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Human leukocyte antigen-DRB1 gene polymorphism and aplastic anemia

A meta-analysis

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Abstract

Background: The human leukocyte antigen-*DRB1* (*HLA-DRB1*) gene plays key roles in mediating immune response and activating autoreactive T-cells during aplastic anemia (AA) etiology. However, inconsistency appeared in the associations between *HLA-DRB1* polymorphism and AA. We aimed to comprehensively clarify their associations in the meta-analysis.

Methods: PubMed, Embase, Web of Science, Science Direct, SinoMed, WanFang Data, China National Knowledge Infrastructure, and Chongqing VIP Chinese Science Database were searched from January 2000 to June 2022. Statistical analysis was performed in STATA 15.0 and Comprehensive Meta-analysis Software 3.0.

Results: A total of 16 studies with 4428 patients were eventually analyzed. The results of the meta-analysis suggested that *HLA-DRB1**0301 could decrease the risk of AA (odd ratio (OR) = 0.600, 95% CI: 0.427, 0.843). Besides, *HLA-DRB1**0901 and *HLA-DRB1**1501 were risk factors of AA (OR = 1.591, 95% CI: 1.045, 2.424; OR = 2.145, 95% CI: 1.501, 3.063; respectively). Sensitivity analysis showed heterogeneity among included studies.

Conclusion: *HLA-DRB1* polymorphisms could play roles in the occurrence of AA, however more population-based studies with larger sample sizes are required to certify our findings.

Abbreviations: AA = aplastic anemia, CIs = confidence intervals, HLA-DRB1 = human leukocyte antigen-DRB1, NOS = Newcastle–Ottawa Scale, OR = odds ratio.

Keywords: aplastic anemia, gene polymorphism, *HLA-DRB1*, protective factor, risk factors

1. Introduction

Aplastic anemia (AA) is an organ-specific and cell-mediated immune disease, as well as a low or acellular hematopoietic failure syndrome. The incidence of AA in China is currently remarkable in all age groups.[1] Besides, while autoimmune damage caused by abnormal activation and hyperfunction of T lymphocytes may result in AA, its pathogenesis was still elusive.[2–4] The immune response induced by oligoclonal cytotoxic T cells, targeting hematopoietic stem cells and progenitor cells may lead to cell apoptosis and bone marrow failure, and symptoms of anemia, hemorrhage, and infection may consequently appear.[2,5]

The human leukocyte antigen (*HLA*) system or complex is a group of related proteins that are encoded by the major histocompatibility complex gene complex in humans. These cell-surface proteins are responsible for the regulation of the immune system.[5,6] The *HLA* system is the largest cluster in the human genome, and it is divided into 3 main sub-regions: the genes of class I, class II, and class III, which are all involved in immune response and suppression. In addition, its genetic polymorphism is closely associated with the susceptibility of a variety of autoimmune diseases, and several studies have assessed its important position in the human immune system.[7–9]

HLA, as an important genetic marker of the immune system, is closely correlated to AA. A large number of researches have suggested that some specific types of *HLA* are susceptible or inhibitory factors of AA.[10] Scholars pointed out that *HLA* with high polymorphism determining the function of the immune system may be closely

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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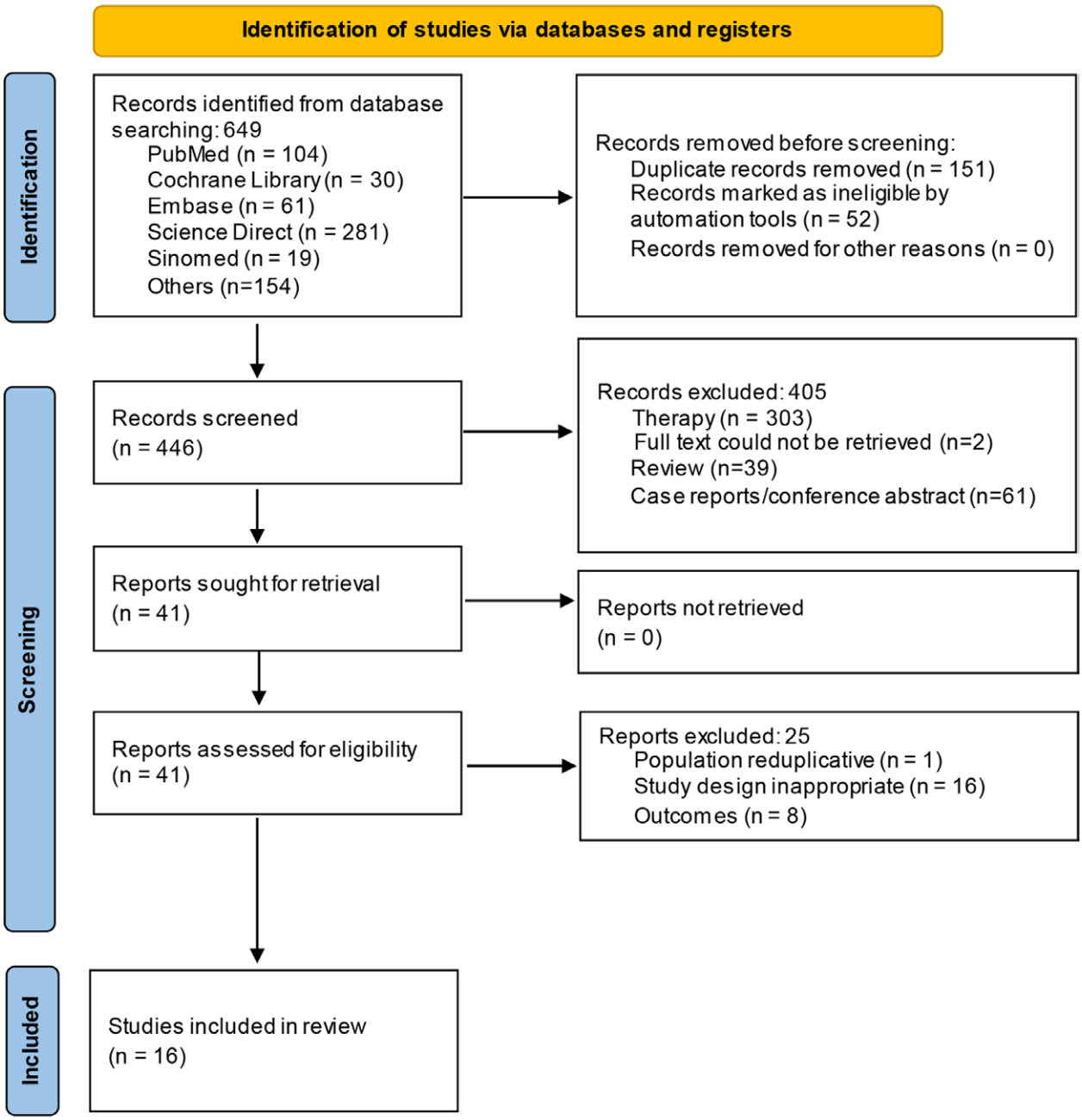

Figure 1. Flowchart of study selection process.

associated with the pathogenesis of AA.[11,12] A recent meta-analysis reported by Liu et al[13] observed that *HLA-DRB1**15 and *HLA-DRB1**15:01 polymorphisms might be associated with increased AA risk in Asians. However, whether *HLA-DRB1* polymorphisms have associations with AA cases who had not accepted therapy has not been systemically summarized. Therefore, exploring the relationship between AA and *HLA-DRB1* polymorphism is essential to further elucidate the pathogenesis of AA, which is of great significance in clinical prognosis, bone marrow transplantation, and the development of more effective preventive and treatment strategies. This meta-analysis was conducted to assess the association between *HLA-DRB1* polymorphism and AA.

2. Materials and methods

The study was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[14] This study was approved by the Ethics Committee of Henan Cancer Hospital, Zhengzhou, China.

2.1. Search strategy

Multiple electronic databases were used to search relevant studies from January 2000 to June 2022, including PubMed, Embase, Web of Science, Science Direct, SinoMed, WanFang Data, China National Knowledge Infrastructure, and Chongqing VIP Chinese Science Database (VIP). The following key terms were used jointly and separately to conduct the literature search: aplastic anemia OR AA, *human leukocyte antigen-DRB1* OR *HLA-DRB1*. No restriction was considered for the language of publication. The studies were initially reviewed by titles and abstracts, and references of eligible studies were also examined for finding further relevant studies.

Table 1

Characteristics of the studies included in the meta-analysis.

Author	Country	Region	Sample size		Genotyping method	Source of controls	Diagnostic criteria of cases	*HLA-DRB1* polymorphism
			Cases	Controls				
Wang, 2018[26]	China	Asia	65	772	PCR-SSO	Hospital	Red Blood Cell Disease Group	0101, 0102, 0301, 0401, 0405, 0406, 0701, 0803, 0901, 1101, 1201, 1202, 1302, 1401, 1403, 1404, 1405, 1501, 1502, 1601, 1602
Yang, 2016[30]	China	Asia	50	183	PCR-SSP	Population	Diagnostic criteria	0101, 0301, 0401, 0701, 0801, 0901, 1001, 1101, 1201, 1301, 1401, 1501, 1601
Wang, 2014a[27]	China	Asia	43	200	PCR-SSP	Population	Diagnostic criteria	0101, 0301, 0401, 0701, 0801, 0901, 1001, 1101, 1201, 1302, 1418, 1501, 1601, 1701
Wang, 2014b[28]	China	Asia	96	600	PCR-SBT	Population	Camitta and on the International Agranulocytosis and Aplastic Anaemia criteria	0101, 0102, 0110, 0301, 0401, 0403, 0404, 0405, 0406, 0407, 0408, 0410, 0701, 0801, 0802, 0803, 0809, 0814, 0901, 1001, 1101, 1104, 1106, 1201, 1202, 1210, 1301, 1302, 1312, 1401, 1402, 1403, 1404, 1405, 1407, 1418, 1425, 1454, 1501, 1502, 1601, 1602
Chen, 2012[18]	China	Asia	80	109	PCR-SSP	Population	The criteria set out by the British Committee	0301, 0901, 1101
Fernández-Torres, 2012[20]	Mexican Republic	North America	36	201	PCR-SSP	Hospital	Camitta and on the International Agranulocytosis and Aplastic Anemia Study (IAAAS) criteria	01, 03, 04, 07, 08, 11, 13, 14, 15, 16
Dhaliwal, 2011[19]	Malaysia	Asia	33	109	PCR-SSP	Hospital	The guidelines enacted by the International Study of Agranulocytosis and Aplastic Anemia	0301, 0403, 0405, 0803, 0901, 1101, 1104, 1106, 1202, 1302, 1404, 1405, 15, 1501, 1502, 1514, 1602
Huo, 2011[12]	China	Asia	115	2264	PCR-SSP	Hospital	NA	01, 03, 04, 07, 08, 09, 10, 11, 12, 13, 14, 15, 16
Rehman, 2009[23]	Pakistani	Asia	61	200	PCR-SSP	Population	NA	01, 03, 04, 07, 09, 1001, 11, 12, 13, 1302, 14, 15
Song, 2008[24]	Korea	Asia	109	800	PCR-SSO PCR-SS-CP	Population	The criteria of the International Study of Agranulocytosis and Aplastic Anemia	0101, 0301, 0401, 0403, 0404, 0405, 0406, 0407, 0408, 0410, 0701, 0802, 0803, 0901, 1001, 1101, 1111, 1201, 1202, 1301, 1302, 1339, 1401, 1402, 1403, 1404, 1405, 1406, 1407, 1412, 1501, 1502, 1602
Yari, 2008[31]	Iran	Asia	35	466	PCR-SSP	Hospital	NA	01, 03, 04, 07, 08, 09, 10, 11, 12, 13, 14, 15, 16
Liang, 2007[22]	China	Asia	82	400	PCR-SSP	Hospital	Diagnostic criteria	0101, 0301, 0401, 0701, 0801, 0901, 1101, 1201, 1301, 1401, 1501, 1601
Sugimori, 2007[25]	Japan	Asia	140	491	PCR-SSP	Population	NA	0101, 0301, 0401, 0403, 0404, 0405, 0406, 0407, 0409, 0410, 0701, 0801, 0802, 0803, 0901, 1001, 1101, 1201, 1202, 1301, 1302, 1401, 1402, 1403, 1405, 1406, 1407, 1501, 1502, 1602
Wang, 2007[29]	China	Asia	56	1000	PCR-SSP	Hospital	NA	01, 03, 04, 07, 08, 09, 10, 11, 12, 13, 14, 15, 16
Oguz, 2002[8]	Turkish	Europe	33	97	PCR-SSP	Population	NA	01, 15(02), 03, 04, 11(05), 13(06), 14(06), 07, (08/09/10/12/16)
Kapusitin, 2001[21]	Russia	Euroupe	44	100	PCR-SSO	Population	Camitta	0101, 0102, 0103, 1501, 1502, 1601, 1602, 0301, 0401, 0402, 0403/6, 0404, 0407, 0408, 0410, 0416, 1101, 1102, 1104, 1201, 1301, 1302, 1303, 1305, 14, 0701, 0801, 0803, 0901, 1001

PCR = polymerase chain reaction, PCR-SSCP = PCR single-strand conformation polymorphism, PCR-SSO = PCR sequence-specific oligonucleotide, PCR-SSP = PCR sequence-specific primers.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows:

(a) Case-control studies;
(b) Studies that compared patients with AA and healthy individuals;
(c) Studies that analyzed the association between *HLA-DRB1* polymorphism and AA.

The exclusion criteria were as follows:

(a) Case studies/meta-analyses/letters to editors/cellular or animal experiments;
(b) Patients with congenital AA;
(c) Limitation in recorded data;
(d) Duplicate studies.

2.3. Data extraction

Two reviewers independently extracted needed information using a customized and standardized form. If the two authors disagree in their judgments, a third author made the final decision. For each study, the following information was

Table 2

Quality assessment of included studies by NOS.

Study	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of intervention	Same method of ascertainment for cases and controls	Non-response rate	Total quality scores
Wang, 2018	☆	☆	—	☆	☆	☆	☆	☆	7
Yang, 2016	☆	☆	☆	—	☆	☆	☆	☆	7
Wang, 2014a	☆	☆	☆	☆	☆	☆	☆	☆	8
Wang, 2014b	☆	☆	☆	—	☆	☆	☆	☆	7
Chen, 2012	☆	☆	☆	☆	☆	☆	☆	☆	8
Fernández-Torres, 2012	☆	☆	—	☆	☆	☆	☆	☆	7
Dhaliwal, 2011	☆	☆	—	☆	☆	☆	☆	☆	7
Huo, 2011	☆	☆	—	☆	—	☆	☆	☆	6
Rehman, 2009	☆	☆	☆	—	☆	☆	☆	☆	7
Song, 2008	☆	☆	☆	—	☆	☆	☆	☆	7
Yari, 2008	☆	☆	—	—	☆	☆	☆	☆	6
Liang, 2007	☆	☆	—	☆	—	☆	☆	☆	6
Sugimori, 2007	☆	☆	☆	—	☆	☆	☆	☆	7
Wang, 2007	☆	☆	—	☆	—	☆	☆	—	5
Oguz, 2002	☆	☆	☆	—	—	☆	☆	☆	6
Kapusitin, 2001	☆	☆	☆	☆	☆☆	☆	☆	☆	9

NOS = Newcastle–Ottawa Scale.

extracted: year of publication, surname, and address of the first author, the sample size of cases and controls, genotyping method, source of controls, diagnostic criteria, and *HLA-DRB1* polymorphism.

2.4. Quality assessment

Two authors independently evaluated the included studies using the Newcastle–Ottawa Scale (NOS).[15] Disagreement was resolved by discussion to produce final scores. Three domains of NOS were assessed: selection of study groups (4 stars); comparability of groups (2 stars); and ascertainment of exposure and outcomes (3 stars) for case-control, respectively. NOS score ranges from 0 to 9. Studies were then classified according to NOS score as poor (0–4), moderate (5–6), or high quality (7–9).

2.5. Statistical analysis

Continuous data were presented as mean with the standardized mean difference, and binary data were expressed as odds ratio (OR) with 95% confidence intervals (CIs) to estimate the differences in relationships among *HLA-DRB1* polymorphism. Heterogeneity was assessed by the I^2 statistic and P values of heterogeneity in this study. If I^2 was > 50% and the P value of heterogeneity < .05, the studies were heterogeneous and the random-effects model was adopted; otherwise, a fixed-effects model was employed for making comparisons. A 2-side P value < .05 was considered statistically significant. We carried out a sensitivity analysis with the leave-one-out method to assess the robustness of our results. To be specific, each publication was removed from the total dataset, and testing of heterogeneity was performed among the remaining publications. The Begg rank correlation[16] and Egger weighted regression methods[17] were used to assess the publication bias (P < .05 was considered indicative of a statistically significant publication bias).

Comprehensive Meta-analysis Software (Version 3.0, The Biostat Inc, Englewood, CO) was used for the generation of forest plots and statistical analyses. The Begg and Egger tests were assessed by STATA 15.0 (Stata Corporation, College Station, TX).

3. Results

3.1. Search results

A total of 649 articles were eventually screened after completing the search process. After reading those articles, 446 articles met the preliminary criteria. Further screening resulted in the exclusion of 405 articles due to the study design, incomplete data, or type of articles. Finally, 16 studies[8,12,18–31] were included for analysis. The flowchart of the study selection process is presented in Figure 1.

3.2. Characteristics of the included studies

An overview of included studies with the main study and baseline characteristics is presented in Table 1. The analysis included 16 studies that were published from 2001 to 2018 with a total

Table 3

Summary results of *HLA-DRB1* polymorphism and aplastic anemia.

								Begg's test	
HLA-DRB1	N	OR	95% CI	*P*	I^2 (%)	$P_{Heterogeneity}$	Q value	*Z*	*P*
*01	6	0.706	0.309, 1.614	.409	56.7	.041	11.547	1.50	.133
*0101	8	0.745	0.545, 1.019	.066	14.2	.319	8.159	1.11	.266
*0102	3	0.823	0.248, 2.733	.750	0.0	.940	2.000	0.00	1.000
*03	6	0.617	0.312, 1.220	.165	56.5	.043	11.494	0.38	.707
*0301	9	0.600	0.427, 0.843	.003	0.0	.552	8.000	0.94	.348
*04	6	0.551	0.317, 0.956	.034	64.0	.016	13.889	1.13	.260
*0401	8	1.183	0.848, 1.650	.322	39.0	.119	11.475	0.62	.536
*0403	4	0.659	0.381, 1.138	.135	59.6	.059	7.426	1.02	.308
*0404	4	0.714	0.311, 1.641	.428	0.0	.932	3.000	−0.34	1.000
*0405	5	1.174	0.696, 1.980	.547	67.0	.016	12.121	0.24	.806
*0406	4	0.456	0.260, 0.797	.006	0.0	.648	3.000	−0.34	1.000
*0407	4	3.895	0.800, 18.971	.092	13.3	.326	3.460	1.70	.089
*0408	3	10.526	0.765, 146.865	.080	0.0	.461	2.000	0.00	1.000
*0410	4	0.574	0.253, 1.304	.185	0.0	.519	3.000	−0.34	1.000
*07	6	1.312	0.951, 1.811	.098	17.8	.298	6.083	0.38	.707
*0701	8	0.998	0.774, 1.287	.990	64.2	.007	19.553	−0.12	1.000
*08	4	1.111	0.745, 1.655	.606	25.0	.262	4.000	1.02	.308
*0801	6	1.469	0.946, 2.281	.087	88.5	<.001	43.478	0.38	.707
*0802	3	0.526	0.301, 0.919	.024	0.0	.785	2.000	0.00	1.000
*0803	5	0.639	0.471, 0.868	.004	28.3	.233	5.579	1.22	.221
*09	4	1.342	0.952, 1.879	.087	54.9	.084	6.652	−0.34	1.000
*0901	10	1.591	1.045, 2.424	.030	96.6	<.001	264.706	0.00	1.000
*10	3	0.781	0.313, 1.949	.596	0.0	.748	2.000	0.00	1.000
*1001	7	0.639	0.351, 1.164	.143	0.0	.465	6.000	0.60	.548
*11	5	0.916	0.662, 1.268	.597	0.0	.942	4.000	0.73	.462
*1101	9	0.909	0.648, 1.276	.583	26.0	.213	10.811	0.31	.754
*12	4	0.959	0.678, 1.358	.815	20.0	.290	3.750	0.34	.734
*1201	8	1.146	0.777, 1.691	.492	48.6	.058	13.619	1.86	.063
*1202	4	0.644	0.416, 0.998	.049	0.0	.505	3.000	0.34	.734
*13	5	1.075	0.761, 1.514	.677	0.0	.587	4.000	0.24	.806
*1301	6	0.537	0.350, 0.823	.004	0.0	.693	5.000	0.00	1.000
*1302	7	0.649	0.473, 0.889	.007	31.7	.186	8.785	0.30	.764
*14	6	0.643	0.451, 0.916	.014	0.0	.428	5.000	0.38	.707
*1401	6	0.959	0.655, 1.403	.827	70.9	.004	17.182	0.75	.452
*1402	3	1.701	0.126, 22.977	.689	70.6	.033	6.803	1.04	.296
*1403	4	0.976	0.434, 2.197	.954	0.0	.944	3.000	0.34	.734
*1404	3	0.768	0.212, 2.785	.688	0.0	.735	2.000	0.00	1.000
*1405	4	1.106	0.678, 1.804	.687	0.0	.561	3.000	0.34	.734
*1407	3	0.306	0.024, 3.840	.359	0.0	.999	2.000	1.04	.296
*15	6	2.716	1.608, 4.588	<.001	70.2	.005	16.779	1.13	.260
*1501	9	2.145	1.501, 3.063	<.001	69.6	.001	26.316	0.10	.917
*1502	7	1.691	1.272, 2.249	<.001	78.8	<.001	28.302	0.90	.368
*16	4	0.910	0.522, 1.588	.741	0.0	.736	3.000	1.02	.308
*1601	6	1.182	0.675, 2.071	.558	77.9	<.001	22.624	0.00	1.000
*1602	5	0.725	0.403, 1.303	.282	23.8	.265	5.249	0.24	.806

CIs = confidence intervals, HLA-DRB1 = human leukocyte antigen-DRB1, OR = odds ratio.

number of 4428 subjects. The sample size ranged from 142 to 909, and there were 698 controls and 3730 cases in the AA group and control group, respectively. Besides, *HLA-DRB1* typing was achieved by polymerase chain reaction (PCR) amplification.

3.3. Quality assessment

NOS for the eligible studies were presented in Table 2. Four studies were evaluated as 7 stars, 6 studies as 6 stars, and the remaining 3 studies as 5 stars. Therefore, 4 studies were classified as high-quality, and 9 studies were assigned as moderate.

3.4. Pooled effect size and heterogeneity

3.4.1. The association between HLA-DRB1*0301 and AA. Nine articles that investigated the association between *HLA-DRB1**0301 polymorphism and AA were included (Table 3). The forest plot for the association between *HLA-DRB1**0301 polymorphism and AA is shown in Figure 2A. The results suggested that *HLA-DRB1**0301 was protective against AA (OR = 0.600, 95% CI: 0.427–0.843) with no evidence of significant heterogeneity (I^2 = 0.0%, $P_{Heterogeneity}$ = 0.552, Q = 8.000).

3.4.2. The association between HLA-DRB1*0901 and AA. Ten articles that investigated the association between *HLA-DRB1**0901 polymorphism and AA were included (Table 3). *HLA-DRB1**0901 could function as a risk factor of AA, and the pooled OR was 1.591 (95% CI: 1.045–2.424). In addition, significant heterogeneity was observed (I^2 = 96.6%, $P_{Heterogeneity}$ < 0.001, Q = 264.706) (Fig. 2B).

3.4.3. The association between HLA-DRB1*1501 and AA. Nine articles that investigated the association between HLA-DRB1-1501 polymorphism and AA were included

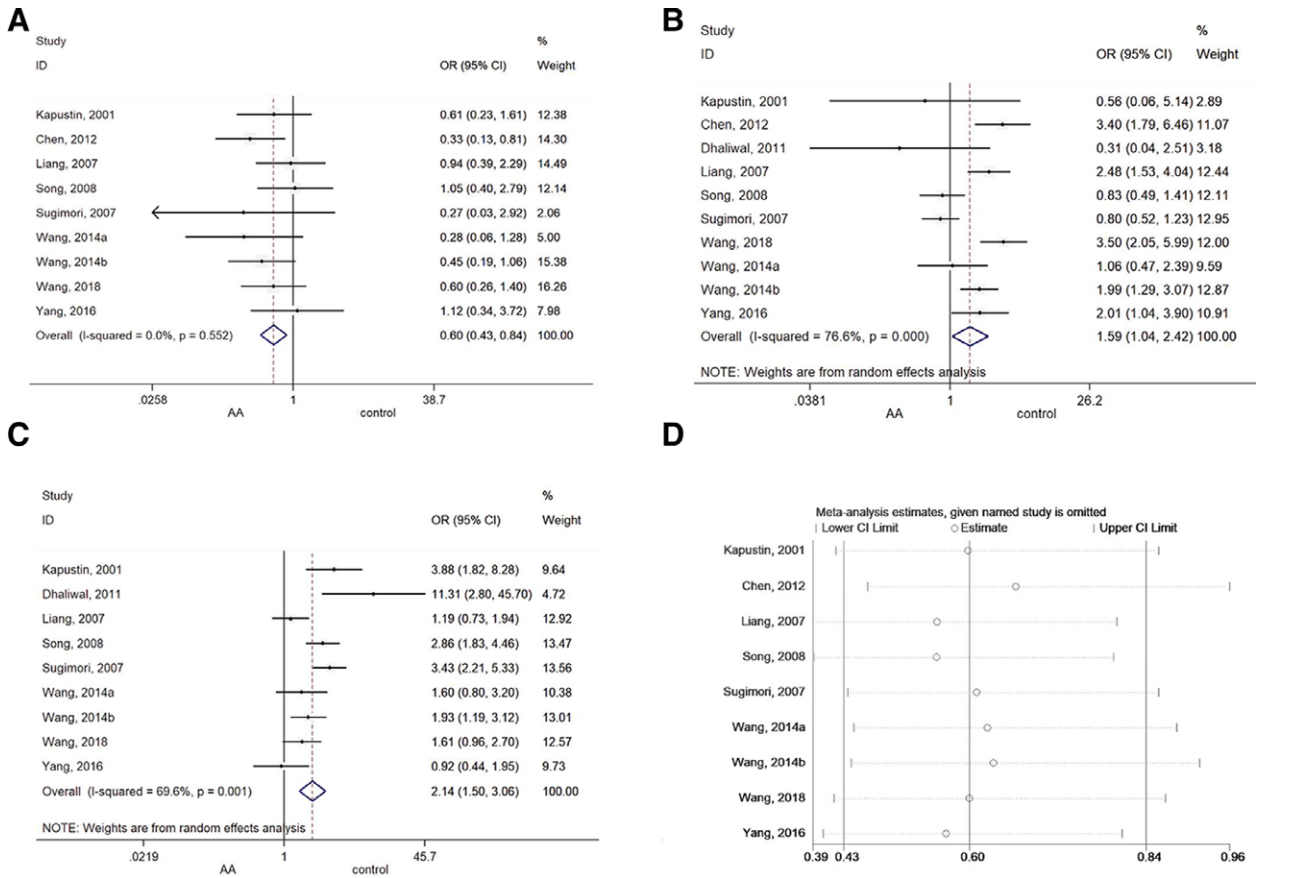

Figure 2. (A–D) A meta-analysis of the HLA-DRB1-0301, HLA-DRB1-0901, and HLA-DRB1-1501 polymorphism and the results of sensitivity analysis of HLA-DRB1-0301. HLA-DRB1 = human leukocyte antigen-DRB1.

(Table 3). *HLA-DRB1**1501 was positively associated with AA (OR = 2.145, 95% CI: 1.501–3.063), with significant heterogeneity among studies (I^2 = 69.6%, $P_{\text{Heterogeneity}}$ = 0.001, Q = 26.316) (Fig. 2C).

3.5. Sensitivity analysis

As shown in Figure 2D, the pooled results were not significantly shaped by any of the studies, indicating that our results are robust.

3.6. Publication bias

The analysis was not suggestive of potential publication bias among the included trials according to Begg rank correlation analysis and Egger weighted regression analysis ($P > .05$). The detailed potential publication bias can be found in Table S1, Supplemental Digital Content, http://links.lww.com/MD/I787.

4. Discussion

In the current meta-analysis, we systematically reviewed and summarized the articles on the associations of *HLA-DRB1* polymorphism and AA. Sixteen studies with a total number of 4428 patients were included and analyzed. The results suggested that *HLA-DRB1**0301 might be protective against AA, whereas *HLA-DRB1**0901 and *HLA-DRB1**1501 are probably the risk factors.

AA is characterized by bone marrow hypocellularity and peripheral cytopenia, but the detailed pathophysiology is still in exploration. Previous studies found that antigen-driven and auto-immune dysregulated T-cell homeostasis results in hematopoietic stem cell injury, which may be a pathogenesis of AA.[32,33] In addition, studies have indicated that several genes such as *HLA*-A, *-B*, *-DRB1* alleles were associated with the pathogenesis and development of AA. In the previous meta-analysis,[13] cases who carried *HLA-DRB1**15 or *HLA-DRB1**15:01 alleles might have a good response rate for the immunosuppressive therapy among AA patients, suggestive of close associations between the *HLA* gene and AA. Meanwhile, the *HLA* gene could involve in mediating immune response and cause an abnormal immune response, which has been observed with the occurrence of immune disease.[8]

The protective function of *HLA-DRB1**03 in Crohn's disease and sickle cell anemia was previously reported, and the mechanisms included the immunomodulatory effects of *HLA-DRB1**03.[34] In the current meta-analysis, *HLA-DRB1**0301 was protective against AA, which was in line with the above findings. Deng et al[33] reported that the frequency of the *HLA-DRB1**0901 gene in the HLA-II group was significantly higher than that in the control group, which indicated the *HLA-DRB1**0901 might have a potential influence on AA. The finding was in concordance with ours, in which the *HLA-DRB1**0901 gene may be a risk factor for AA. Oguz et al[8] demonstrated that the expression of *HLA-DRBl**1501 was significantly higher in the muscles of Chinese (especially those living in northern China), Slavic, Japanese, and Korean than that in the healthy controls. In addition, the association of *HLA-DR2* or its split *DR15* (*HLA-DRB1**1501) with susceptibility to AA has been well documented in different ethnic groups, which once again corroborated the results of this meta-analysis. Regarding the high expression level of *HLA-DRBl**1501 in the AA group, this gene may act as a risk factor for AA.

However, this study contains some limitations. Firstly, relatively limited studies were included in this meta-analysis, thus a greater number of research on *HLA-DRB1* polymorphism should be conducted. Secondly, a high level of heterogeneity was observed in the analysis of *HLA-DRBl**0901, which might be attributed to limited sample size, different study designs, and population heterogeneity. Therefore, the random effects model should be employed to decline this negative influence.

5. Conclusion

In conclusion, *HLA-DRBl**0301 could be protective against AA, while *HLA-DRBl**0901 and *HLA-DRBl**1501 might act as risk factors for AA.

Author contributions

Conceptualization: Baijun Fang.
Data curation: Ning Li, Lijie Liang.
Formal analysis: Ning Li.
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