Systematic Review and Meta-Analysis

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HLA-DRB1 polymorphisms and alopecia areata disease risk

A systematic review and meta-analysis

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Abstract

Background: Published studies have reported conflicting and heterogeneous results regarding the association between human leukocyte antigen (*HLA*)-*DRB1* polymorphisms and alopecia areata (AA). This study aimed to review and quantitatively analyze the association between *HLA-DRB1* polymorphisms and AA.

Methods: In this study, all relevant publications were searched through December 2016. Odds ratios (ORs) and confidence intervals (CIs) for comparisons between case and control groups were calculated. Stata 14.0 software was used to perform statistical analysis. This research does not require formal ethical approval because the data used in this analysis do not involve personal information and thus do not affect privacy.

Results: Twelve articles were identified. For *HLA-DRB1*04* and *HLA-DRB1*16* polymorphisms, the OR (95% CIs) was 1.49 (1.24–1.78) and 1.61 (1.08–2.41), and *P* was <.01 and <.01, respectively. For *HLA-DRB1*0301, HLA-DRB1*09*, and *HLA-DRB1*13* polymorphisms, the OR (95% CIs) was 0.42 (0.28–0.63), 0.74 (0.55–0.99), and 0.62 (0.40–0.98), and *P* was <.01, <.01, and <.01, respectively. Statistical evidence revealed no publication bias ($P > .05$).

Conclusion: The present meta-analysis suggested that *HLA-DRB1*04* and *HLA-DRB1*16* polymorphisms might be associated with increased AA risk, while *HLA-DRB1*0301*, *HLA-DRB1*09*, and *HLA-DRB1*13* polymorphisms might decrease the AA risk. Studies with adequate methodological quality on gene–gene and gene–environment interactions are needed to validate the results in the future.

Abbreviations: AA = alopecia areata, CI = confidence interval, CNKI = Cochrane Library China National Knowledge Infrastructure, HLA = human leukocyte antigen, NOS = Newcastle-Ottawa Scale, OR = odds ratio, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Keywords: alopecia areata, *DRB1*, human leukocyte antigen, odds ratio, polymorphism, risk

1. Introduction

Alopecia areata (AA) is a cell-mediated autoimmune disease causing an unpredictable hair loss with no overt epidermal changes. The lifetime risk of AA is estimated to be 1.7%. It affects both sexes and people of all races, but is more prevalent in children.[1] In AA, abnormal immune damage leads to round or oval patches, which may advance to all scalp hair (alopecia totalis) or all body hair (alopecia universalis).[2]

Human leukocyte antigen (HLA)-*DRB1* polymorphisms have been discussed in many types of autoimmune diseases, for instance, aplastic anemia,[3] systemic lupus erythematosus and lupus nephritis,[4] Vogt–Koyanagi–Harada disease,[5] and multiple sclerosis.[6] As one of the autoimmune diseases which caused by several major susceptibility genes, AA is genetically associated with alleles of HLA in different ethnic groups.[7] CD4+ lymphocytes play an important role in AA inflammatory processes. They have been proposed to recognize the antigen and major histocompatibility complex (MHC) class II complexes on macrophages and Langerhans cells, and the expression may be induced on other nucleated cells, leading to AA.[8,9] It is noticed that *HLA-DR* and *HLA-DQ* alleles are responsible for presenting the antigen to CD4+ T cells.[10]

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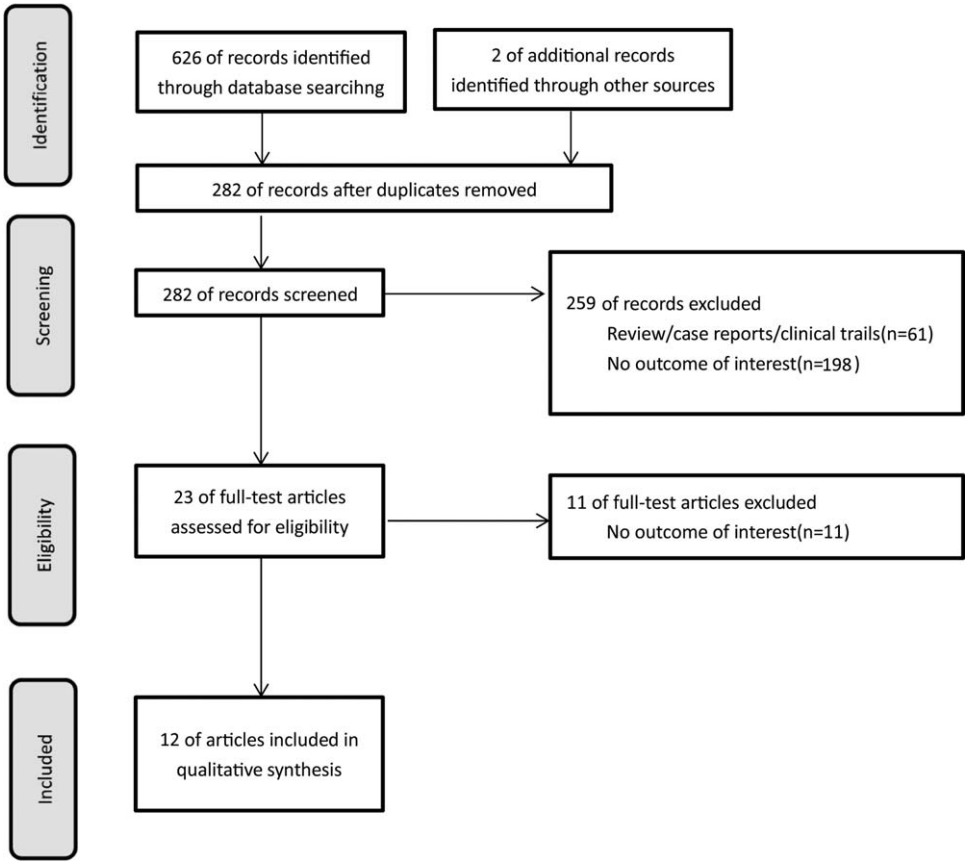

Figure 1. Flow diagram of the study selection process.

One genome-wide association study (GWAS) discussed the relationship between HLA and AA.[1] It revealed HLA-DR as a key etiologic driver. The study indicated *HLA-DRB1*04:01* polymorphisms as the potential risk factor for AA (OR = 1.64). GWAS explored the genetic architecture of complex diseases, but was limited in detecting any other kinds of genetic variants such as deletions associated with a high percentage of autoimmune diseases.[11]

Previous individual studies have been concerned with the association between *HLA-DRB1* polymorphisms and AA. Three studies indicated *HLA-DRB1*04* allele as a risk factor for the development of AA.[12–14] However, the results were inconsistent with the findings of other studies.[15–20] Moreover, one study suggested a lower occurrence of *HLA-DRB1*15* polymorphisms in AA,[21] whereas others found no association.[13,15,16,18–20]

A number of conflicting studies have reported the relationship between *HLA-DRB1* polymorphisms and AA risk in small samples,[12–23] but no definite consensus existed. Therefore, this meta-analysis aimed to examine the relationship between *HLA-DRB1* polymorphisms and AA. Since a single study might have been underpowered to clarify the genes with AA risk, the purpose of this study was to increase the statistical power and evaluate the evidence from studies by summarizing it quantitatively with a meta-analytic approach.

2. Materials and methods

This study was performed following the standards of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria[24] (Supplemental Table 1, http://links.lww.com/MD/C384) and the recommendations of the Cochrane Collaboration.[25] A protocol for this systematic review has been published in PROSPERO with the registration number CRD42015023718 (Supplemental File 1, http://links.lww.com/MD/C384).

2.1. Search strategy

We carried out an electronic search of multiple databases, including PubMed, Embase, Cochrane database, Chinese China National Knowledge Infrastructure, Chinese Biomedical Literature Database, Wang Fang, and Chinese Social Sciences Citation Index, through December 2016 for all studies on the association between HLA polymorphisms and AA by using the following keywords ("Alopecia areata" or "nonscarring hair loss" or "ophiasis" or "alopecia celsi" or "alopecia universalis" or "alopecia totalis") and ("human leukocyte antigen" or "HLA" or "major histocompatibility complex" or "DRB1" or "MHC") (Supplemental Table 2, http://links.lww.com/MD/C384). No language restrictions were imposed in this research. We also searched the references of the included studies and e-mailed the study authors to identify additional studies and collect missing data.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: studies concerned with the association between *HLA-DRB1* polymorphisms and AA; and

Table 1

Characteristics of studies included in the meta-analysis.

NO	First authors	Year	Country	Numbers		Sex (M/F)		Age		Detection methods	NOS	Genes
				Cases	Controls	Cases	Controls	Cases	Controls			
1	Akar	2002	Turkey	65	50	42/13	36/14	19–57	-	PCR-SSP	4	*01,*03,*04,*07,*08,*09,*10,*11,*12,*13,*14,*15,*16
2	Barahmani	2008	USA	291	152	-	-	-	-	PCR-SSO	4	*0301
3	Aliagaoglu	2005	Turkey	63	76	42/21	46/30	17–60	-	PCR-SSP	4	*11,*15
4	Megiorni	2011	Italy	85	210	22/63	120/90	34 ± 14.7	38 ± 6.54	PCR-SSP/PCR-SSO	5	*01,*03,*04,*07,*08,*09,*10,*11,*12,*13,*14,*15,*16
5	Broniarczyk-Dyla	2002	Poland	52	152	39/13	-	33.4 (10–64)	-	PCR-SSO	4	*01,*03,*04,*07,*08,*09,*10,*11,*12,*13,*14,*15/16
6	Marques	2006	Belgium	88	99	27/61	-	30.7 ± 2.3	-	PCR-SSP/PCR-SSO	4	*11
7	Qi	2009	China	158	172	76/82	134/38	37.8 ± 12.7 (17–61)	39.4 ± 10.0 (17–61)	PCR-SSP	7	*03,*04,*11
8	Tao	2011	China	112	5645	50/62	-	-	-	PCR-SBT	5	*01,*03,*04,*07,*08,*09,*11,*12,*13,*14,*15,*16
9	Entz	2006	Germany, Belgium	161	165	61/100	-	53 (5–78)	-	PCR-SSP	6	*01,*03,*0301,*04,*07,*09,*10,*11,*15/16
10	Zhang	2010	China	121	24930	-	-	-	-	PCR-SSO	5	*01,*03,*04,*07,*08,*09,*10,*11,*12,*13,*14,*15,*16
11	Attia	2010	Egypt	54	580	36/18	-	20–65	-	PCR-SSO	7	*01,*03,*04,*07,*08,*11,*13,*15
12	Barbosa	2016	Brazil	33	112	17/16	49/63	36.7 ± 18.0	31.7 ± 13.9	PCR-SSO	6	*01,*03,*04,*07,*08,*09,*10,*11,*12,*13,*14,*15,*16

PCR-SBT = polymerase chain reaction with sequence-based typing, PCR-SSO = polymerase chain reaction with sequence-specific oligonucleotide, PCR-SSP = polymerase chain reaction with sequence-specific primer.

sufficient data on odds ratio (OR) with a 95% confidence interval (CI).

The exclusion criteria were as follows: reviews, comments, editorials, or basic science or animal studies; genotype frequency not revealed or the relevant data not obtained by contacting authors; and duplicate studies.

2.3. Study selection

Two review authors initially screened the titles and abstracts independently. The full text versions of any studies of potential relevance were retrieved and examined carefully according to inclusion and exclusion criteria. Only the most recent study was included when there were overlapping data or even repeating data. Any discrepancies were adjudicated by regular conferences involving the third reviewer (Prof Chen). She downloaded the full text of the inconsistent studies and discussed step by step according to the inclusion and exclusion criteria.

2.4. Data extraction

Data extraction was performed independently by 2 investigators using a predetermined extraction form. The third participant was consulted for discussion to reach an agreement concerning discrepancies. The following items were extracted from each study: first author's last name, publication year, country, the Newcastle-Ottawa Scale (NOS), numbers of cases and controls, gene detection method, genes involved, and frequency of *HLA-DRB1* alleles.

2.5. Quality assessment for individual studies

A scoring system based on the NOS was used to determine the quality of each study. Items assessed included selection, comparability of cases/controls, and exposure. The score of overall quality ranged from 0 to 9. The NOS score was divided into 3 levels (high quality, score ≥ 7; moderate quality, $4 \leq$ score < 7; low quality, score > 4). Disagreements were settled as described earlier.

2.6. Statistical analysis

All statistical analyses were conducted using Stata 14.0 (Stata Corporation, TX). Dichotomous data were reported as OR (calculated by the χ^2 test). The pooled ORs and the 95% CIs used for assessing the strength of association were determined by the Z test. Heterogeneity across studies was checked by the Cochran Q statistic and the I^2 test.[26] If a 2-sided P value $<.05$ was considered as statistically significant, then a random-effects model was used (shown as "D + L").[27] Otherwise, a fixed-effects model was applied (shown as "M-H").[28] When I^2 was $>50\%$ indicating high heterogeneity, subgroup analyses were used. Subgroup analyses were performed by area to reveal whether it could lead to heterogeneity. Meta-regression was used to reveal whether continent, country, or NOS score could lead to heterogeneity.

A sensitivity analysis was performed by sequential omission of individual studies to evaluate the stability of outcomes.[29] Harbord[30] and Egger[31] tests were conducted to evaluate the publication bias with a P value $<.05$ for considering statistical significance. If publication bias was indicated with statistical significance, a trim-and-fill analysis was performed.[32]

Table 2

Meta-analysis of associations between *HLA-DRB1* alleles and alopecia areata.

Alleles	No. of studies	AA case n/N	Control n/N	Heterogeneity		Model	OR (95% CI_S)	P	Z	Harbord	Egger
				P	I^2 (%)					P	P
*DRB1*01*	8	96/683	1992/31844	0.727	0	F	1.05 (0.80, 1.38)	.665	0.43	.917	.643
*DRB1*03*	9	95/841	2344/32018	<0.01	79.0	R	0.78 (0.43, 1.40)	.406	0.83	.375	.558
DRB1*0301	**2**	**49/452**	**73/317**	**0.211**	**36.2**	**F**	**0.42 (0.28, 0.63)**	**<.01**	**4.25**	-	-
DRB1*04	**9**	**266/841**	**7100/32016**	**0.081**	**43.0**	**R**	**1.49 (1.24, 1.78)**	**<.01**	**2.87**	.281	.201
*DRB1*07*	8	122/683	7331/31844	0.010	62.0	R	0.91 (0.72, 1.14)	.714	0.37	.978	.405
*DRB1*08*	7	37/522	3573/31679	0.046	53.2	R	1.02 (0.56, 1.87)	.943	0.07	.080	.358
DRB1*09	**7**	**57/529**	**8312/3126452**	**0.441**	**0**	**F**	**0.74 (0.55, 0.99)**	**.044**	**2.02**	.675	.688
*DRB1*10*	6	10/517	764/25619	0.937	0	F	0.55 (0.27, 1.11)	.107	1.61	.854	.956
*DRB1*11*	11	260/992	4470/32191	<0.01	66.4	R	1.19 (0.85, 1.67)	.304	1.03	.800	.485
*DRB1*12*	6	57/468	6459/31099	0.165	36.3	F	0.80 (0.59,1.08)	.427	0.79	.655	.988
DRB1*13	**7**	**59/522**	**3485/31679**	**0.043**	**53.9**	**R**	**0.62 (0.40, 0.98)**	**.042**	**2.03**	.221	.900
*DRB1*14*	6	48/468	3842/31099	0.822	0	F	0.87 (0.63, 1.21)	.472	0.72	.109	.063
*DRB1*15*	7	136/533	10690/31603	0.029	57.2	R	1.00 (0.69, 1.45)	.999	<0.01	.290	.169
*DRB1*16*	5	57/444	1660/32538	<0.01	92.4	R	2.60 (0.74, 9.14)	.135	1.49	.222	.408
DRB1*16#	**4**	**40/332**	**1606/26893**	**0.600**	**0**	**F**	**1.61 (1.08, 2.41)**	**.021**	**2.31**	.704	.732
*DRB1*15/16*	2	85/213	109/317	0.071	69.3	F	1.32 (0.91, 1.91)	.141	1.47	-	-

AA indicates alopecia areata; *n*, the number of positive events; *N*, the number of total events.
Bold values indicate statistical significant results.
[#] After exclusion of the study by Tao.[13]

3. Results

3.1. Study characteristics

We conducted this study under PRISMA statement (Fig. 1). Through literature searches, 626 studies discussed the association of HLA polymorphism and AA. After reading titles and abstracts, 22 studies were identified. Unfortunately, 10 articles were eliminated due to some reasons. The Supplemental Table 3, http://links.lww.com/MD/C384 lists the reasons for the exclusion of these studies. Finally, 12 studies[12–23] consisting 1283 cases and 32,343 controls were included, 2 of which were graduation theses of postgraduate students.[13,14] Zhang et al[19] included

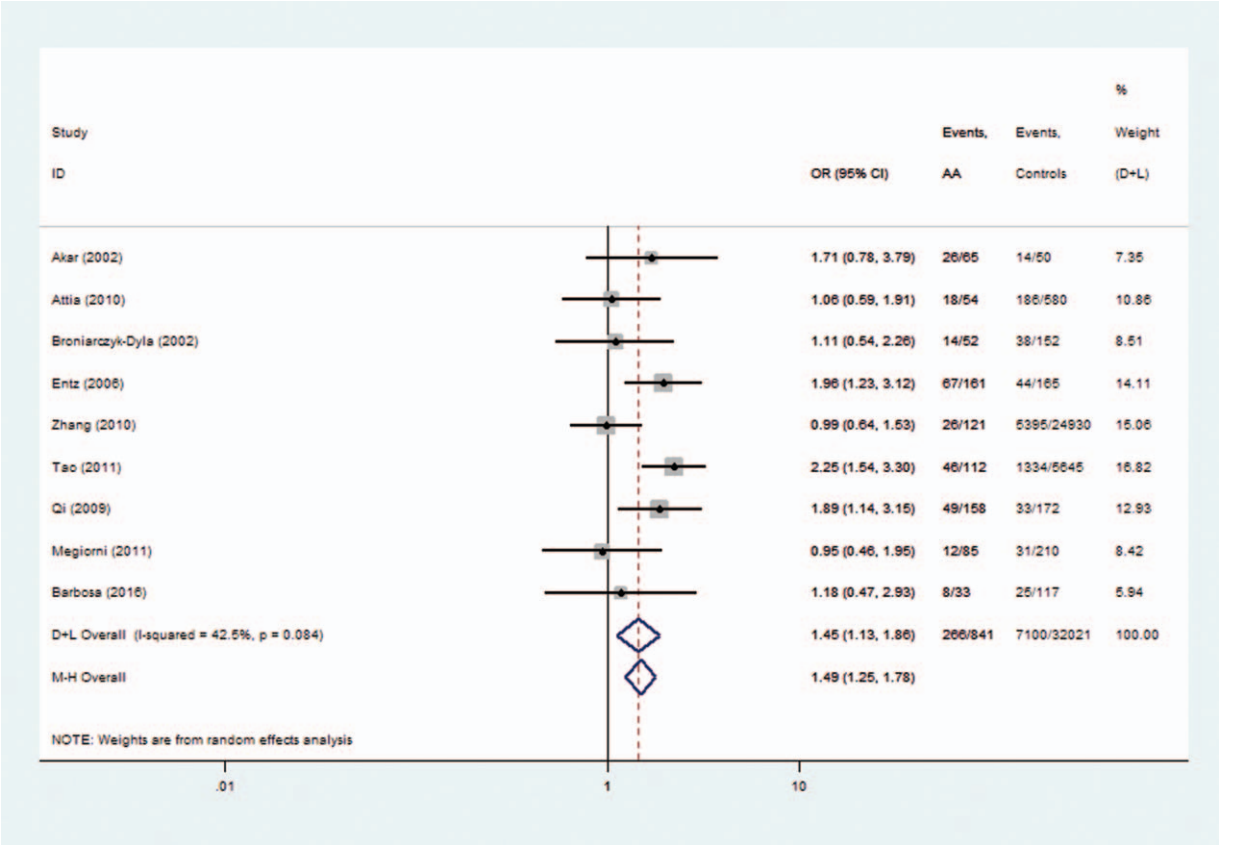

Figure 2. Forest plot of HLA-DRB1*04 polymorphism and alopecia areata.

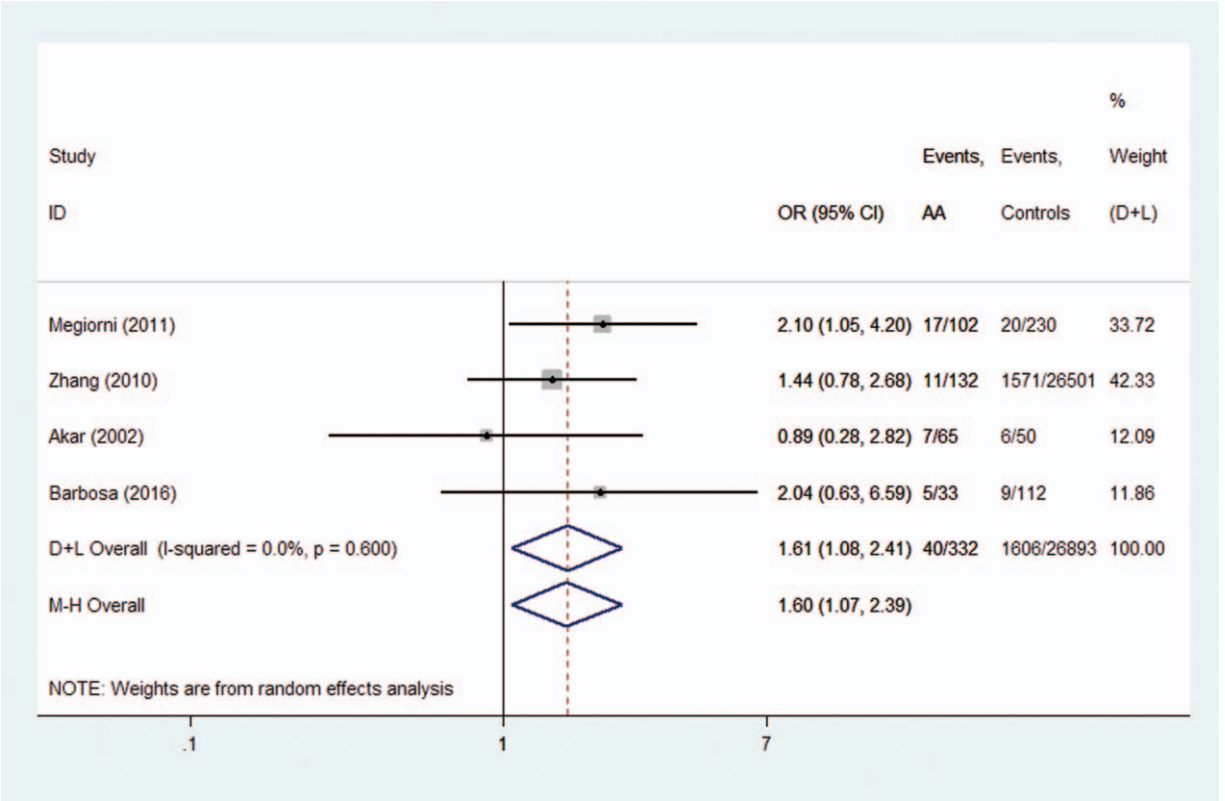

Figure 3. Forest plot of HLA-DRB1*16 polymorphism and alopecia areata.

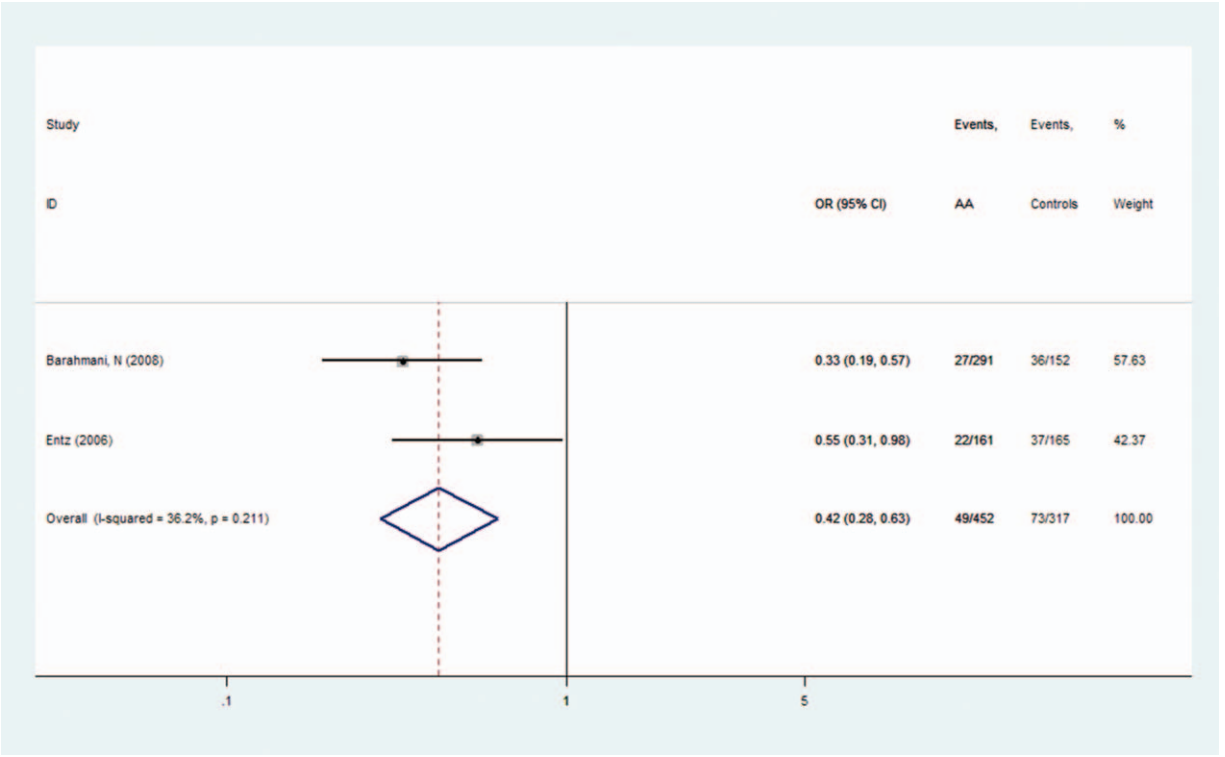

Figure 4. Forest plot of HLA-DRB1*0301 polymorphism and alopecia areata.

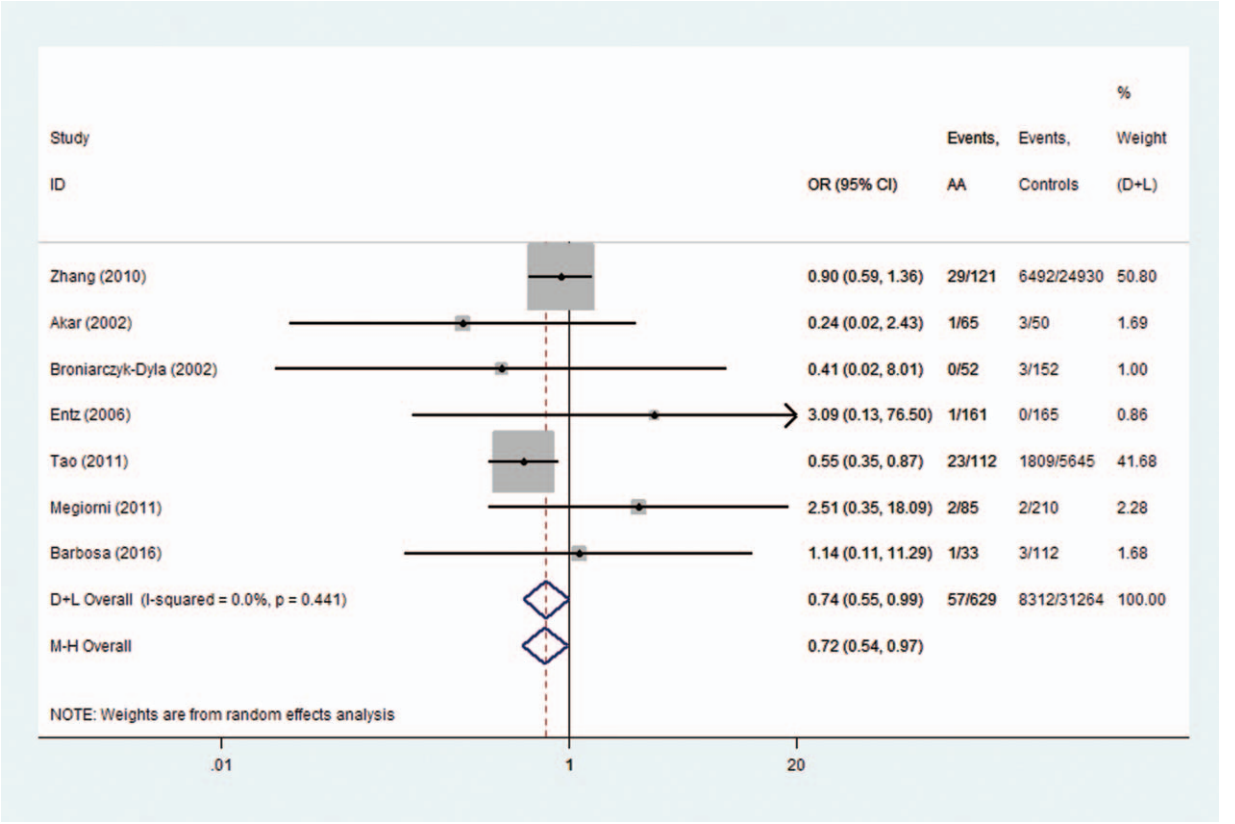

Figure 5. Forest plot of HLA-DRB1*09 polymorphism and alopecia areata.

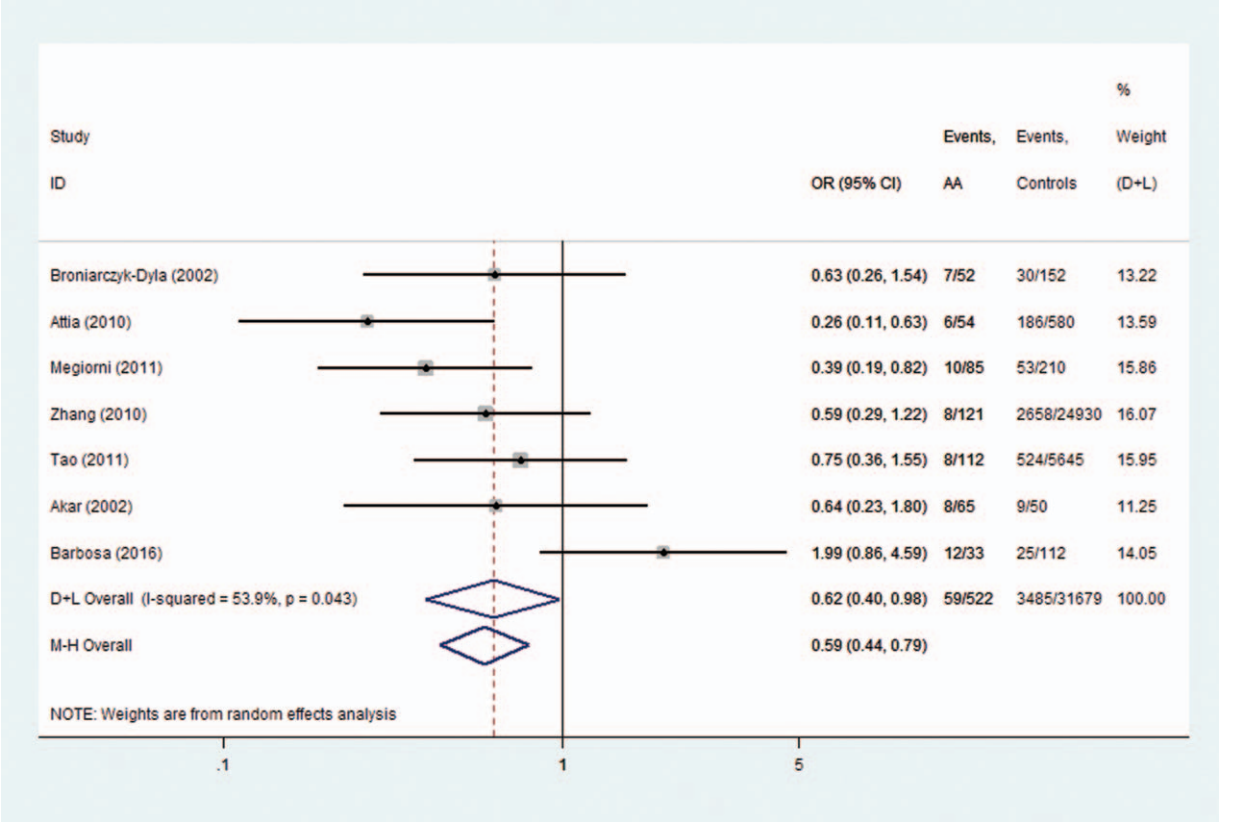

Figure 6. Forest plot of HLA-DRB1*13 polymorphism and alopecia areata.

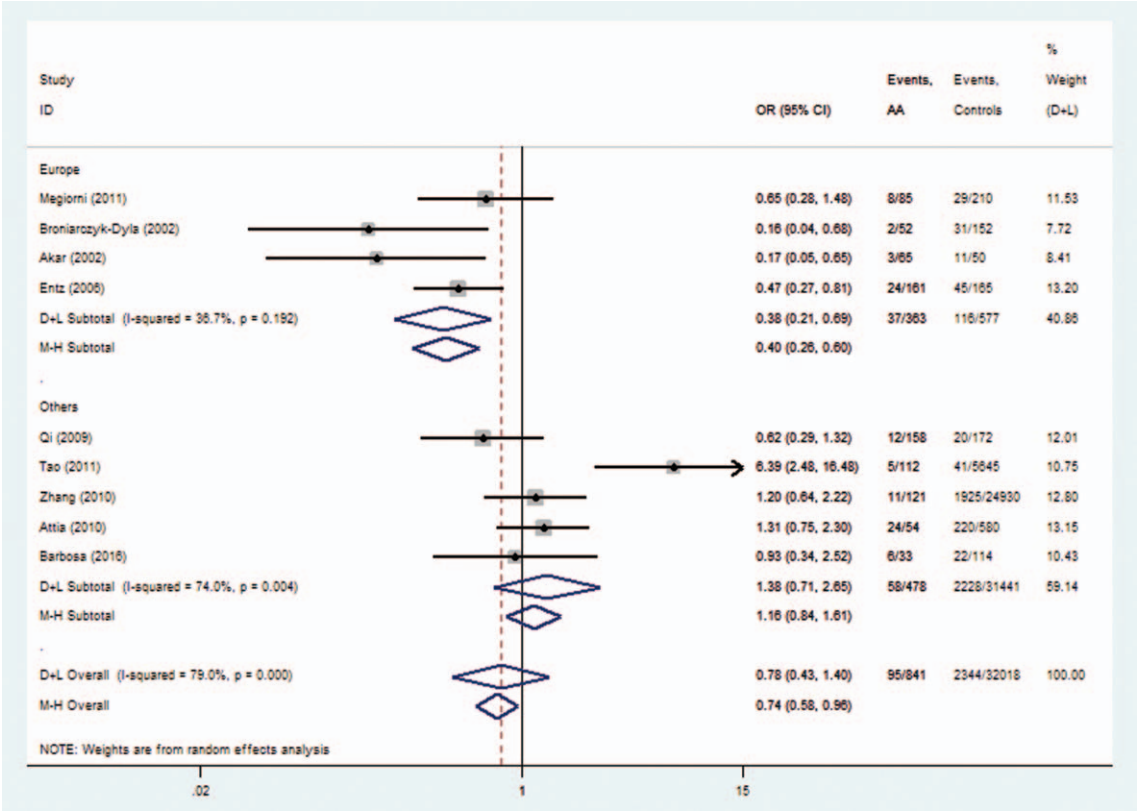

Figure 7. Forest plot of HLA-DRB1*03 polymorphism and alopecia areata.

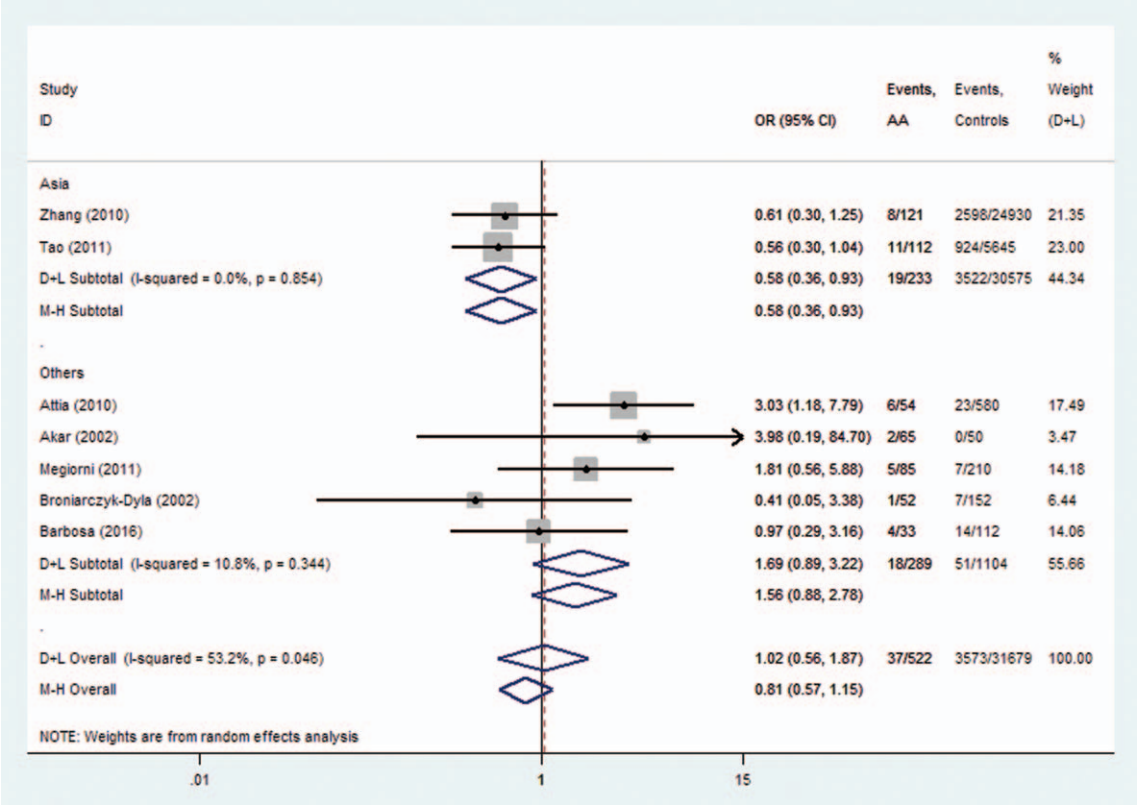

Figure 8. Forest plot of HLA-DRB1*08 polymorphism and alopecia areata.

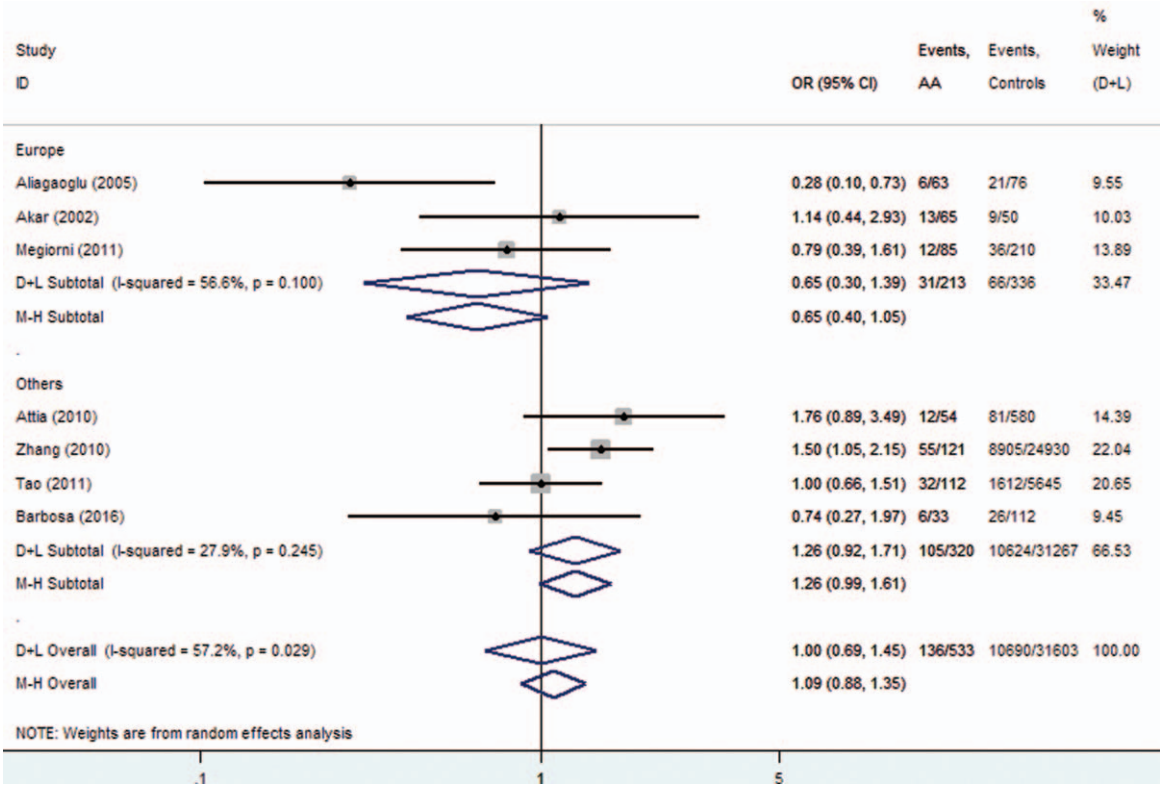

Figure 9. Forest plot of HLA-DRB1*15 polymorphism and alopecia areata.

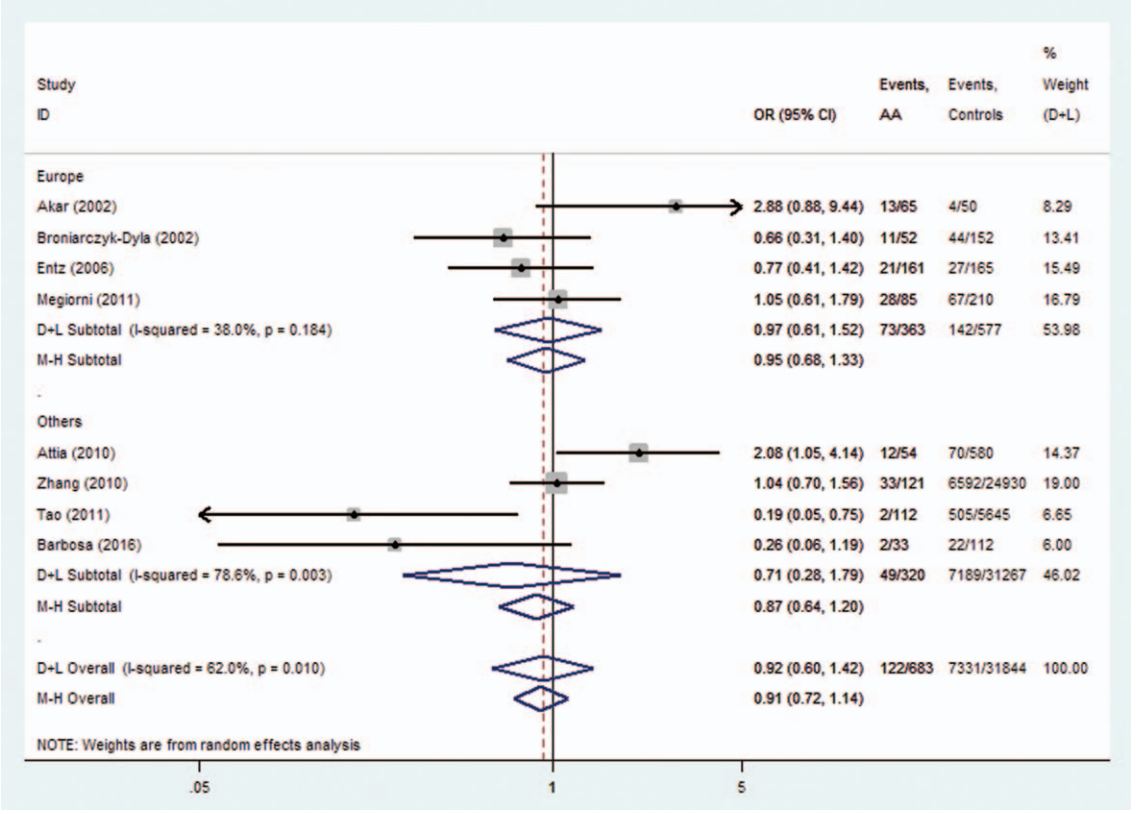

Figure 10. Forest plot of HLA-DRB1*07 polymorphism and alopecia areata.

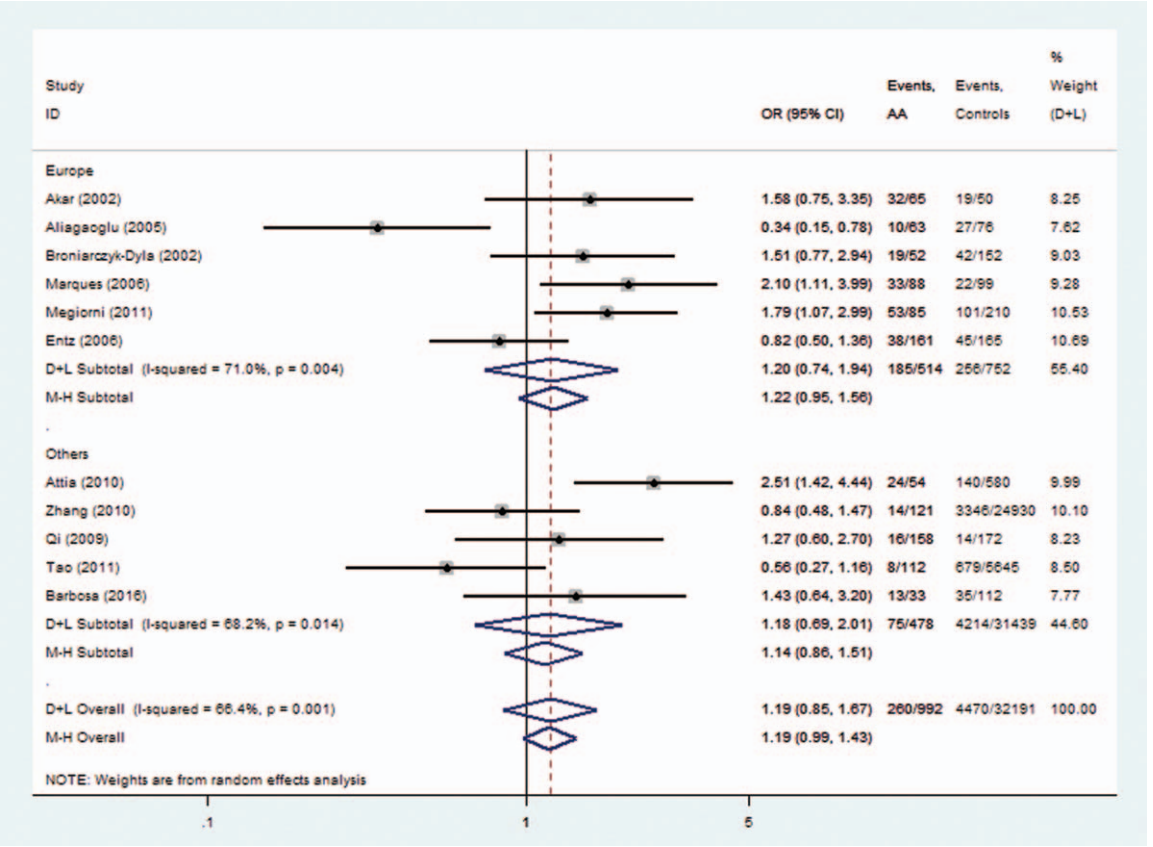

Figure 11. Forest plot of HLA-DRB1*11 polymorphism and alopecia areata.

121 cases and 24,930 controls, which accounted for huge different sample sizes in 2 groups. Table 1 lists the included studies and their main characteristics. These studies covered Europe, Asia, America, and Africa. The average NOS score was 5.08, which revealed that the methodological quality was of average level (Table 1 and Supplemental Table 4, http://links.lww.com/MD/C384). Of the 12 studies, 2 were of high quality[14,16] and 10 of moderate quality[12,13,15,17–23] (Supplemental Table 4, http://links.lww.com/MD/C384).

3.2. Quantitative synthesis

Table 2 lists the main results of the meta-analysis. In total, 13 *HLA-DRB1* allele families and 1 specific allele were extracted from the studies to investigate their relationships to AA.

Two allele families (*HLA-DRB1*04* and *HLA-DRB1*16*) conferred a significantly increased risk. For *HLA-DRB1*04* polymorphisms, the analysis of the pooled data of 8 case-control studies[9–16,20] revealed a significant increase in frequency (31.6% compared with 22.2% in controls), with an evidence of heterogeneity (I^2 = 43.0%, P = .081). A random-effects model was used for calculating OR. Overall OR (95% CIs) was 1.49 (1.24–1.78) with $P < 0.01$ (Fig. 2). For *HLA-DRB1*16* polymorphisms, the analysis of the pooled data of 4 case-control studies revealed a significant increase in frequency (12.0% compared with 6.0% in controls), with no evidence of heterogeneity (I^2 = 0.0%, P = .600). A fixed-effects model was used for calculating OR. Overall OR (95% CIs) was 1.60 (1.07–2.39) with $P < .05$ (Fig. 3).

*HLA-DRB1*0301*, *HLA-DRB1*09*, and *HLA-DRB1*13* polymorphisms conferred a significant protective effect for AA. A low heterogeneity for *HLA-DRB1*0301* (I^2 = 36.2%, P = .211), *HLA-DRB1*09* (I^2 = 0%, P = .441), and *HLA-DRB1*13* (I^2 = 53.9%, P = .043) polymorphisms was observed. A fixed-effects model was used for calculating OR for *HLA-DRB1*0301*,*09* and a random-effects model was used for calculating OR for *HLA-DRB1*13*. The OR (95% CIs) was 0.42 (0.28–0.63) for *HLA-DRB1*0301* (Fig. 4), 0.74 (0.55–0.99) for *HLA-DRB1*09* (Fig. 5), and 0.62 (0.40–0.98) for *HLA-DRB1*13* polymorphisms (Fig. 6).

For *HLA-DRB1*01*, *DRB1*03*, *DRB1*07*, *DRB1*08*, *DRB1*10*, *DRB1*11*, *DRB1*12*, *DRB1*14*, *DRB1*15*, and *DRB1*15/16* alleles, no evidence of association in statistics between *HLA-DRB1* polymorphisms and AA was found (Table 2 and Supplemental File 2, http://links.lww.com/MD/C384).

3.3. Subgroup analysis

The subgroup analysis was conducted on *HLA-DRB1*03*, *DRB1*07*, *DRB1*08*, *DRB1*11*, and *DRB1*15* polymorphisms. For *HLA-DRB1*03* polymorphisms, the analysis of the pooled data of 5 case-control studies revealed low heterogeneity in the Europe subgroup (P = .192). A fixed-effects model was used for calculating OR. Overall OR (95% CIs) was 0.40 (0.26–0.60) with $P < .01$ (Fig. 7). For *HLA-DRB1*08*, a low heterogeneity was observed in the Asia subgroup (P = .854). Overall OR (95% CIs) was 0.58 (0.36–0.93) with $P < .01$ (Fig. 8). However, no evidence of association in statistics was found

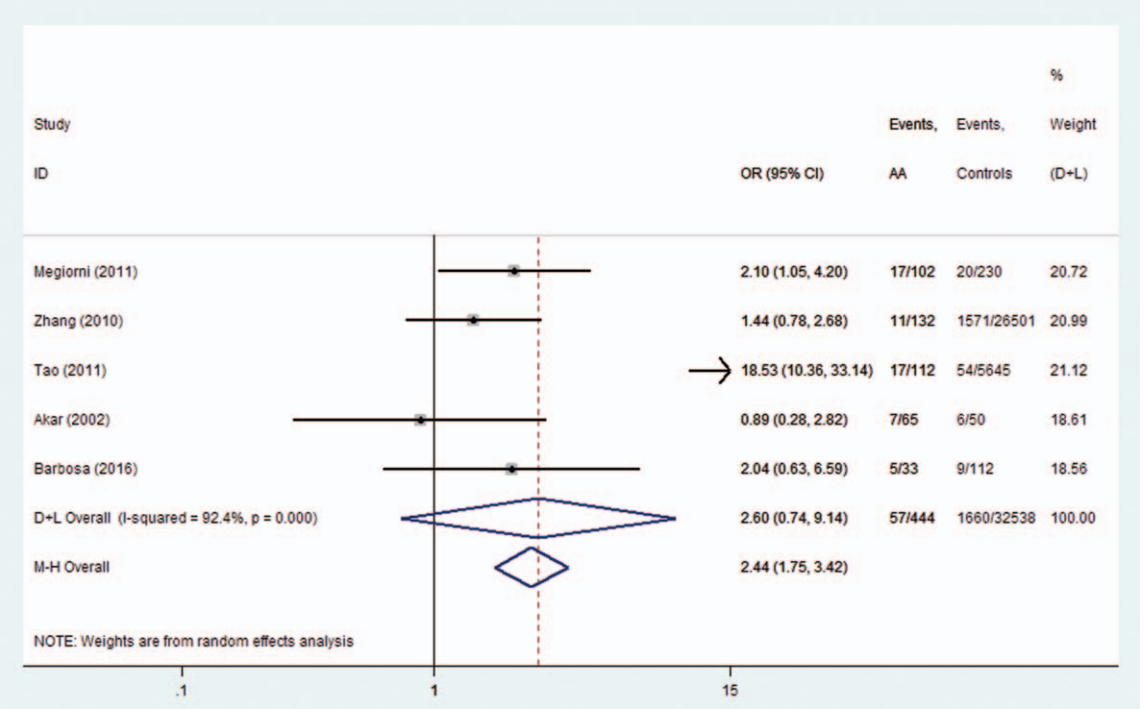

Figure 12. Forest plot of HLA-DRB1*16[#] polymorphism and alopecia areata.

between *HLA-DRB1*15* (Fig. 9), *HLA-DRB1*07* (Fig. 10), and *HLA-DRB1*11* (Fig. 11) polymorphisms and AA in the subgroup analysis.

3.4. Sensitivity analyses

A single report involved in the meta-analysis was removed each time to reflect the influence of the individual dataset on the pooled OR. A significant deviation was detected in the study by Tao[13] when analyzing the association between *HLA-DRB1*16* polymorphisms and AA. After the exclusion of this study, heterogeneity decreased from 92.4% (Fig. 12) to 0% (Fig. 3). The trim-and-fill analysis suggested that no studies (comparisons) were missing from the dataset. It turned out that *HLA-DRB1*16* polymorphisms conferred a significantly increased risk (Fig. 3).

For others, the corresponding pooled ORs were not materially changed (data not shown), indicating that the results were statistically robust.

3.5. Publication bias

Harbord and Eggers tests were not significant in any comparison ($P > .05$, shown in Table 2). The shape of the funnel plot was relatively symmetric for most alleles (Supplemental File 3, http://links.lww.com/MD/C384). They all indicated a low probability of publication bias.

Table 3

Meta-regression.

Alleles	Continent		Country		NOS score	
	β	*P*-value	β	*P*-value	β	*P*-value
*DRB1*01*	0.061	.765	0.115	.218	0.073	.651
*DRB1*03*	0.171	.679	0.170	.325	0.278	.278
*DRB1*04*	0.023	.871	0.007	.934	0.038	.786
*DRB1*07*	0.254	.385	0.249	.109	0.038	.879
*DRB1*08*	0.246	.412	0.064	.730	0.285	.306
*DRB1*09*	0.266	.597	0.187	.329	0.846	.265
*DRB1*10*	0.005	.993	0.009	.971	0.441	.427
*DRB1*11*	0.025	.935	0.003	.968	0.042	.750
*DRB1*12*	0.331	.526	0.182	.510	0.265	.229
*DRB1*13*	0.336	.108	0.2673	.067	0.084	.766
*DRB1*14*	0.076	.835	0.216	.316	0.025	.957
*DRB1*15*	0.162	.473	0.038	.850	0.141	.509
*DRB1*16*	0.376	.678	0.243	.714	0.914	.144
*DRB1*16*[#]	0.023	.946	0.113	.648	0.305	.412

[#] After exclusion of the study by Tao.[13]

3.6. Influence of continent, country, and NOS score

The results of meta-regression analysis showed that continent, country, or NOS score did not account for heterogeneity (Table 3).

4. Discussion

A comprehensive evaluation is provided by this systematic review to find out the relationship of *HLA-DRB1* polymorphisms with AA. According to inclusion and exclusion criteria, a total of 1283 cases and 32,343 controls from 12 case-control studies[12–23] were selected and analyzed. The present study revealed that *HLA-DRB1*04* and *HLA-DRB1*16* polymorphisms might be associated with increased AA risk, while *HLA-DRB1*0301*, *HLA-DRB1*09*, and *HLA-DRB1*13* polymorphisms might decrease the AA risk.

The associations between HLA polymorphisms and AA risk have been intensively studied.[12–23] For HLA-*DRB1*04* polymorphisms, 5 of 8 studies indicated that OR >1 but the 95% CIs cross 1. First, a single study with limited sample size might have been underpowered to clarify the genes with AA risk. Second, a single study can only represent one ethnic background. So after summarizing it quantitatively with a meta-analytic approach, the pooled results indicated that HLA-*DRB1*04* polymorphisms might be potential risk factors for AA (OR = 1.49, Fig. 2). A similar situation occurs when analyzing the association of *HLA-DRB1*09, HLA-DRB1*16*, and *HLA-DRB1*13* polymorphisms with AA. The purpose of this study was to increase the statistical power, evaluate the evidence from studies by summarizing it quantitatively with a meta-analytic approach, and get a reliable conclusion.

One genome-wide meta-analysis discussed the relationship between HLA and AA.[1] The study indicated *HLA-DRB1*04:01* polymorphisms as the potential risk factors for AA (OR = 1.64). It included 2489 cases and 5287 controls from the United States and Central Europe. Many studies implied that ethnic difference might be associated with the genotype distribution. Besides the United States and Europe, the present study included Asian and African countries. The results revealed that *HLA-DRB1*04* polymorphisms might be a risk factor for AA, which is a supplement of the previous meta-analyses.

Heterogeneity could potentially impact the results of all meta-analyses.[3] In our research, statistical heterogeneity was noticed among some analyses. We therefore explored the sources of heterogeneity to examine whether the results were robust. First, we have conducted meta-regression analysis to reveal whether continent, country, or NOS score could lead to heterogeneity. However, meta-regression indicated that these covariates were not statistically significant ($P > .05$). Second, sensitivity analyses were performed. It indicated that after the exclusion of the study by Tao,[13] heterogeneity decreased from 92.4% (Fig. 12) to 0% (Fig. 3) when studying the association of *HLA-DRB1*16* polymorphisms with AA. Additionally, subgroup analyses revealed that geographical factors might have led to the heterogeneity when studying the association of *HLA-DRB1*03* and *HLA-DRB1*08* polymorphisms with AA. However, because of the limited studies included in the subgroup analyses, further studies and analyses are needed to validate the findings.

To avoid local literature bias,[33] we obtained and included both English and Chinese language reports. And yet, some shortcomings of the analysis could not be neglected. First, the number of included studies was limited because the incidence of *HLA-DRB1* genotypes was low. Enough information could not be obtained on clinical type and magnitude for subgroup analysis due to the limited number of included studies. Second, it was uncertain whether the cases were comparably representative, although significant publication bias between studies was not detected.

5. Conclusion

The present study revealed that *HLA-DRB1*04* and *HLA-DRB1*16* polymorphisms might be associated with increased AA risk, while *HLA-DRB1*0301*, *HLA-DRB1*09*, *HLA-DRB1*13* polymorphisms might decrease the AA risk. Studies with adequate methodological quality on gene–gene and gene–environment interactions are needed to validate the results in the future.

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