.29 (42/452)	0.91 (0.52, 1.57)/3	0.723	F
	B*39	5.79 (18/311)	6.43 (64/996)	1.17 (0.65, 2.12)/4	0.603	F
	B*40	29.84 (114/382)	30.13 (141/468)	1.09 (0.55, 2.17)/3	0.801	R
	B*41	2.74 (2/73)	2.14 (3/140)	1.45 (0.27, 7.73)/2	0.666	F
	B*42	5.00 (2/40)	0.00 (0/40)	5.26 (0.24, 113.11)/1	0.289	F
	B*44	26.64 (551/2068)	12.28 (283/2305)	1.25 (0.54, 2.92)/5	0.602	R
	B*45	0.00 (0/33)	1.00 (1/100)	0.99 (0.04, 24.89)/1	0.995	F
	B*46	9.63 (31/322)	15.05 (59/392)	0.55 (0.15, 1.97)/3	0.358	R
	B*47	6.82 (15/220)	6.53 (23/352)	0.93 (0.48, 1.83)/2	0.840	F
	B*48	0.00 (0/40)	2.50 (1/40)	0.33 (0.01, 8.22)/1	0.495	F
	B*49	0.00 (0/33)	6.00 (6/100)	0.22 (0.01, 3.96)/1	0.302	F
	B*50	0.00 (0/128)	4.00 (8/200)	0.15 (0.02, 1.12)/2	0.065	F
	B*51	11.17 (231/2068)	16.62 (383/2305)	0.90 (0.59, 1.39)/5	0.642	R
	B*52	4.82 (15/311)	14.16 (141/996)	0.57 (0.19, 1.67)/4	0.305	R
	B*53	15.07 (11/73)	8.57 (12/140)	1.19 (0.47, 3.05)/2	0.714	F
	B*54	10.91 (24/220)	11.65 (41/352)	0.79 (0.46, 1.35)/2	0.379	F
	B*56	9.09 (3/33)	5.00 (5/100)	1.90 (0.43, 8.42)/1	0.398	F
	B*57	1.82 (4/220)	1.42 (5/352)	1.29 (0.36, 4.62)/2	0.697	F
	B*58	3.64 (8/220)	3.41 (12/352)	0.98 (0.40, 2.40)/2	0.965	F
	B*59	0.00 (0/40)	2.50 (1/40)	0.33 (0.10, 8.22)/1	0.495	F
	B*60	0.00 (0/33)	5.00 (5/100)	0.26 (0.01, 4.81)/1	0.365	F
	B*61	0.00 (0/33)	1.00 (1/100)	0.99 (0.04, 24.89)/1	0.995	F
	B*62	3.03 (1/33)	2.00 (2/100)	1.53 (0.13, 17.45)/1	0.731	F
	B*63	3.53 (3/85)	1.00 (2/200)	2.95 (0.13, 67.39)/2	0.498	R
	B*67	2.67 (5/187)	1.59 (4/252)	1.70 (0.45, 6.43)/1	0.432	F
	B*70	0.00 (0/40)	5.00 (2/40)	0.19 (0.01, 4.09)/1	0.289	F
	B*73	5.00 (2/40)	0.00 (0/40)	5.26 (0.24, 113.11)/1	0.289	F
	B*75	0.00 (0/33)	1.00 (1/100)	0.99 (0.04, 24.89)/1	0.995	F
	B*78	0.00 (0/40)	2.50 (1/40)	0.33 (0.01, 8.22)/1	0.495	F
	Bw*04	50.00 (20/40)	60.00 (24/40)	0.67 (0.27, 1.62)/1	0.370	F
	Bw*35	2.00 (2/100)	5.17 (6/116)	0.37 (0.07, 1.90)/1	0.235	F

	Bw*46	7.69 (3/39)	0.55 (3/544)	15.03 (2.93, 77.12)/1	0.001	F
	Bw*48	7.69 (3/39)	3.68 (20/544)	2.18 (0.62, 7.69)/1	0.224	F
	Bw*54	17.95 (7/39)	17.83 (97/544)	1.01 (0.43, 2.35)/1	0.985	F
	Bw*55	12.82 (5/39)	4.41 (24/544)	3.19 (1.14, 8.87)/1	0.027	F
	Bw*60	12.82 (5/39)	8.64 (47/544)	1.56 (0.58, 4.17)/1	0.380	F
	Bw*61	25.64 (10/39)	25.92 (141/544)	0.99 (0.47, 2.07)/1	0.969	F
	Bw*62	15.38 (6/39)	15.44 (84/544)	1.00 (0.40, 2.45)/1	0.992	F
European	B*07	11.11 (9/81)	20.59 (236/1146)	0.49 (0.24, 0.99)/2	0.047	F
	B*08	5.56 (5/90)	14.10 (85/603)	0.31 (0.12, 0.79)/2	0.015	F
	B*13	12.12 (4/33)	6.55 (29/443)	1.97 (0.65, 5.98)/1	0.232	F
	B*14	8.64 (7/81)	3.32 (38/1146)	2.74 (1.19, 6.34)/2	0.018	F
	B*15	3.03 (1/33)	7.45 (33/443)	0.39 (0.05, 2.93)/1	0.359	F
	B*16	12.12 (4/33)	8.58 (38/443)	1.47 (0.49, 4.40)/1	0.491	F
	B*17	6.06 (2/33)	6.55 (29/443)	0.92 (0.21, 4.04)/1	0.913	F
	B*18	12.12 (4/33)	14.67 (65/443)	0.80 (0.27, 2.36)/1	0.689	F
	B*21	9.52 (12/126)	10.47 (87/831)	0.88 (0.46, 1.68)/2	0.706	F
	B*22	6.06 (2/33)	2.03 (9/443)	3.11 (0.64, 15.03)/1	0.158	F
	B*27	9.29 (17/183)	3.94 (39/991)	2.24 (1.20, 4.20)/3	0.011	F
	B*35	23.02 (29/126)	28.40 (236/831)	0.84 (0.40, 1.74)/2	0.631	R
	B*37	15.15 (5/33)	3.16 (14/443)	5.47 (1.84, 16.28)/1	0.002	F
	B*40	3.03 (1/33)	2.48 (11/443)	1.23 (0.15, 9.81)/1	0.847	F
	B*41	3.03 (1/33)	0.90 (4/443)	3.43 (0.37, 31.59)/1	0.277	F
	B*44	0.90 (4/33)	14.00 (62/443)	0.85 (0.29, 2.49)/1	0.764	F
	B*51	27.27 (9/33)	18.06 (80/443)	1.70 (0.76, 3.80)/1	0.195	F
	Bw*56	3.23 (3/93)	0.26 (1/388)	12.90 (1.33, 125.46)/1	0.028	F
	Bw*60	17.65 (18/102)	7.50 (30/400)	2.64 (1.41, 4.96)/1	0.003	F
American	B*05	8.33 (4/48)	18.69 (20/107)	0.40 (0.13, 1.23)/1	0.109	F
	B*07	21.95 (36/164)	17.43 (61/350)	1.37 (0.86, 2.20)/2	0.190	F
	B*08	12.20 (20/164)	10.00 (35/350)	1.25 (0.70, 2.24)/2	0.455	F
	B*12	33.33 (16/48)	25.23 (27/107)	1.48 (0.71, 3.11)/1	0.299	F
	B*13	4.88 (8/164)	4.86 (17/350)	1.00 (0.42, 2.36)/2	0.991	F
	B*14	4.88 (8/164)	10.86 (38/350)	0.42 (0.19, 0.92)/2	0.030	F
	B*15	16.46 (27/164)	11.14 (39/350)	1.58 (0.92, 2.71)/2	0.100	F
	B*17	20.83 (10/48)	12.15 (13/107)	1.90 (0.77, 4.71)/1	0.164	F
	B*18	3.66 (6/164)	10.00 (35/350)	0.33 (0.14, 0.81)/2	0.016	F
	B*27	3.66 (6/164)	2.86 (10/350)	1.33 (0.49, 3.60)/2	0.576	F
	B*35	15.52 (18/116)	23.05 (56/243)	0.61 (0.34, 1.10)/1	0.101	F
	B*37	3.45 (4/116)	2.88 (7/243)	1.20 (0.35, 4.20)/1	0.771	F
	B*38	4.31 (5/116)	4.53 (11/243)	0.95 (0.32, 2.80)/1	0.926	F
	B*39	7.76 (9/116)	5.76 (14/243)	1.38 (0.58, 3.28)/1	0.471	F
	B*40	4.88 (8/164)	8.00 (28/350)	0.59 (0.26, 1.32)/2	0.196	F
	B*41	0.86 (1/116)	0.82 (2/243)	1.05 (0.09, 11.67)/1	0.970	F
	B*42	6.03 (7/116)	6.17 (15/243)	0.98 (0.39, 2.46)/1	0.959	F
	B*44	22.41 (26/116)	24.28 (59/243)	0.90 (0.53, 1.52)/1	0.697	F
	B*45	1.72 (2/116)	3.29 (8/243)	0.52 (0.11, 2.47)/1	0.407	F
	B*48	0.86 (1/116)	0.00 (0/243)	6.32 (0.26, 156.45)/1	0.260	F
	B*49	6.90 (8/116)	4.94 (12/243)	1.43 (0.57, 3.59)/1	0.451	F
	B*50	12.07 (14/116)	5.35 (13/243)	2.43 (1.10, 5.35)/1	0.028	F
	B*51	19.83 (23/116)	16.87(41/243)	1.22 (0.69, 2.15)/1	0.494	F

B*52	1.72 (2/116)	5.35 (13/243)	0.31 (0.07, 1.40)/1	0.128	F
B*53	6.03 (7/116)	2.05 (5/243)	3.06 (0.95, 9.85)/1	0.061	F
B*55	0.86 (1/116)	4.12 (10/243)	0.20 (0.03, 1.60)/1	0.130	F
B*57	5.17 (6/116)	4.94 (12/243)	1.05 (0.38, 2.87)/1	0.924	F
B*58	7.76 (9/116)	5.35 (13/243)	1.49 (0.62, 3.59)/1	0.376	F
B*78	0.00 (0/116)	0.41 (1/243)	0.69 (0.03, 17.16)/1	0.823	F
B*81	0.86 (1/116)	0.41 (1/243)	2.10 (0.13, 33.94)/1	0.600	F
Bw*16	2.08 (1/48)	1.87 (2/107)	1.12 (0.10, 12.62)/1	0.929	F
Bw*22	4.17 (2/48)	5.61 (6/107)	0.73 (0.14, 3.76)/1	0.709	F
Bw*35	31.25 (15/48)	38.32 (41/107)	0.73 (0.35, 1.51)/1	0.398	F

HLA-B, human leukocyte antigen-B; N, total number of subjects; n, positive number of subjects; OR, odds ratio; CI, confidence interval; Article number, total number of the articles studied on HLA-B alleles; R, random effects model; F, fixed effects model.

Asians, Europeans and Americans. However, 8 (HLA-B*07, B*08, B*13, B*14, B*18, B*27, B*35 and B*37) of them were inconsistent in their association with vitiligo risk.

Subgroup analysis according to clinical type

Table 4 indicates the results of subgroup analysis based on clinical type. Among the 53 HLA-B alleles studied in patients with nonsegmental vitiligo, 6 (HLA-B*27, B*50, Bw*06, Bw*46, Bw*55 and Bw*56) were significantly associated with increased risk of nonsegmental vitiligo, and 2 (HLA-B*35 and B*52) were associated with decreased risk. The remaining 45 alleles were not associated with nonsegmental vitiligo. Of the 12 HLA-B alleles reported in cases of segmental vitiligo, 1 (HLA-B*07) was significantly associated with increased risk of segmental vitiligo, and the rest 11 were not associated.

Twelve alleles (HLA-B*05, B*07, B*08, B*12, B*13, B*15, B*16, B*17, B*27, B*40, Bw*22 and Bw*35) were common to both types of vitiligo, but 2 (HLA-B*07 and B*27) of them were inconsistent in their association with vitiligo risk.

Subgroup analysis according to typing methods

Table 5 presents the results of subgroup analysis based on typing methods. Two kinds of HLA-B typing methods were applied: serological methods (LCT) and molecular methods (PCR-SSP, PCR-SSOP and PCR-SSO). Of the 57 HLA-B alleles detected by serological methods, 6 (HLA-B*13, Bw*06, Bw*46, Bw*55, Bw*56 and Bw*60) were significantly associated with increased risk of vitiligo, and 1 (HLA-B*35) were associated with decreased risk. The remaining 50 alleles were not associated with vitiligo. Among the 32 HLA-B alleles detected by molecular methods, 3 (HLA-B*13, B*27 and B*50) were significantly associated with increased risk of vitiligo, and 2 (HLA-B*18 and B*40) were associated with decreased risk. The rest 27 alleles were not associated.

Twenty-eight alleles (HLA-B*07, B*08, B*13, B*14, B*15, B*18, B*27, B*35, B*37, B*38, B*39, B*40, B*41, B*42, B*44, B*45, B*46, B*47, B*48, B*49, B*50, B*51, B*52, B*53, B*54, B*57, B*58 and B*78) were common to both typing methods, whereas 5 (HLA-B*18, B*27, B*35, B*40 and B*50) of them were inconsistent in their association with vitiligo risk.

Sensitivity analysis and publication bias

Among the 61 HLA-B alleles investigated in 18 included studies, HLA-B*07, B*08 and B*27 were reported in more than 10 studies and were therefore chosen for sensitivity analysis and assessment of publication bias. As shown in **Figure 5A-C**, sensitivity analyses indicated that no single study substantially influenced the pooled ORs qualitatively. Begg's funnel plots and Egger's test were performed to assess publication bias. No obvious publication bias was found in the results for HLA-B*07 and B*27 (P = 0.604 and 0.279, respectively) (**Figure 6A** and **6C**), while publication bias was not ruled out in the result for HLA-B*08 (P = 0.024) (**Figure 6B**).

Discussion

The pathogenesis of vitiligo has not yet been elucidated. It is currently regarded as a com-

Table 4. Association between HLA-B alleles and vitiligo risk in terms of clinical type

Clinical type	Allele	Cases% (n/N)	Controls% (n/N)	OR (95% CI)/Article number	*P*	Effects model
Nonsegmental	B*05	30.00 (33/110)	33.33 (52/156)	0.61 (0.12, 3.09)/2	0.552	R
	B*07	12.95 (47/363)	16.03 (288/1797)	1.28 (0.65, 2.50)/6	0.478	R
	B*08	5.66 (94/1660)	10.03 (241/2403)	0.84 (0.43, 1.63)/6	0.600	R
	B*10	0.00 (0/40)	2.50 (1/40)	0.33 (0.01, 8.22)/1	0.495	F
	B*12	12.73 (14/110)	7.69 (12/156)	1.90 (0.83, 4.35)/2	0.129	F
	B*13	25.24 (107/424)	9.78 (170/1738)	1.77 (0.76, 4.12)/7	0.185	R
	B*14	5.03 (10/199)	4.97 (71/1429)	0.80 (0.15, 4.16)/4	0.788	R
	B*15	22.60 (87/385)	13.57 (162/1194)	1.46 (0.62, 3.47)/6	0.389	R
	B*16	7.69 (11/143)	8.35 (50/599)	1.03 (0.49, 2.16)/3	0.941	F
	B*17	10.49 (15/143)	10.02 (60/599)	0.67 (0.35, 1.26)/3	0.212	F
	B*18	6.31 (7/111)	13.99 (96/686)	0.46 (0.21, 1.02)/2	0.057	F
	B*21	18.93 (39/206)	10.98 (100/911)	1.24 (0.31, 4.95)/4	0.760	R
	B*22	2.74 (2/73)	2.69 (13/483)	0.68 (0.02, 27.89)/2	0.837	R
	B*27	11.30 (46/407)	3.47 (69/1986)	2.57 (1.69, 3.89)/6	< 0.001	F
	B*35	13.00 (49/377)	21.94 (419/1910)	0.65 (0.47, 0.90)/6	0.010	F
	B*37	7.29 (113/1550)	4.36 (98/2247)	1.72 (0.68, 4.34)/4	0.255	R
	B*38	5.23 (9/172)	5.86 (29/495)	0.88 (0.41, 1.89)/2	0.743	F
	B*39	6.16 (13/211)	7.03 (73/1039)	1.02 (0.54, 1.91)/3	0.959	F
	B*40	21.74 (75/345)	15.08 (174/1154)	0.97 (0.54, 1.73)/5	0.907	R
	B*41	2.65 (4/151)	0.83 (6/726)	2.96 (0.71, 12.27)/3	0.135	F
	B*42	5.08 (6/118)	5.30 (15/283)	1.10 (0.41, 2.96)/2	0.844	F
	B*44	28.26 (449/1589)	13.62 (380/2791)	1.13 (0.43, 2.96)/5	0.803	R
	B*45	2.56 (2/78)	3.29 (8/243)	0.77 (0.16, 3.72)/1	0.748	F
	B*46	10.45 (14/134)	15.75 (46/292)	0.73 (0.38, 1.40)/2	0.347	F
	B*47	8.51 (8/94)	8.33 (21/252)	1.02 (0.44, 2.40)/1	0.958	F
	B*48	0.85 (1/118)	0.35 (1/283)	1.59 (0.25, 10.17)/2	0.622	F
	B*49	6.41 (5/78)	4.94 (12/243)	1.32 (0.45, 3.87)/1	0.615	F
	B*50	12.82 (10/78)	5.35 (13/243)	2.60 (1.09, 6.20)/1	0.031	F
	B*51	11.89 (189/1589)	16.37 (457/2791)	1.00 (0.60, 1.67)/5	0.992	R
	B*52	3.97 (8/211)	12.70 (132/1039)	0.43 (0.20, 0.92)/3	0.029	F
	B*53	13.56 (16/118)	4.59 (13/283)	2.05 (0.92, 4.55)/2	0.078	F
	B*54	10.64 (10/94)	15.87 (40/252)	0.63 (0.30, 1.32)/1	0.221	F
	B*55	1.28 (1/78)	4.12 (10/243)	0.30 (0.04, 2.40)/1	0.258	F
	B*57	2.91 (5/172)	3.23 (16/495)	0.93 (0.33, 2.59)/2	0.888	F
	B*58	4.65 (8/172)	4.85 (24/495)	0.97 (0.43, 2.20)/2	0.941	F
	B*59	0.00 (0/40)	2.50 (1/40)	0.33 (0.01, 8.22)/1	0.495	F
	B*67	3.19 (3/94)	1.59 (4/252)	2.04 (0.45, 9.31)/1	0.355	F
	B*70	0.00 (0/40)	5.00 (2/40)	0.19 (0.01, 4.09)/1	0.289	F
	B*73	5.00 (2/40)	0.00 (0/40)	5.26 (0.24, 113.11)/1	0.289	F
	B*78	0.00 (0/118)	0.71 (2/283)	0.56 (0.06, 5.41)/2	0.614	F
	B*81	1.28 (1/78)	0.41 (1/243)	3.14 (0.19, 50.84)/1	0.420	F
	Bw*04	50.00 (20/40)	60.00 (24/40)	0.67 (0.27, 1.62)/1	0.370	F
	Bw*06	81.11 (73/90)	51.52 (68/132)	3.95 (2.10, 7.45)/2	< 0.001	F
	Bw*22	4.29 (3/70)	12.93 (15/116)	0.30 (0.08, 1.08)/1	0.066	F
	Bw*35	2.86 (2/70)	5.17 (6/116)	0.54 (0.11, 2.75)/1	0.457	F
	Bw*46	7.69 (3/39)	0.55 (3/544)	15.03 (2.93, 77.12)/1	0.001	F

	Bw*48	7.69 (3/39)	3.68 (20/544)	2.18 (0.62, 7.69)/1	0.224	F
	Bw*54	17.95 (7/39)	17.83 (97/544)	1.01 (0.43, 2.35)/1	0.985	F
	Bw*55	12.82 (5/39)	4.41 (24/544)	3.19 (1.14, 8.87)/1	0.027	F
	Bw*56	3.23 (3/93)	0.26 (1/388)	12.90 (1.33, 125.46)/1	0.028	F
	Bw*60	12.82 (5/39)	8.64 (47/544)	1.56 (0.58, 4.17)/1	0.380	F
	Bw*61	25.64 (10/39)	25.92 (141/544)	0.99 (0.47, 2.07)/1	0.969	F
	Bw*62	15.38 (6/39)	15.44 (84/544)	1.00 (0.40, 2.45)/1	0.992	F
Segmental	B*05	36.67 (11/30)	21.55 (25/116)	2.11 (0.89, 5.00)/1	0.091	F
	B*07	20.00 (6/30)	3.45 (4/116)	7.00 (1.83, 26.73)/1	0.004	F
	B*08	0.00 (0/30)	0.86 (1/116)	1.26 (0.05, 31.76)/1	0.887	F
	B*12	16.67 (5/30)	9.48 (11/116)	1.91 (0.61, 5.99)/1	0.268	F
	B*13	40.00 (22/55)	19.91 (43/216)	3.05 (0.88, 10.66)/2	0.080	R
	B*15	21.82 (12/55)	22.22 (48/216)	0.84 (0.05, 14.97)/2	0.908	R
	B*16	10.00 (3/30)	8.62 (10/116)	1.18 (0.30, 4.58)/1	0.813	F
	B*17	16.67 (5/30)	24.14 (28/116)	0.63 (0.22, 1.80)/1	0.386	F
	B*27	13.33 (4/30)	6.90 (8/116)	2.08 (0.58, 7.43)/1	0.261	F
	B*40	30.91 (17/55)	26.39 (57/216)	1.17 (0.16, 8.38)/2	0.872	R
	Bw*22	3.33 (1/30)	12.93 (15/116)	0.23 (0.03, 1.83)/1	0.166	F
	Bw*35	0.00 (0/30)	5.17 (6/116)	0.28 (0.02, 5.09)/1	0.389	F

HLA-B, human leukocyte antigen-B; N, total number of subjects; n, positive number of subjects; OR, odds ratio; CI, confidence interval; Article number, total number of the articles studied on HLA-B alleles; R, random effects model; F, fixed effects model.

plex, multifactorial and polygenic disease [3]. Previous studies have identified many genetic loci for vitiligo, including several single-nucleotide polymorphisms (rs11966200, rs9468925, rs12206499 and rs532098) [31, 32] and some candidate genes (HLA class I, HLA class II and PTPN22) [12, 14, 16, 33, 34]. In the present study, we performed a meta-analysis to comprehensively evaluate the association between 61 HLA-B alleles and vitiligo risk. Eighteen case-control studies [11-28] with a total of 2967 vitiligo cases and 5599 controls were finally identified from database searches and reference review. Overall, 7 alleles (HLA-B*13, B*27, Bw*06, Bw*46, Bw*55, Bw*56 and Bw*60) were significantly associated with increased risk of vitiligo, while 3 alleles (HLA-B*18, B*35 and B*52) were associated with decreased risk. In addition, the rest 51 alleles were not associated with vitiligo. To the best of our knowledge, this is the first meta-analysis on the association between numerous HLA-B alleles and vitiligo risk.

There were 14 alleles common to three ethnicities (Asians, Europeans and Americans) and 12 alleles common to both types of vitiligo (non-segmental and segmental). In the subgroup analysis stratified by ethnicity, the association of 6 alleles with vitiligo risk was consistent in three populations, whereas that of the rest 8 alleles (HLA-B*07, B*08, B*13, B*14, B*18, B*27, B*35 and B*37) was inconsistent. The possible reasons for these inconsistencies might be the difference in ethnicity or the relatively small number of included studies for some alleles. Subgroup analysis according to clinical type showed that 2 (HLA-B*07 and B*27) of 12 common alleles were inconsistent in their association with both types of vitiligo. It suggests that the association between these 2 alleles and vitiligo risk may be dependent on clinical type. However, we should interpret this association with great caution, because only 2 studies [17, 26] presented relevant data on segmental vitiligo and were included in this meta-analysis.

HLA-B typing is critical for the accuracy of the results of a study. Serological and molecular methods were involved in the 18 studies of this meta-analysis, and the latter had a higher resolution. In the subgroup analysis stratified by typing methods, 28 alleles were common to both typing methods (serological and molecular), while 5 (HLA-B*18, B*27, B*35, B*40 and B*50) of them were inconsistent in their association with vitiligo risk. It suggests that the association of these 5 alleles with vitiligo risk may vary in terms of typing methods.

Table 5. Association between HLA-B alleles and vitiligo risk in terms of typing methods

Typing methods	Allele	Cases% (n/N)	Controls% (n/N)	OR (95% CI)/Article number	*P*	Effects model
Serological	B*05	19.85 (78/393)	19.57 (181/925)	0.77 (0.43, 1.38)/6	0.387	R
	B*07	12.74 (67/526)	15.98 (347/2171)	1.07 (0.57, 2.02)/9	0.823	R
	B*08	7.10 (38/535)	9.03 (147/1628)	0.97 (0.65, 1.45)/9	0.876	F
	B*10	0.00 (0/40)	2.50 (1/40)	0.33 (0.01, 8.22)/1	0.495	F
	B*12	18.06 (65/360)	19.15 (158/825)	1.36 (0.96, 1.94)/5	0.086	F
	B*13	23.01 (107/465)	7.74 (148/1912)	2.06 (1.21, 3.51)/8	0.008	R
	B*14	4.53 (15/331)	6.50 (127/1955)	0.66 (0.24, 1.84)/7	0.427	R
	B*15	18.58 (73/393)	8.28 (105/1268)	1.31 (0.42, 4.07)/6	0.635	R
	B*16	4.53 (16/353)	6.23 (56/899)	0.96 (0.52, 1.78)/6	0.892	F
	B*17	9.89 (44/445)	9.72 (133/1368)	0.84 (0.57, 1.24)/7	0.378	F
	B*18	6.17 (15/243)	10.56 (128/1212)	0.70 (0.39, 1.23)/5	0.212	F
	B*21	18.93 (39/206)	10.98 (100/911)	1.24 (0.31, 4.95)/4	0.760	R
	B*22	5.95 (10/168)	3.43 (20/583)	1.10 (0.26, 4.75)/3	0.895	R
	B*27	6.70 (42/627)	3.85 (97/2520)	1.42 (0.96, 2.10)/10	0.077	F
	B*35	14.55 (56/385)	24.02 (412/1715)	0.67 (0.49, 0.92)/7	0.014	F
	B*37	2.10 (5/238)	2.53 (28/1105)	0.75 (0.08, 6.82)/4	0.797	R
	B*38	11.76 (10/85)	12.00 (24/200)	0.92 (0.42, 2.04)/2	0.840	F
	B*39	4.84 (6/124)	6.72 (50/744)	1.18 (0.48, 2.85)/3	0.721	F
	B*40	20.68 (73/353)	8.63 (106/1228)	1.23 (0.85, 1.78)/5	0.277	F
	B*41	2.83 (3/106)	1.20 (7/583)	1.84 (0.46, 7.25)/3	0.387	F
	B*42	5.00 (2/40)	0.00 (0/40)	5.26 (0.24, 113.11)/1	0.289	F
	B*44	12.10 (19/157)	14.24 (169/1187)	0.85 (0.50, 1.45)/4	0.556	F
	B*45	0.00 (0/33)	1.00 (1/100)	0.99 (0.04, 24.89)/1	0.995	F
	B*46	2.96 (4/135)	10.00 (14/140)	0.45 (0.03, 6.04)/2	0.550	R
	B*47	0.00 (0/33)	2.00 (2/100)	0.59 (0.03, 12.56)/1	0.734	F
	B*48	0.00 (0/40)	2.50 (1/40)	0.33 (0.01, 8.22)/1	0.495	F
	B*49	0.00 (0/33)	6.00 (6/100)	0.22 (0.01, 3.96)/1	0.302	F
	B*50	0.00 (0/128)	4.00 (8/200)	0.15 (0.02, 1.12)/2	0.065	F
	B*51	27.39 (43/157)	18.62 (221/1187)	1.40 (0.84, 2.10)/4	0.101	F
	B*52	4.84 (6/124)	17.20 (128/744)	0.45 (0.10, 2.01)/3	0.297	R
	B*53	15.07 (11/73)	8.57 (12/140)	1.19 (0.47, 3.05)/2	0.714	F
	B*54	0.00 (0/33)	1.00 (1/100)	0.99 (0.04, 24.89)/1	0.995	F
	B*57	0.00 (0/33)	1.00 (1/100)	0.99 (0.04, 24.89)/1	0.995	F
	B*58	0.00 (0/33)	1.00 (1/100)	0.99 (0.04, 24.89)/1	0.995	F
	B*59	0.00 (0/40)	2.50 (1/40)	0.33 (0.01, 8.22)/1	0.495	F
	B*60	0.00 (0/33)	5.00 (5/100)	0.26 (0.01, 4.81)/1	0.365	F
	B*61	0.00 (0/33)	1.00 (1/100)	0.99 (0.04, 24.89)/1	0.995	F
	B*62	3.03 (1/33)	2.00 (2/100)	1.53 (0.13, 17.45)/1	0.731	F
	B*63	3.53 (3/85)	1.00 (2/200)	2.95 (0.13, 67.39)/2	0.498	R
	B*70	0.00 (0/40)	5.00 (2/40)	0.19 (0.01, 4.09)/1	0.289	F
	B*73	5.00 (2/40)	0.00 (0/40)	5.26 (0.24, 113.11)/1	0.289	F
	B*75	0.00 (0/33)	1.00 (1/100)	0.99 (0.04, 24.89)/1	0.995	F
	B*78	0.00 (0/40)	2.50 (1/40)	0.33 (0.01, 8.22)/1	0.495	F
	Bw*04	50.00 (20/40)	60.00 (24/40)	0.67 (0.27, 1.62)/1	0.370	F
	Bw*06	81.11 (73/90)	51.52 (68/132)	3.95 (2.10, 7.45)/2	< 0.001	F
	Bw*16	11.20 (14/125)	12.30 (70/569)	1.17 (0.63, 2.20)/2	0.619	F

	Bw*21	13.60 (17/125)	12.48 (71/569)	1.33 (0.75, 2.38)/2	0.330	F
	Bw*22	7.11 (16/225)	7.15 (49/685)	0.73 (0.17, 3.18)/3	0.680	R
	Bw*35	17.33 (39/225)	27.30 (187/685)	0.80 (0.53, 1.21)/3	0.287	F
	Bw*46	7.69 (3/39)	0.55 (3/544)	15.03 (2.93, 77.12)/1	0.001	F
	Bw*48	7.69 (3/39)	3.68 (20/544)	2.18 (0.62, 7.69)/1	0.224	F
	Bw*54	17.95 (7/39)	17.83 (97/544)	1.01 (0.43, 2.35)/1	0.985	F
	Bw*55	12.82 (5/39)	4.41 (24/544)	3.19 (1.14, 8.87)/1	0.027	F
	Bw*56	7.69 (3/93)	0.26 (1/388)	12.90 (1.33, 125.46)/1	0.028	F
	Bw*60	16.31 (23/141)	8.16 (77/944)	2.26 (1.34, 3.81)/2	0.002	F
	Bw*61	25.64 (10/39)	25.92 (141/544)	0.99 (0.47, 2.07)/1	0.969	F
	Bw*62	15.38 (6/39)	15.44 (84/544)	1.00 (0.40, 2.45)/1	0.992	F
Molecular	B*07	9.57 (29/303)	8.89 (44/495)	1.22 (0.74, 2.00)/2	0.445	F
	B*08	5.58 (115/2060)	9.92 (179/1804)	0.90 (0.35, 2.28)/3	0.823	R
	B*13	28.71 (87/303)	17.37 (86/495)	1.71 (1.19, 2.46)/2	0.004	F
	B*14	5.17 (6/116)	11.52 (28/243)	0.42 (0.17, 1.04)/1	0.061	F
	B*15	15.84 (48/303)	16.16 (80/495)	1.02 (0.39, 2.64)/2	0.965	R
	B*18	4.31 (5/116)	12.76 (31/243)	0.31 (0.12, 0.81)/1	0.018	F
	B*27	14.85 (45/303)	6.46 (32/495)	2.27 (1.39, 3.69)/2	0.001	F
	B*35	7.92 (24/303)	13.54 (67/495)	0.64 (0.39, 1.06)/2	0.083	F
	B*37	6.89 (142/2060)	4.66 (84/1804)	0.96 (0.31, 3.00)/3	0.949	R
	B*38	5.61 (17/303)	5.86 (29/495)	0.91 (0.49, 1.69)/2	0.766	F
	B*39	6.93 (21/303)	5.66 (28/495)	1.26 (0.70, 2.26)/2	0.447	F
	B*40	17.49 (53/303)	21.41 (106/495)	0.65 (0.44, 0.95)/2	0.026	F
	B*41	0.86 (1/116)	0.82 (2/243)	1.05 (0.09, 11.67)/1	0.970	F
	B*42	6.03 (7/116)	6.17 (15/243)	0.98 (0.39, 2.46)/1	0.959	F
	B*44	27.28 (562/2060)	13.03 (235/1804)	1.49 (0.53, 4.13)/3	0.448	R
	B*45	1.72 (2/116)	3.29 (8/243)	0.52 (0.11, 2.47)/1	0.407	F
	B*46	14.44 (27/187)	17.86 (45/252)	0.78 (0.46, 1.31)/1	0.340	F
	B*47	8.02 (15/187)	8.33 (21/252)	0.96 (0.48, 1.92)/1	0.906	F
	B*48	0.86 (1/116)	0.00 (0/243)	6.32 (0.26, 156.45)/1	0.260	F
	B*49	6.90 (8/116)	4.94 (12/243)	1.43 (0.57, 3.59)/1	0.451	F
	B*50	12.07 (14/116)	5.35 (13/243)	2.43 (1.10, 5.35)/1	0.028	F
	B*51	10.68 (220/2060)	15.69 (283/1804)	0.78 (0.49, 1.23)/3	0.284	R
	B*52	3.63 (11/303)	5.25 (26/495)	0.66 (0.32, 1.37)/2	0.261	F
	B*53	6.03 (7/116)	2.06 (5/243)	3.06 (0.95, 9.85)/1	0.061	F
	B*54	12.83 (24/187)	15.87 (40/252)	0.78 (0.45, 1.35)/1	0.373	F
	B*55	0.86 (1/116)	4.12 (10/243)	0.20 (0.03, 1.60)/1	0.130	F
	B*56	9.09 (3/33)	5.00 (5/100)	1.90 (0.43, 8.42)/1	0.398	F
	B*57	3.30 (10/303)	3.23 (16/495)	1.15 (0.51, 2.58)/2	0.744	F
	B*58	5.61 (17/303)	4.85 (24/495)	1.22 (0.64, 2.30)/2	0.551	F
	B*67	2.67 (5/187)	1.59 (4/252)	1.70 (0.45, 6.43)/1	0.432	F
	B*78	0.00 (0/116)	0.41 (1/243)	0.69 (0.03, 17.16)/1	0.823	F
	B*81	0.86 (1/116)	0.41 (1/243)	2.10 (0.13, 33.94)/1	0.600	F

HLA-B, human leukocyte antigen-B; N, total number of subjects; n, positive number of subjects; OR, odds ratio; CI, confidence interval; Article number, total number of the articles studied on HLA-B alleles; R, random effects model; F, fixed effects model.

Of the 61 HLA-B alleles in the current meta-analysis, only 3 alleles (HLA-B*07, B*08 and B*27) were each reported in more than 10 studies. No heterogeneity was detected among the studies for HLA-B*27, but there was obvious heterogeneity across the studies for HLA-

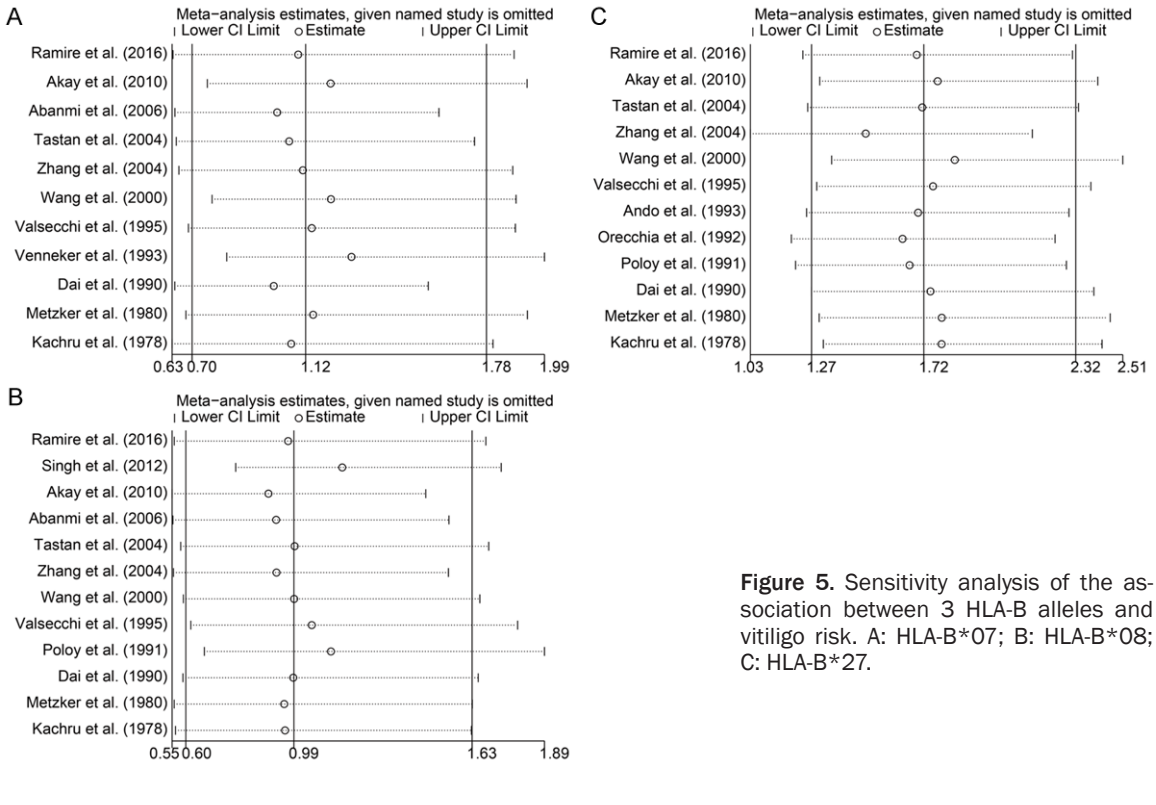

Figure 5. Sensitivity analysis of the association between 3 HLA-B alleles and vitiligo risk. A: HLA-B*07; B: HLA-B*08; C: HLA-B*27.

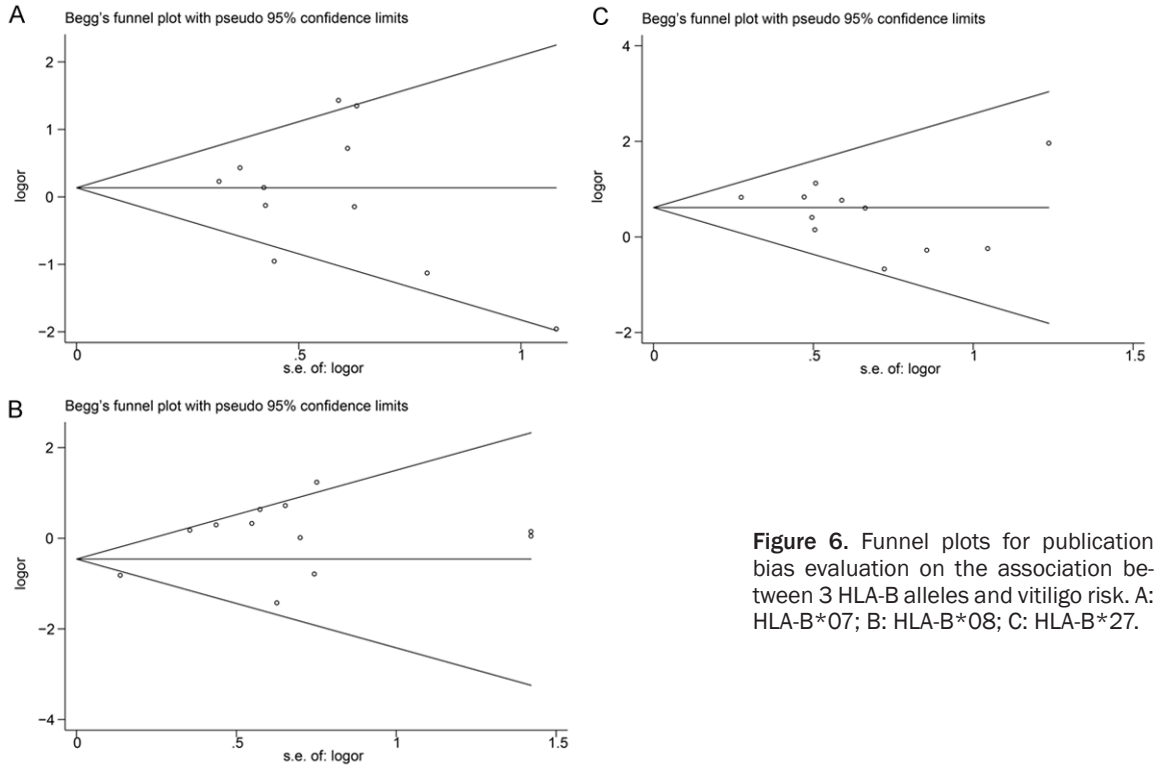

Figure 6. Funnel plots for publication bias evaluation on the association between 3 HLA-B alleles and vitiligo risk. A: HLA-B*07; B: HLA-B*08; C: HLA-B*27.

B*07 and B*08, which might be caused by the differences in ethnicity, clinical type and typing methods. Sensitivity analyses indicated that the results for these 3 alleles were statistically

reliable. No publication bias was found in the results for HLA-B*07 and B*27 based on the funnel plot analysis and Egger's test. However, publication bias had a significant influence on the result for HLA-B*08. Therefore, except for HLA-B*07 and B*27, the association between the remaining 59 alleles and vitiligo risk needs to be further studied.

Some limitations of this study should be addressed. First, this meta-analysis only included published studies, which may lead to a potential publication bias. Second, the number of included studies for some HLA-B alleles was relatively small, which limited the statistical power to reveal the real association. Third, vitiligo may result from interactions of various genetic and environmental factors. Lack of the original data limited our further evaluation of potential gene-gene and gene-environment interactions. Finally, we were not able to perform subgroup for each HLA-B allele due to the limited number of eligible studies, which may affect the results.

In summary, our meta-analysis suggests that HLA-B*13, B*27, Bw*06, Bw*46, Bw*55, Bw*56 and Bw*60 are associated with increased risk of vitiligo, while HLA-B*18, B*35 and B*52 are associated with decreased risk of vitiligo. Moreover, the association of some alleles varies in terms of ethnicity, clinical type and typing methods. Considering the limitations listed above, more well-designed studies with larger sample sizes are still needed to further validate our findings.

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Disclosure of conflict of interest

None.

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