Association of *HLA-DR3* and *HLA-DR15* Polymorphisms with Risk of Systemic Lupus Erythematosus

Ke Xue[1], Wen-Quan Niu[2], Yong Cui[1]

[1]Department of Dermatology, China-Japan Friendship Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China
[2]Institute of Clinical Medicine, China-Japan Friendship Hospital, Beijing 100029, China

Abstract

Background: Systemic lupus erythematosus (SLE) is an autoimmune disease under genetic control. Growing evidences support the genetic predisposition of *HLA-DRB1* gene polymorphisms to SLE, yet the results are not often reproducible. The purpose of this study was to assess the association of two polymorphisms of *HLA-DRB1* gene (*HLA-DR3* and *HLA-DR15*) with the risk of SLE via a comprehensive meta-analysis.

Methods: This study complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Case-control studies on *HLA-DRB1* and SLE were searched from PubMed, Elsevier Science, Springer Link, Medline, and Cochrane Library database as of June 2018. Analysis was based on the random-effects model using STATA software version 14.0.

Results: A total of 23 studies were retained for analysis, including 5261 cases and 9838 controls. Overall analysis revealed that *HLA-DR3* and *HLA-DR15* polymorphisms were associated with the significant risk of SLE (odds ratio [*OR*]: 1.60, 95% confidence interval (*CI*): 1.316–1.934, $P = 0.129$ and *OR*: 1.68, 95% *CI*: 1.334–2.112, $P = 0.001$, respectively). Subgroup analyses demonstrated that for both *HLA-DR3* and *HLA-DR15* polymorphisms, ethnicity was a possible source of heterogeneity. Specifically, *HLA-DR3* polymorphism was not associated with SLE in White populations (*OR*: 1.60, 95% *CI*: 1.320–1.960, $P = 0.522$) and *HLA-DR15* polymorphism in East Asian populations (*OR*: 1.65, 95% *CI*: 1.248–2.173, $P = 0.001$). In addition, source of control was another possible source for both *HLA-DR3* and *HLA-DR15* polymorphisms, with observable significance for *HLA-DR3* in only population-based studies (*OR*: 1.65, 95% *CI*: 1.370–1.990, $P = 0.244$) and for *HLA-DR15* in both population-based and hospital-based studies (*OR*: 1.38, 95% *CI*: 1.078–1.760, $P = 0.123$ and *OR*: 2.08, 95% *CI*: 1.738–2.490, $P = 0.881$, respectively).

Conclusions: *HLA-DRB1* gene may be a SLE-susceptibility gene, and it shows evident ethnic heterogeneity. Further prospective validations across multiple ethnical groups are warranted.

Key words: *HLA-DR15*; *HLA-DR3*; *HLA-DRB1*; Meta-Analysis; Systemic Lupus Erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease predominantly affecting women, and its clinical features always include hematological abnormalities, skin and joint diseases, renal disease, and neuropsychiatric complications.[1,2] SLE is characterized by the development of dysregulated autoreactive B-cell-derived autoantibodies directed against nuclear and cellular components and the activation of complex inflammatory cascades, thereby resulting in multisystem organ damage.[1,2]

It is well established that the pathogenesis of SLE is multifactorial, to which genetic, endocrine immunologic, and environmental factors contribute interactively.[1,2] A better understanding of the genetic basis of SLE has recently emerged from studies of families, candidate genes, and genome-wide scanning. There is evidence that monozygotic twins were observed to have a much higher rate of disease concordance than dizygotic twins, indicating a strong genetic component in SLE.[3] In addition, more than 52 candidate loci

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Address for correspondence: Dr. Yong Cui, Department of Dermatology, China-Japan Friendship Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China
E-Mail: wuhucuiyong@vip.163.com

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in predisposition to SLE have been identified by a large panel of genome-wide association studies across various ethnical groups in the past two decades.[4-9] It is of interest to notice that a majority of SLE candidate genes and loci are functionally relevant to immune system, in particular the genes located in human lymphocyte antigen (HLA) regions.[10] The HLA gene is mapped on chromosome 6p21.3, and it encodes the major histocompatibility complex proteins in humans,[11] which has a pivotal role in the regulation of immune system. The genomic sequences of HLA gene are highly polymorphic, and growing evidence indicate that its different alleles are able to modulate the adaptive immune system.[11] It is widely recognized that dysregulation of antigen presentation by HLA proteins to T-cells leads to abnormal T-cell-mediated adaptive response, which may explain why different HLA gene alleles contribute to the pathogenic development of SLE.[1,2] Several HLA haplotypes were strongly linked to the pathogenic development of SLE. For example, three HLA haplotypes were significantly associated with SLE susceptibility in Caucasians.[12] In addition, Natalia *et al*.[13] conducted a meta-analysis, showing that *HLA-DR2* and *HLA-DR3* genes were associations with the risk of SLE in Latin Americans.

Although the association between HLA genes and SLE has been widely evaluated, the results are not often reproducible, and most studies are limited by small sample sizes and genetic heterogeneity.[12,14,15] It is universally recognized that individual studies in small sample size may have not enough statistical power to detect a small risk factor or give a fluctuated estimation. Genetic heterogeneity is an inevitable problem in any disease identification strategy that can be avoided when large homogeneous populations are used. To overcome these limitations and fill this gap in knowledge, we designed the present meta-analysis of all case-control studies in the medical literature to comprehensively assess the genetic association of *HLA-DR3* and *HLA-DR15* polymorphisms in *HLA-DRB1* gene with the risk of having SLE.

Methods

The conduct of this meta-analysis conformed to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[16]

Literature search strategy

The electronic databases used for literature search included PubMed, Springer Link, Elsevier Science, and Cochrane Library database, and search process was conducted independently by two investigators (Xue K and Niu WQ), restricting the publications included to English language studies and humans only. The key words included "systemic lupus erythematosus" or "SLE" and "human lymphocyte antigen" or "HLA" or "HLA-DRB" or "*HLA-DR3*" or "*HLA-DR15*". In addition, hand searching of the reference lists of retrieved articles was also conducted.

Study selection

Studies were included if they satisfied the following criteria: (1) the diagnosis of SLE according to the American College of Rheumatology 1979 or 1982 revised classification criteria; (2) study design: cross-sectional or nested case-control design; (3) raw data including odds ratio (*OR*) with 95% confidence interval (95% *CI*) were provided, or enough information to calculate *OR* was supplied in the study; and (4) the article was published in peer-reviewed journals as original contributions, rather than in the form of conference abstract or poster or case series or letter to the editor.

Data extraction

Two investigators (Xue K and Niu WQ) independently extracted data from each eligible study using a standardized data extraction form, and any discrepancies were resolved by adjudicated by a third investigator (Cui Y). The items extracted included the first author's family name, publication year, country or area where the study was performed, sample size, ethnicity, diagnostic method, genotyping method, and genetic distributions of *HLA-DR3* and *HLA-DR15* polymorphisms in SLE patients and controls.

Statistical analysis

In a random-effects model, the *OR* and 95% *CI* for the risk prediction of *HLA-DR3* and *HLA-DR15* polymorphisms for SLE were calculated. The Chi-squared test and inconsistency index (I^2) statistic were used to quantify the heterogeneity of effect-size estimates both in overall and subgroup analyses. I^2 statistics were used to quantify the percentage of the total variance between-study heterogeneity; $Pm < 0.05$ was considered statistically significant. 95% *CI*s were analyzed to determine the diagnostic accuracy of SLE.

The proportion of the total variation increases with the percentage of I^2. Hardy-Weinberg equilibrium was test in control groups. Random-effects model was constructed to calculate the *P* value for heterogeneity. Based on the ascending order of publication dates, a cumulative analysis was performed to identify the impact of the first published study on the following publications and the evolution of the pooled estimates over time. Subgroup analysis and meta-regression analysis were conducted to estimate the potential confounding factors such as race, control source, and matched status between patients and controls. The Begg's funnel plot was employed to assess the probability of publication bias. The trim-and-fill method was employed to estimate the number of potentially missing studies caused by publication bias. All statistical analyses were conducted using STATA software (Version 14.0, StataCorp, College Station, TX, USA).

Results

Eligible studies

Based on literature search strategy, a total of 238 potentially relevant articles were identified. Among them, only 16 studies were eligible for the association of *HLA-DR3* allele with the risk of SLE and 11 studies for the association of *HLA-DR15*. A flow diagram of the selection process with detailed reasons for exclusion is shown in Figure 1.

Study characteristics

The characteristics of all eligible studies in this meta-analysis are presented in Table 1. Twenty-three studies including a total of 5261 patients with SLE and 9838 controls were used to evaluate the association of *HLA-DR3* and *HLA-DR15* polymorphisms with the risk of SLE. Among the 23 qualified studies, seven studies included East Asian populations,[17-23] five studies included White populations,[24-28] five studies included mixed populations,[29-33] three studies included Middle Eastern populations,[34-36] and three studies included African populations.[37-39] Ten studies involving SLE patients and controls matched on gender and age. Seven studies recruited controls from hospitals and 17 studies from populations.

After excluding studies, no changes in overall estimates were found which violated the Hardy-Weinberg equilibrium.

Overall analysis

There were 16 and 11 studies with *HLA-DR3* and *HLA-DR15* polymorphisms, respectively. Under random-effects models, overall analysis revealed that *HLA-DR3* and *HLA-DR15* polymorphisms were associated with the significant risk of SLE (*OR*: 1.595, 95% *CI*: 1.316–1.934, *P* = 0.129 and *OR*: 1.678, 95% *CI*: 1.334–2.112, *P* = 0.001, respectively) [Figure 2a and 2b].

Subgroup analysis

To explore potential sources of between-study heterogeneity, we conducted a set of subgroup analyses. In subgroup analysis for *HLA-DR3* polymorphism, we found the following results: 47.32% (*OR*: 1.610, 95% *CI*: 1.320–1.960, *P* = 0.522) in White populations, 17.9% (*OR*: 1.470, 95% *CI*: 0.980–2.210, *P* = 0.626) in matched studies, and 88.37% (*OR*: 1.650, 95% *CI*: 1.370–1.990, *P* = 0.244) in studies involving population-based controls [Figures 3a, 4a and 4c].

For *HLA-DR15* subgroup analyses, we found the following results: 73.98% (*OR*: 1.646, 95% *CI*: 1.248–2.173, *P* = 0.001) in East Asian populations, 51.46% (*OR*: 1.519, 95% *CI*: 1.084–2.130, *P* < 0.050) in matched studies, and 55.46% (*OR*: 1.378, 95% *CI*: 1.078–1.760, *P* = 0.123) in studies involving population-based controls [Figures 3b and 4b, 4d].

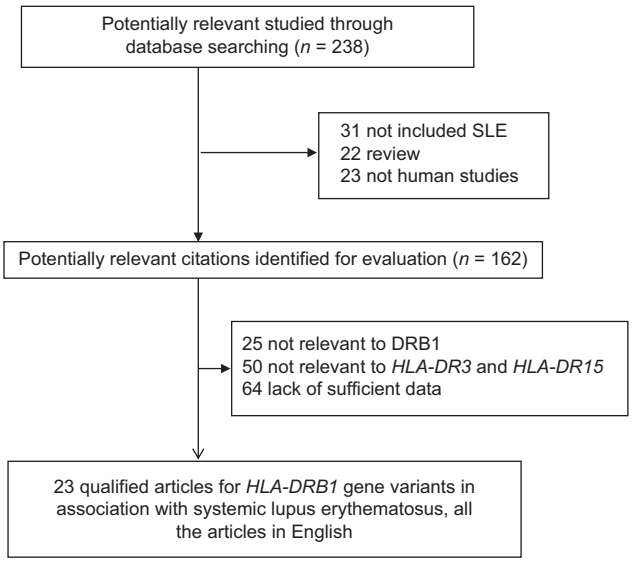

Figure 1: Flow diagram of search strategy and study selection on polymorphisms of *HLA-DRB1* gene with the risk of SLE. SLE: Systemic lupus erythematosus.

Cumulative analysis

The cumulative analysis for *HLA-DR3* and *HLA-DR15* polymorphisms in association with the risk of SLE was conducted, showing stable *OR*s and 95% *CI*s, and none of these studies affected pooled *OR*s and 95% *CI*s [Figure 5a and 5b]. The pooled estimates of the *HLA-DR3* polymorphism remained stable with the accumulation of genetic data over time.

Publication bias

The probability of publication bias was justified by the Begg's funnel plots, which was proved to be relatively symmetric for both *HLA-DR3* and *HLA-DR15*

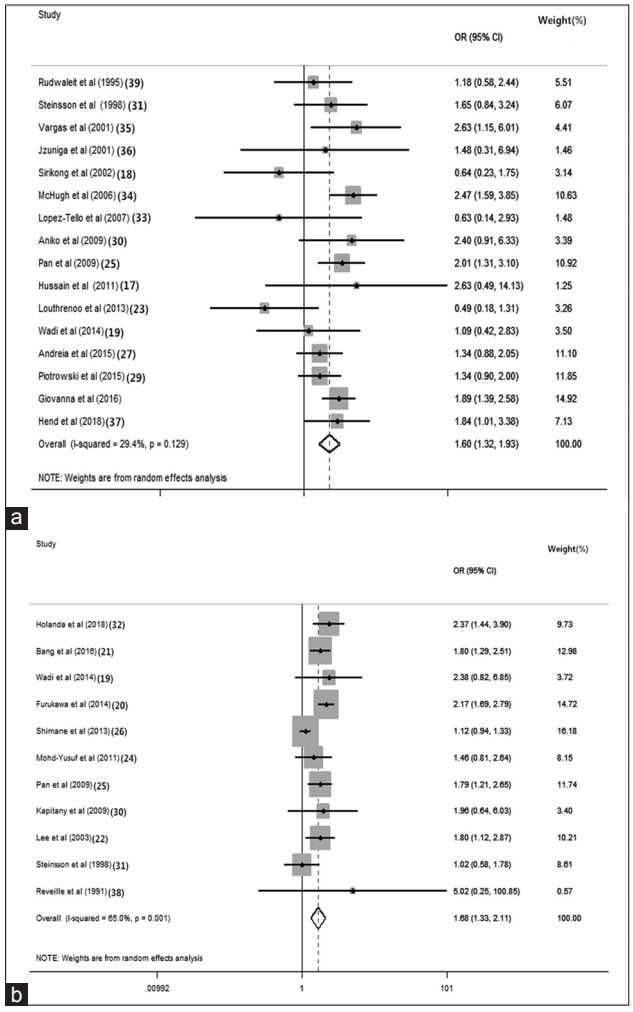

Figure 2: Forest plots for meta-analysis of *HLA-DRB1* gene. (a) Overall analysis association between *HLA-DR3* polymorphisms and the significant risk of SLE. (b) Overall analysis association between *HLA-DR15* polymorphisms and the significant risk of SLE. The *OR*s with 95% *CI* were calculated by the Mantel–Haenszel method. The gray squares represent the studies in relation to their weights. *CI*: Confidence interval; *OR*: Odds ratio; I^2: Higgins test.

Table 1: Characteristicsof 23 studies included in the meta-analysis

Author (year)	Ethnicity	Assessment method	Detection methods	Controlsource
Hend *et al*. (2018)[36]	African	ARC	PCR-SSP	Hospital
Giovanna *et al*. (2016)[27]	White	ARC	PCR-SSP	Population
Piotrowski *et al*. (2015)[28]	White	ARC	PCR-SSP	Population
Andreia *et al*. (2015)[26]	White	ARC	PCR-SSP	Hospital
Louthrenoo *et al*. (2013)[22]	East Asian	ARC	PCR-SSP	Population
Wadi *et al*. (2014)[18]	Middle Eastern	ARC	PCR-SSP	Hospital
Hussain *et al*. (2011)[16]	Middle Eastern	ARC	PCR-SSP	Population
Pan *et al*. (2009)[24]	East Asian	ARC	PCR-SSP	Population
Aniko *et al*. (2009)[29]	White	ARC	PCR-SSP	Population
Lopez-Tello *et al*. (2007)[32]	Mixed	ARC	PCR-SSP	Population
McHugh *et al*. (2006)[33]	Mixed	ARC	PCR-SSP	Population
Sirikong *et al*. (2002)[17]	Middle Eastern	ARC	PCR-SSP	Hospital
Vargas *et al*. (2001)[34]	Mixed	ARC	PCR-SSP	Population
Steinsson *et al*. (1998)[30]	White	ARC	PCR-SSP	Population
Rudwaleit *et al*. (1995)[38]	African	ARC	PCR-SSP	Population
Jzuniga *et al*. (2001)[35]	Mixed	ARC	PCR-SSP	Population
Holanda *et al*. (2018)[31]	Mixed	ARC	PCR-SSP	Hospital
Bang *et al*. (2016)[20]	East Asian	ARC	PCR-SSP	Hospital
Furukawa *et al*. (2014)[19]	East Asian	ARC	PCR-SSP	Hospital
Shimane *et al*. (2013)[25]	East Asian	ARC	PCR-SSP	Population
Mohd-Yusuf *et al*. (2011)[23]	East Asian	ARC	PCR-SSP	Population
Lee *et al*. (2003)[21]	East Asian	ARC	PCR-SSP	Population
Reveille *et al*. (1991)[37]	African-American	ARC	PCR-SSP	Population

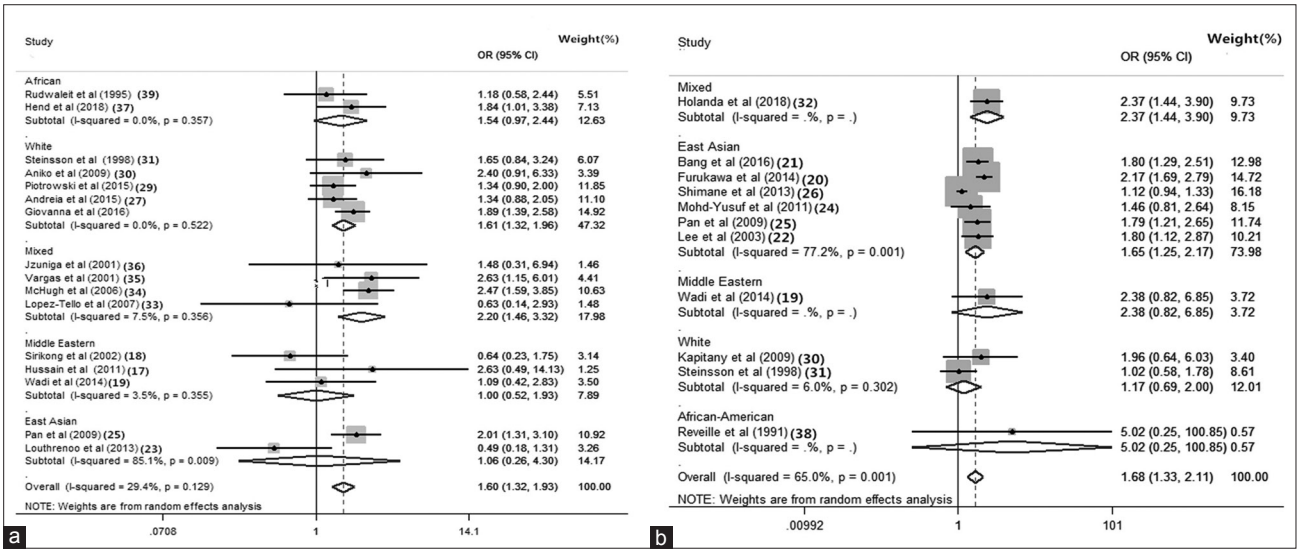

Figure 3: Meta-analysis forest plot of HLA by ethnicity. (a) The association between *HLA-DR3* alleles and the significant risk of SLE with different ethnicity. (b) The association between *HLA-DR15* alleles and the significant risk of SLE with different ethnicity. *CI*: Confidence interval; *OR*: Odds ratio; I^2: Higgins test.

polymorphisms. By contrast, five potentially missing studies were required to make the funnel plot symmetrical [Figure 6a and 6b].

Discussion

It is well recognized that meta-analysis is a powerful tool to summarize results of individual studies, and it can increase statistical power and resolution.[40,41] In this present meta-analysis of published case-control studies, our findings indicated that *HLA-DR3* and *HLA-DR15* polymorphisms are associated with the significant risk of SLE, consistent with the results of most previous studies. The included literature usually does not report in detail to assess the validity and clinical characteristics of the preliminary study. It is best to avoid this in the initial trials. Unfortunately, for many of the biases in the study, such as poor distribution concealment, the precise effects are not known and cannot be corrected. To shed light on this issue, our subgroup analysis demonstrated that the association between *HLA-DR3* polymorphism

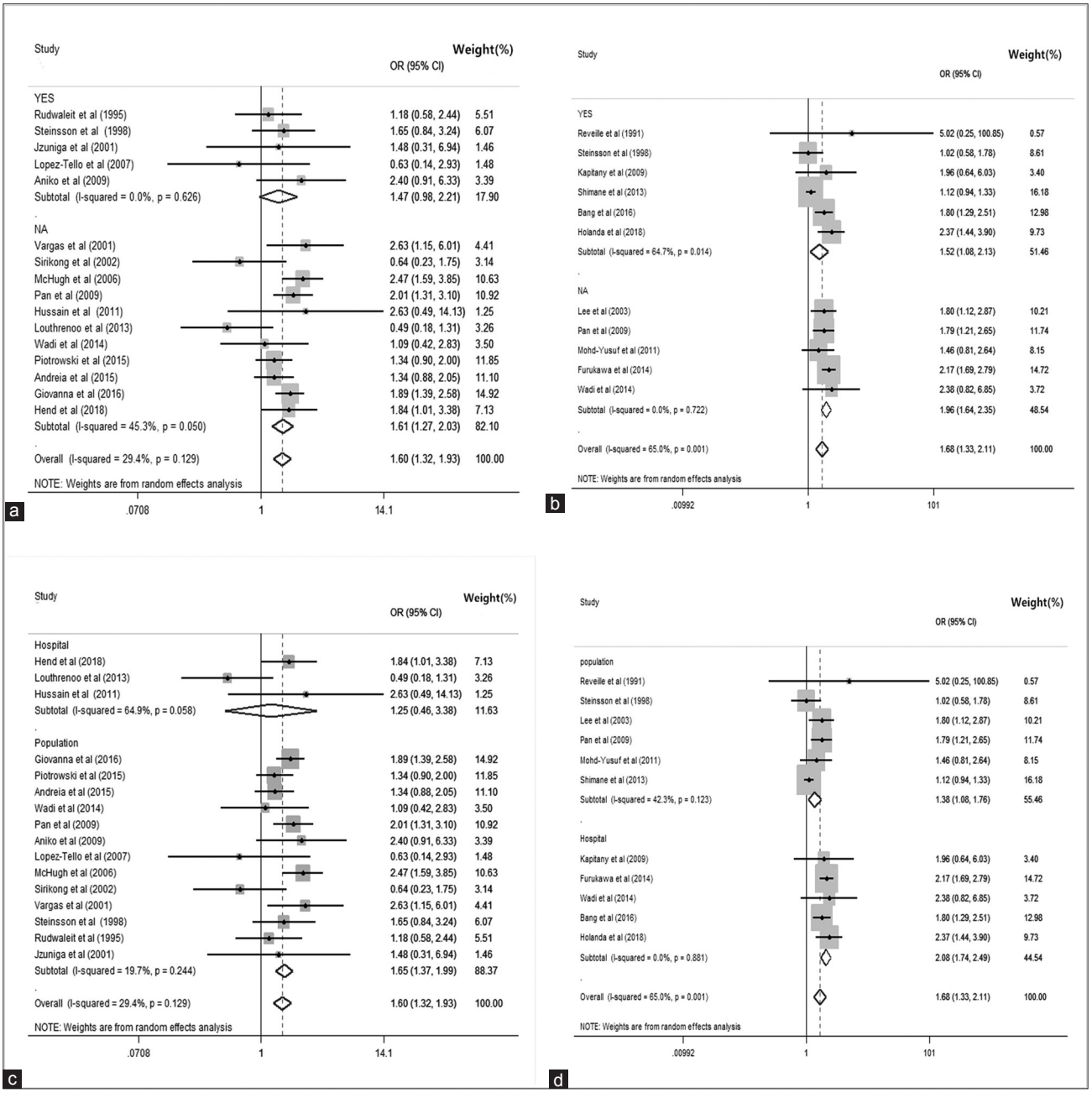

Figure 4: Meta-analysis forest plot of HLA alleles with matching situation and hospital/population-sourced data. (a) Meta-analysis forest plot of *HLA-DR3* alleles with matched or not applicable; (b) meta-analysis forest plot of *HLA-DR15* alleles with matched or NA; (c) meta-analysis forest plot of *HLA-DR3* alleles with hospital/population-sourced data; (d) meta-analysis forest plot of *HLA-DR15* alleles with hospital/population-sourced data. SLE: Systemic lupus erythematosus; *CI*: Confidence interval; *OR*: Odds ratio; I^2: Higgins test; NA: Not applicable.

and SLE was significant in White populations, while the association between *HLA-DR15* polymorphism and SLE was only significant in East Asian populations, indicating strong evidence of genetic heterogeneity across different racial or ethnical groups. A meta-regression model was built to explore other sources of between-study heterogeneity by combining covariates of various research levels. A large part of the heterogeneity for *HLA-DR15* polymorphism under random-effects models was consistent with the results of subgroup analysis of differences in hospital or population (regression coefficient: 0.43; $P = 0.003$). The race source (coefficient: 0.151; $P = 0.051$) and other factors (matched or not applicable [NA]: coefficient: −0.276; $P = 0.091$) contributed no heterogeneous with SLE. As meta-regression analysis involved the limitation of sample size, it may not be fully to detect differences in small or moderate sample. Unfortunately, in this *HLA-DR3* meta-analysis, randomized effector regression analysis showed no significance for these polymorphisms. It is important to remind that meta-regression does not have the methodological rigor of a designed study that is tended to test the effect of these covariates. Sensitivity analysis showed that none of the studies influenced the overall results significantly [Supplementary Figure 1a and 1b]. There are

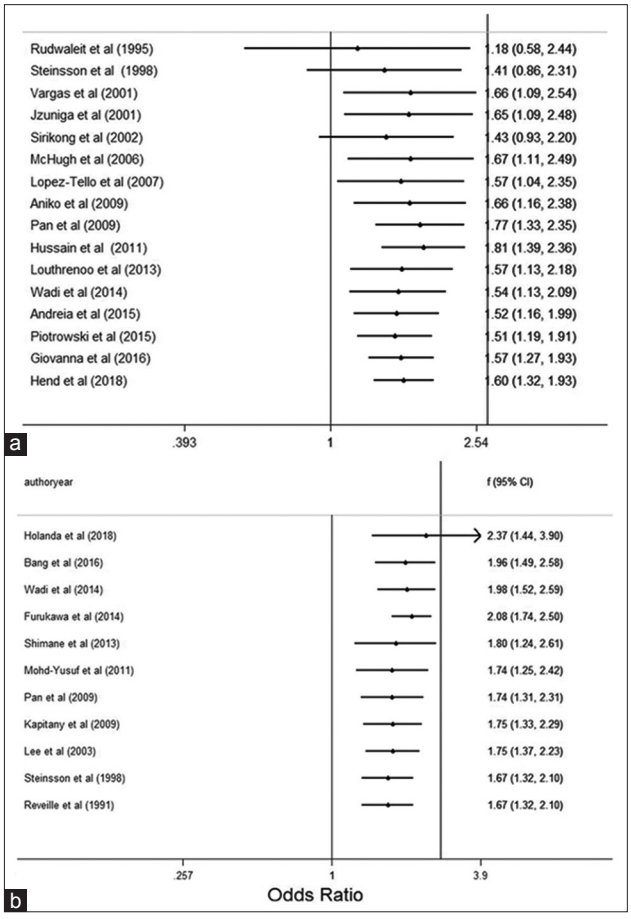

Figure 5: Forest plot for cumulative analysis of HLA. (a) Forest plot for cumulative analysis of *HLA-DR3*; (b) forest plot for cumulative analysis of *HLA-DR15*. HLA: Human lymphocyte antigen.

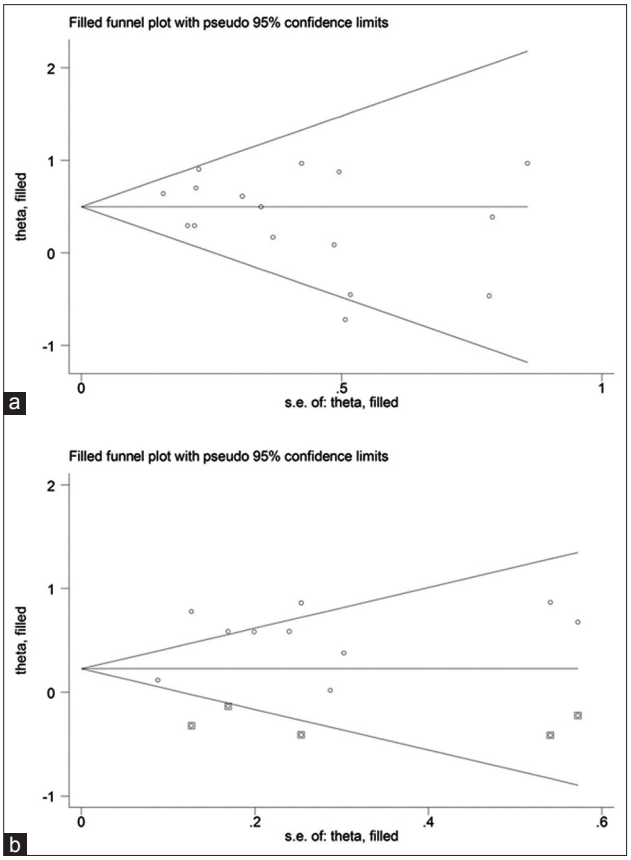

Figure 6: Fill funnel plots and Egger's linear regression test for publication bias. (a) Fill funnel plots for studies investigating the effect of *HLA-DR3*; (b) fill funnel plots for studies investigating the effect of *HLA-DR15*. Each spot represents a separate study. Hollow circles are the actual studies included in this meta-analysis, and solid squares are missing studies required to achieve symmetry.

several causes of heterogeneity: artefactual, methodological, and clinical. It will not always be possible to examine all sources of clinical heterogeneity.

SLE is a complex multistep and multifactorial disease. There is strong evidence for a genetic component in the pathogenesis of SLE.[1,2,4] HLA proteins regulate the immune response of autoreactive T-cells that can help B-cells to recognize the same autoantigen and produce autoantibodies, further resulting in the multisystem organ damage.[1,2] A large panel of case-control studies and meta-analyses have been undertaken and demonstrated that in HLA, genetic variation represents a major susceptibility factor for SLE. However, many previous studies are limited by insufficient sample sizes, which may lead to unstable or fluctuated effect-size estimates. Meta-analysis is deemed as a good method widely used for gathering results from individual studies with the same objectives. We thus performed a comprehensive meta-analysis of all available case-control studies to assess the association of two polymorphisms, *HLA-DR3* and *HLA-DR15* in *HLA-DRB1* gene with the risk of having SLE in the medical literature.

A series of case-control studies and meta-analyses have demonstrated that *HLA-DRB1* is one of the most important susceptibility genes in SLE pathogenesis. For instance, *HLA-DR3*, HLA-DR9, and *HLA-DR15* polymorphisms were identified as significant risk factors for SLE, while HLA-DR4, HLA-DR11, and HLA-DR14 polymorphisms were identified as protective factors for SLE. In the present meta-analysis, integrating 23 studies including 5261 patients and 9838 controls, we found that *HLA-DR3* showed an *OR* of 1.595 ($P < 0.01$) and *HLA-DR15* showed *OR* of 1.678 ($P = 0.001$), indicating the susceptibility of *HLA-DR3* and *HLA-DR15* polymorphisms to SLE.

To explore potential sources of heterogeneity across studies, we conducted a set of subgroup analyses, such as by ethnicity. Ethnic and genetic heterogeneities have been reported leading to the complexity of its clinical presentation.[12] Many meta-analyses demonstrated that ethnicity could affect the association between HLA gene polymorphisms and SLE predisposition. The distribution of HLA risk alleles and haplotypes and the association of HLA with the risk of SLE varied across racial and ethnical groups, and it is of importance to conduct genetic association studies in homogeneous populations.[12,14,15] In this study, for the *HLA-DR3* subgroup analyses, 47.32% (*OR*: 1.611, $P = 0.522$) in White populations, and in the *HLA-DR15*

subgroup analyses, 73.98% (*OR*: 1.646, $P < 0.01$) in East Asian populations, indicating that *HLA-DR3* was a risk factor for the development of SLE in White populations and HLA-DR15 in East Asian populations. This study further revealed that the frequencies of the *HLA-DRB1* polymorphisms in SLE patients differed remarkably across ethnic groups.

Why the frequency of the *HLA-DRB1* polymorphisms in SLE patients may be different across ethnic groups? A recent study showed that *HLA-DR3* could restrict T-cell epitope on SmD79–93 (one of the SmD proteins) to activate T-cells reactive, thereby inducing autoimmune response to lupus-associated antigen SmD in SLE.[42] SmD79–93 and its molecular mimics could induce autoantibodies against SmD in SLE, which have been demonstrated mainly in lupus patients of North America.[43] This might explain why the association between *HLA-DR3* and SLE patients was significant in White populations in this present meta-analysis. Moreover, the significant association between HLA-DR15 and SLE in East Asian populations indicated that there may be similar mechanism for HLA-DR15 regulating T-cell immune response in SLE of East Asian populations, which is worth for further investigations.

Some limitations need to be acknowledged in this meta-analysis. First, a wide range of articles to identify the role of *HLA-DR3* and *HLA-DR15* gene polymorphisms in SLE development were included in our study, and some specific differences existed within these articles that may lead to a potential source of bias. Second, all available articles in this study were published data; there may be some relevant articles with insufficient raw data or some unpublished studies with negative results which were not identified in our meta-analysis. Although no hints of publication bias were noticed in this meta-analysis, publication bias cannot be excluded absolutely. Third, although control groups of selected articles in our meta-analysis were mainly healthy, some specific genetic effects may exit. Moreover, it could not be entirely ruled out that whether these genetic effects will influence SLE incidence in the future. Fourth, although significant heterogeneity of *HLA-DR3* and *HLA-DR15* polymorphisms in different population was demonstrated in this meta-analysis, several other reasons may account for the heterogeneity, such as endocrine immunologic and environmental factors. Thus, more functional studies or meta-analyses should be performed to figure out this question in the future. Fifth, based on our analyses of ethnicity, matched status, and source of control groups, the association of *HLA-DR3* and *HLA-DR15* polymorphisms with lupus nephritis or other complications was not included.

In summary, our findings indicate that *HLA-DR3* and *HLA-DR15* polymorphisms are significantly associated with the risk of SLE. Based on ethnicity analysis, we further found that the association between *HLA-DR3* and SLE was significant in White populations, while the association between *HLA-DR15* and SLE was significant in East Asian populations. Our results enrich the repertoire of HLA genes that have potential roles in the pathogenesis of SLE, and we agree that more biological studies are needed to further confirm these associations and explain different association of different population.

Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

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Conflicts of interest

There are no conflicts of interest.

References

1. Han EC. Systemic lupus erythematosus. N Engl J Med 2012;366:573-4. doi: 10.1056/NEJMc1115196.
2. Rapoport M, Bloch O. Systemic lupus erythematosus. N Engl J Med 2012;366:574. doi: 10.1056/NEJMc1115196.
3. Block SR, Winfield JB, Lockshin MD, D'Angelo WA, Christian CL. Studies of twins with systemic lupus erythematosus. A review of the literature and presentation of 12 additional sets. Am J Med 1975;59:533-52. doi: 10.1016/0002-9343(75)90277-6.
4. Bentham J, Morris DL, Graham DS, Pinder CL, Tombleson P, Behrens TW, *et al.* Genetic association analyses implicate aberrant regulation of innate and adaptive immunity genes in the pathogenesis of systemic lupus erythematosus. Nat Genet 2015;47:1457-64. doi: 10.1038/ng.3434.
5. Gateva V, Sandling JK, Hom G, Taylor KE, Chung SA, Sun X, *et al.* A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. Nat Genet 2009;41:1228-33. doi: 10.1038/ng.468.
6. Han JW, Zheng HF, Cui Y, Sun LD, Ye DQ, Hu Z, *et al.* Genome-wide association study in a Chinese Han population identifies nine new susceptibility loci for systemic lupus erythematosus. Nat Genet 2009;41:1234-7. doi: 10.1038/ng.472.
7. International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), Harley JB, Alarcón-Riquelme ME, Criswell LA, Jacob CO, Kimberly RP, *et al.* Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat Genet 2008;40:204-10. doi: 10.1038/ng.81.
8. Ito I, Kawasaki A, Ito S, Hayashi T, Goto D, Matsumoto I, *et al.* Replication of the association between the C8orf13-BLK region and systemic lupus erythematosus in a Japanese population. Arthritis Rheum 2009;60:553-8. doi: 10.1002/art.24246.
9. Morris DL, Sheng Y, Zhang Y, Wang YF, Zhu Z, Tombleson P, *et al.* Genome-wide association meta-analysis in Chinese and European individuals identifies ten new loci associated with systemic lupus erythematosus. Nat Genet 2016;48:940-6. doi: 10.1038/ng.3603.
10. Ghodke-Puranik Y, Niewold TB. Immunogenetics of systemic lupus erythematosus: A comprehensive review. J Autoimmun 2015;64:125-36. doi: 10.1016/j.jaut.2015.08.004.
11. Sestak AL, Fürnrohr BG, Harley JB, Merrill JT, Namjou B. The genetics of systemic lupus erythematosus and implications for targeted therapy. Ann Rheum Dis 2011;70 Suppl 1:i37-43. doi: 10.1136/ard.2010.138057.
12. Wong M, Tsao BP. Current topics in human SLE genetics. Springer Semin Immunopathol 2006;28:97-107. doi: 10.1007/s00281-006-0031-6.

13. Castaño-Rodríguez N, Diaz-Gallo LM, Pineda-Tamayo R, Rojas-Villarraga A, Anaya JM. Meta-analysis of HLA-DRB1 and HLA-DQB1 polymorphisms in Latin American patients with systemic lupus erythematosus. Autoimmun Rev 2008;7:322-30. doi: 10.1016/j.autrev.2007.12.002.
14. Smikle M, Christian N, DeCeulaer K, Barton E, Roye-Green K, Dowe G, *et al.* HLA-DRB alleles and systemic lupus erythematosus in Jamaicans. South Med J 2002;95:717-9. doi: 10.1097/00007611-200295070-00011.
15. Gerbase-Delima M, Pinto LC, Grumach A, Carneiro-Sampaio MM. HLA antigens and haplotypes in IgA-deficient Brazilian paediatric patients. Eur J Immunogenet 1998;25:281-5. doi: 10.1111/j.1399-0039.1988.tb01659.x.
16. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. BMJ 2009;339:b2535. doi: 10.1136/bmj.b2535.
17. Hussain N, Jaffery G, Sabri AN, Hasnain S. HLA association in SLE patients from Lahore-Pakistan. Bosn J Basic Med Sci 2011;11:20-6. doi: 10.17305/bjbms.2011.2618.
18. Sirikong M, Tsuchiya N, Chandanayingyong D, Bejrachandra S, Suthipinittharm P, Luangtrakool K, *et al.* Association of HLA-DRB1*1502-DQB1*0501 haplotype with susceptibility to systemic lupus erythematosus in Thais. Tissue Antigens 2002;59:113-7. doi: 10.1034/j.1399-0039.2002.590206.x.
19. Wadi W, Elhefny NE, Mahgoub EH, Almogren A, Hamam KD, Al-Hamed HA, *et al.* Relation between HLA typing and clinical presentations in systemic lupus erythematosus patients in Al-Qassim region, Saudi Arabia. Int J Health Sci (Qassim) 2014;8:159-65. doi: 10.12816/0006082.
20. Furukawa H, Kawasaki A, Oka S, Ito I, Shimada K, Sugii S, *et al.* Human leukocyte antigens and systemic lupus erythematosus: A protective role for the HLA-DR6 alleles DRB1*13:02 and *14:03. PLoS One 2014;9:e87792. doi: 10.1371/journal.pone.0087792.
21. Kim K, Bang SY, Yoo DH, Cho SK, Choi CB, Sung YK, *et al.* Imputing variants in HLA-DR beta genes reveals that HLA-DRB1 is solely associated with rheumatoid arthritis and systemic lupus erythematosus. PLoS One 2016;11:e0150283. doi: 10.1371/journal.pone.0150283.
22. Lee HS, Chung YH, Kim TG, Kim TH, Jun JB, Jung S, *et al.* Independent association of HLA-DR and FCgamma receptor polymorphisms in Korean patients with systemic lupus erythematosus. Rheumatology (Oxford) 2003;42:1501-7. doi: 10.1093/rheumatology/keg404.
23. Louthrenoo W, Kasitanon N, Wichainun R, Wangkaew S, Sukitawut W, Ohnogi Y, *et al.* The genetic contribution of HLA-DRB5*01:01 to systemic lupus erythematosus in Thailand. Int J Immunogenet 2013;40:126-30. doi: 10.1111/j.1744-313X.2012.01145.x.
24. Mohd-Yusuf Y, Phipps ME, Chow SK, Yeap SS. HLA-A*11 and novel associations in Malays and Chinese with systemic lupus erythematosus. Immunol Lett 2011;139:68-72. doi: 10.1016/j.imlet.2011.05.001.
25. Pan CF, Wu CJ, Chen HH, Dang CW, Chang FM, Liu HF, *et al.* Molecular analysis of HLA-DRB1 allelic associations with systemic lupus erythematous and lupus nephritis in Taiwan. Lupus 2009;18:698-704. doi: 10.1177/0961203308101955.
26. Shimane K, Kochi Y, Suzuki A, Okada Y, Ishii T, Horita T, *et al.* An association analysis of HLA-DRB1 with systemic lupus erythematosus and rheumatoid arthritis in a Japanese population: Effects of *09:01 allele on disease phenotypes. Rheumatology (Oxford) 2013;52:1172-82. doi: 10.1093/rheumatology/kes427.
27. Bettencourt A, Carvalho C, Leal B, Brás S, Lopes D, Martins da Silva A, *et al.* The protective role of HLA-DRB1(*) 13 in autoimmune diseases. J Immunol Res 2015;2015:948723. doi: 10.1155/2015/948723.
28. Cruz GI, Shao X, Quach H, Ho KA, Sterba K, Noble JA, *et al.* A child's HLA-DRB1 genotype increases maternal risk of systemic lupus erythematosus. J Autoimmun 2016;74:201-7. doi: 10.1016/j.jaut.2016.06.017.
29. Piotrowski P, Wudarski M, Sowińska A, Olesińska M, Jagodziński PP. TNF-308 G/A polymorphism and risk of systemic lupus erythematosus in the Polish population. Mod Rheumatol 2015;25:719-23. doi: 10.3109/14397595.2015.1008778.
30. Kapitany A, Tarr T, Gyetvai A, Szodoray P, Tumpek J, Poor G, *et al.* Human leukocyte antigen-DRB1 and -DQB1 genotyping in lupus patients with and without antiphospholipid syndrome. Ann N Y Acad Sci 2009;1173:545-51. doi: 10.1111/j.1749-6632.2009.04642.x.
31. Steinsson K, Jónsdóttir S, Arason GJ, Kristjánsdóttir H, Fossdal R, Skaftadóttir I, *et al.* A study of the association of HLA DR, DQ, and complement C4 alleles with systemic lupus erythematosus in Iceland. Ann Rheum Dis 1998;57:503-5. doi: 10.1136/ard.57.8.503.
32. de Holanda MI, Klumb E, Imada A, Lima LA, Alcântara I, Gregório F, *et al.* The prevalence of HLA alleles in a lupus nephritis population. Transpl Immunol 2018;47:37-43. doi: 10.1016/j.trim.2018.02.001.
33. López-Tello A, Rodríguez-Carreón AA, Jurado F, Yamamoto-Furusho JK, Castillo-Vázquez M, Chávez-Muñoz C, *et al.* Association of HLA-DRB1*16 with chronic discoid lupus erythematosus in MEXICAN mestizo patients. Clin Exp Dermatol 2007;32:435-8. doi: 10.1111/j.1365-2230.2007.02391.x.
34. McHugh NJ, Owen P, Cox B, Dunphy J, Welsh K. MHC class II, tumour necrosis factor alpha, and lymphotoxin alpha gene haplotype associations with serological subsets of systemic lupus erythematosus. Ann Rheum Dis 2006;65:488-94. doi: 10.1136/ard.2005.039842.
35. Vargas-Alarcón G, Salgado N, Granados J, Gómez-Casado E, Martinez-Laso J, Alcocer-Varela J, *et al*. Class II allele and haplotype frequencies in Mexican systemic lupus erythematosus patients: The relevance of considering homologous chromosomes in determining susceptibility. Hum Immunol 2001;62:814-20. doi: 10.1016/s0198-8859(01)00267-1.
36. Zúñiga J, Vargas-Alarcón G, Hernández-Pacheco G, Portal-Celhay C, Yamamoto-Furusho JK, Granados J. Tumor necrosis factor-alpha promoter polymorphisms in Mexican patients with systemic lupus erythematosus (SLE). Genes Immun 2001;2:363-6. doi: 10.1038/sj.gene.6363793.
37. Hachicha H, Kammoun A, Mahfoudh N, Marzouk S, Feki S, Fakhfakh R, *et al.* Human leukocyte antigens-DRB1*03 is associated with systemic lupus erythematosus and anti-SSB production in South Tunisia. Int J Health Sci (Qassim) 2018;12:21-7. doi: 10.1016/s0198-8859(01)00267-1.
38. Reveille JD, Barger BO, Hodge TW. HLA-DR2-DRB1 allele frequencies in DR2-positive black Americans with and without systemic lupus erythematosus. Tissue Antigens 1991;38:178-80. doi: 10.1111/j.1399-0039.1991.tb01892.x.
39. Rudwaleit M, Tikly M, Gibson K, Pile K, Wordsworth P. HLA class II antigens associated with systemic lupus erythematosus in black South Africans. Ann Rheum Dis 1995;54:678-80. doi: 10.1136/ard.54.8.678.
40. Wang JY, Tian GH, Li YP, Wu TX, Bian ZX, Du L, *et al.* Systematic reviews/meta-analyses of integrative medicine in Chinese need regulation and monitoring urgently and some suggestions for its solutions. Chin J Integr Med 2018;24:83-6. doi: 10.1007/s11655-017-2427-7.
41. Uman LS. Systematic reviews and meta-analyses. J Can Acad Child Adolesc Psychiatry 2011;20:57-9. doi: 10.1016/b978-0-12-415794-1.00013-6.
42. Deshmukh US, Sim DL, Dai C, Kannapell CJ, Gaskin F, Rajagopalan G, *et al.* HLA-DR3 restricted T cell epitope mimicry in induction of autoimmune response to lupus-associated antigen Smd. J Autoimmun 2011;37:254-62. doi: 10.1016/j.jaut.2011.07.002.
43. Migliorini P, Baldini C, Rocchi V, Bombardieri S. Anti-Sm and anti-RNP antibodies. Autoimmunity 2005;38:47-54. doi: 10.1080/08916930400022715.

系统性红斑狼疮*HLA-DR3*和*HLA-DR15*基因多态性Meta分析

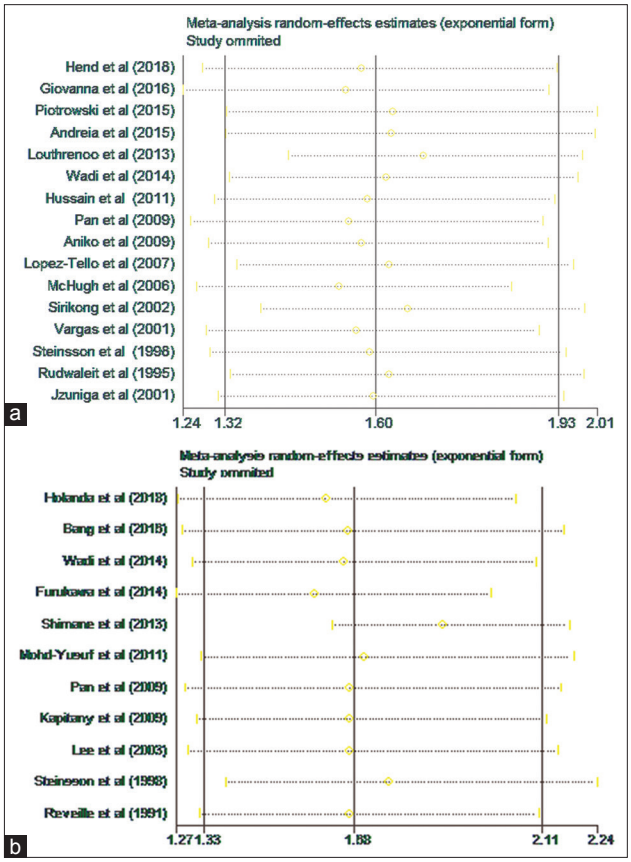
摘要

背景：系统性红斑狼疮是一种遗传性自身免疫疾病，研究发现其发病与*HLA-DRB1*基因遗传多态性相关。本研究旨在通过荟萃分析评估*HLA-DRB1*基因的两个基因多态性（*HLA-DR3*和*HLA-DR15*）与SLE风险之间的关系。

方法：本研究符合PRISMA声明。从PubMed，Elsevier Science，Springer Link，Medline和Cochrane图书馆数据库中搜索了截至2018年6月对*HLA-DRB1*和SLE的病例对照研究。通过STATA14.0软件建立随机效应模型进行分析。

结果：本文共纳入23篇文献进行分析，包括5261例和9838例对照。总体分析显示，*HLA-DR3*和*HLA-DR15*多态性与SLE的显着风险相关（优势比[*OR*]：1.595,95％置信区间（*CI*）：1.316-1.934，*P* <0.01和OR：1.678,95 ％*CI*：1.334-2.112，分别为*P* <0.001）。亚组分析表明， *HLA-DR3*和*HLA-DR15*多态性，种族是异质性的可能来源。具体而言，*HLA-DR3*多态性与白人群体中的SLE显著相关（*OR*：1.60,95％*CI*：1.29-1.99，*P* <0.01），以及东亚人群中的*HLA-DR15*多态性（*OR*：1.646,95％*CI*：1.248-2.173，*P*<0.01）。此外，患者来源是*HLA-DR3*和*HLA-DR15*异质性的另一个可能来源，社区来源的人群分析研究中可发现*HLA-DR3*异质性有统计学意义（*OR*：1.65,95％*CI*：1.37-1.99，*P*<0.01）。在*HLA-DR15*社区/医院人群来源分析中，同样具有统计学意义（*OR*：1.378,95％*CI*：1.078-1.760，*P* <0.01和*OR*：2.08,95％*CI*：1.738-2.49，*P* <0.01）。

结论： *HLA-DRB1*基因可能是SLE易感基因，具有种族异质性。



Supplementary Figure 1: Sensitivity analysis of *HLA*. (a) Sensitivity analysis of *HLA-DR3*; (b) sensitivity analysis of *HLA-DR15*.