Association of HLA-DRB1 Gene Polymorphism with Risk of Asthma: A Meta-Analysis

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Background: The relationship between HLA-DRB1 alleles and asthma is controversial. The purpose of this study was to evaluate the relationship between HLA-DRB1 alleles and risk of asthma.

Material/Methods: We searched PubMed, Chinese National Knowledge Infrastructure (CNKI), Wan Fang (Chinese) database, and Chinese Biomedical Medical databases (CBM) to find studies on the relationship between HLA-DRB1 alleles and risk of asthma. We calculated the pooled odds ratio (OR) and 95% confidence interval (CI) using STATA 12.0. Finally, a total of 24 studies were included in this meta-analysis.

Results: The results revealed that DRB1*03 was positively associated with risk of asthma (OR=1.51, 95%CI=1.27–1.80), and DRB1*15 was negatively associated with risk of asthma (OR=0.63, 95%CI=0.42–0.93), but no association was found in other HLA-DRB1 alleles. Subgroup analysis by age revealed that DRB1*03, DRB1*04, DRB1*09, and DRB1*15 were associated with asthma in children. Subgroup analysis by ethnicity showed that DRB1*03 and DRB1*15 were associated with asthma in whites, and DRB1*07 and DRB1*14 were associated with asthma in Asians.

Conclusions: This results of this meta-analysis suggest that HLA-DRB1 alleles are associated with asthma.

MeSH Keywords: Anti-Asthmatic Agents • HLA Antigens • Meta-Analysis • Polymorphism, Single Nucleotide

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Background

Asthma is characterized by recurrent episodes of airway obstruction, which reverse either spontaneously or after use of medication, and is usually associated with bronchial hyper-responsiveness and evidence of chronic airway inflammation [1]. There are more than 300 million people suffering from asthma worldwide, and it occurs in all countries regardless of the level of development [2]. Asthma prevalence increased from 7.3% in 2001 to 8.4% in 2010, when 25.7 million persons had asthma in the United States [3]. Asthma can increase mortality and morbidity, and is an important public health challenge [4]. Therefore, prevention and control of asthma have great significance.

Asthma is a multifactor disease caused by interactions between genetic and environmental factors. Genetic studies have attracted much attention with the development of genome-wide association studies and genome-wide linkage studies. For example, IREB2 gene rs2568494 polymorphism has been shown to be associated with susceptibility to chronic obstructive pulmonary disease [5]. IL13 gene polymorphisms contribute to the development of pediatric asthma [6]. The human leukocyte antigen (HLA) super-locus is a genomic region in chromosome position 6p21 that encodes the 6 classical transplantation HLA genes and at least 132 protein-coding genes that have important roles in the regulation of the immune system, as well as some other fundamental molecular and cellular processes [7]. The HLA region associated with asthma is the DR loci [8]. Cho et al. [9] found that HLA-DRB1*07 AND HLA-DRB1*04 were associated with asthma in Korean adults. Lama et al. suggested a significantly higher frequency of HLA-DRB1*03 in asthmatics than in controls among the Indian pediatric population [10]. Kauppinen et al. [11] showed that HLA-DRB1*0101, HLA-DRB1*0301 and HLA-DRB1*0404 were associated with asthma in people with allergic asthma in Finland [11]. However, some other studies have found no statistically significant associations between HLA-DRB1 alleles and asthma [12,13].

In view of several contradictory conclusions based on small sample size studies, we performed the current meta-analysis to determine if there is an association between HLA-DRB1 alleles and asthma.

Material and Methods

Literature search

PubMed, Chinese National Knowledge Infrastructure (CNKI), Wan Fang (Chinese) databases, and Chinese Biomedical Medical databases (CBM) were searched using the search terms: ‘asthma’ or ‘asthmatic’, ‘human leukocyte antigen’ or ‘HLA’, and ‘polymorphism’ or ‘mutation’ or ‘variant’ or ‘allele’. The date of the last search was December 10, 2015.

Figure 1. Flow chart of this meta-analysis.
Inclusion and exclusion criteria

Inclusion criteria were: cohort study or case-control; enough data available; and English or Chinese language.

Data extraction

Two reviewers (Yingshui Yao and Jie Li) selected all potential studies separately. If there was disagreement, the reviewers would solve it by discussion or judgement by a third reviewer (Lijun Zhu). The following data were extracted: first author, year of publication, country, ethnicity, age (children or not), number of HLA-DRB1 alleles studied, detection methods, and numbers of cases and controls.

Statistical analysis

The pooled OR with 95% CI was analyzed using the Z test to assess the strength of the associations between HLA-DRB1 alleles and asthma. Heterogeneity assumption was evaluated by the $\chi^2$-based Q-test and $I^2$ test [14]. If $P>0.10$ (Q-test) or $I^2<50\%$, the fixed-effects model (the Mantel-Haenszel method) was used [15]. Otherwise, the random-effects model (the DerSimonian and Laird method) was used [16]. The Begg’s rank correlation method and the Egger’s linear regression method were used to assess potential publication bias [17,18]. The meta-analysis was carried out using STATA version 12.0 (Stata Corp, College Station, TX) software. $P<0.05$ meant there was statistically significant. All $P$ values are 2-tailed.

| First author | Year | Country (ethnicity) | Children or not | No. of DRB1 alleles studied | Detection methods | No. of cases | No. of controls |
|--------------|------|---------------------|----------------|-----------------------------|------------------|--------------|----------------|
| Bignon JS    | 1994 | Italy (whites)      | Not            | 2                           | PCR-SSP          | 56           | 32             |
| Soriano JB   | 1997 | Spain (whites)      | Not            | 11                          | PCR-SSP          | 145          | 168            |
| Cho SH       | 2000 | Korea (Asians)      | Not            | 11                          | PCR-SSP          | 91           | 98             |
| Horne C      | 2000 | Canada (whites)     | Not            | 6                           | PCR-SSP          | 56           | 63             |
| Mapp CE      | 2000 | Italy (whites)      | Not            | 2                           | PCR-SSP          | 67           | 128            |
| Wang CG      | 2000 | China (Asians)      | Not            | 3                           | PCR-SSP          | 64           | 104            |
| Li L         | 2003 | China (Asians)      | Children       | 9                           | PCR-SSOP         | 40           | 92             |
| Choi JH      | 2004 | Korea (Asians)      | Not            | 3                           | PCR-SSP          | 149          | 91             |
| Li CP        | 2005 | China (Asians)      | Not            | 3                           | PCR-SSP          | 60           | 30             |
| Lu JR        | 2006 | China (Asians)      | Children       | 11                          | PCR-SSP          | 78           | 82             |
| Juhn YI      | 2007 | USA (whites)        | Children       | 2                           | PCR-SSP          | 81           | 231            |
| Munthe-Kaas MC | 2007 | Norway (whites)    | Children       | 7                           | PCR-SSOP         | 330          | 1260           |
| Wang JW      | 2007 | China (Asians)      | Children       | 12                          | PCR-SSP          | 45           | 45             |
| Movahedi M   | 2008 | Iran (whites)       | Children       | 12                          | PCR-SSP          | 112          | 80             |
| Choi JH      | 2009 | Korea (Asians)      | Not            | 3                           | PCR-SSP          | 84           | 174            |
| Ivković-Jureković I | 2011 | Croatia (whites)   | Children       | 8                           | PCR-SSOP         | 143          | 163            |
| Zhu SF       | 2011 | China (Asians)      | Not            | 2                           | PCR-SSP          | 45           | 46             |
| Chen LP      | 2012 | China (Asians)      | Not            | 1                           | PCR-SSP          | 100          | 100            |
| Kauppinen A  | 2012 | Finland (whites)    | Not            | 6                           | PCR-SSP          | 40           | 151            |
| Dzurilla M   | 2013 | Slovakia (whites)   | Not            | 13                          | PCR-SSP          | 109          | 130            |
| Xie QL       | 2013 | China (Asians)      | No             | 1                           | PCR-SSP          | 84           | 168            |
| Mishra MN    | 2014 | India (whites)      | Children       | 13                          | PCR-SSP          | 103          | 152            |
| Bottero P    | 2014 | Italy (whites)      | Not            | 8                           | PCR-SSP          | 159          | 1808           |
| Lama M       | 2014 | India (whites)      | Children       | 4                           | PCR-SSP          | 105          | 110            |

Table 1. Characteristics of studies included in the meta-analysis.
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Table 2. Meta-analysis of associations between HLA-DRB1 alleles and asthma.

| Alleles | No. of study | Case | Control | Heterogeneity | Test of association | P value for Egger's (Begg's) test |
|---------|--------------|------|---------|---------------|---------------------|----------------------------------|
|         |              |      |         | \( \chi^2 \) | OR (95%CI) | Z | P |
| 01      | 10           | 180/1216 | 306/2336 | 15.31 | 0.083 | 41.2 | F | 1.04 (0.84–1.28) | 0.36 | 0.721 | 0.366 (0.210) |
| 03      | 11           | 276/1389 | 607/4247 | 12.32 | 0.264 | 18.9 | F | 1.51 (1.27–1.80) | 4.61 | 0.000 | 0.728 (1.000) |
| 04      | 14           | 359/1601 | 839/4449 | 40.61 | 0.000 | 68.0 | R | 1.09 (0.82–1.46) | 0.61 | 0.540 | 0.904 (0.913) |
| 07      | 12           | 300/1415 | 774/4108 | 27.32 | 0.004 | 59.7 | R | 1.23 (0.91–1.67) | 1.35 | 0.177 | 0.040 (0.115) |
| 08      | 8            | 86/723  | 98/847  | 7.68  | 0.361 | 8.9  | F | 1.02 (0.74–1.41) | 0.13 | 0.896 | 0.103 (1.000) |
| 09      | 7            | 57/725  | 86/2530 | 3.38  | 0.760 | 0.0 | F | 1.39 (0.93–2.09) | 1.59 | 0.111 | 0.575 (1.000) |
| 10      | 7            | 44/611  | 47/767  | 6.47  | 0.373 | 7.2  | F | 1.23 (0.79–1.91) | 0.92 | 0.358 | 0.569 (0.764) |
| 11      | 11           | 314/1355| 1238/4078| 18.85 | 0.042 | 47.0 | R | 1.18 (0.89–1.56) | 1.16 | 0.245 | 0.732 (0.876) |
| 12      | 10           | 92/987  | 138/2765| 9.12  | 0.426 | 1.3  | F | 1.18 (0.86–1.61) | 1.04 | 0.298 | 0.599 (0.858) |
| 13      | 10           | 242/1277| 766/3996| 12.63 | 0.180 | 28.8 | F | 0.93 (0.77–1.11) | 0.84 | 0.403 | 0.979 (0.474) |
| 14      | 9            | 97/819  | 318/2651| 21.48 | 0.006 | 62.8 | R | 0.93 (0.57–1.54) | 0.28 | 0.783 | 0.410 (0.754) |
| 15      | 6            | 136/808 | 389/1832| 11.91 | 0.036 | 58.0 | R | 0.63 (0.42–0.93) | 2.31 | 0.021 | 0.762 (0.707) |
| 16      | 4            | 42/433  | 63/527  | 0.67  | 0.881 | 0.0 | F | 0.74 (0.49–1.13) | 1.41 | 0.160 | 0.866 (1.000) |
| 0101    | 5            | 60/441  | 100/559 | 16.57 | 0.002 | 75.9 | R | 0.85 (0.39–1.83) | 0.42 | 0.673 | 0.039 (0.027) |
| 0301    | 6            | 55/477  | 85/521  | 8.31  | 0.140 | 39.8 | F | 0.75 (0.51–1.12) | 1.42 | 0.156 | 0.404 (0.452) |
| 0701    | 4            | 51/280  | 92/488  | 2.51  | 0.473 | 0.0 | F | 0.75 (0.50–1.12) | 1.43 | 0.153 | 0.076 (0.308) |
| 0901    | 7            | 112/483 | 129/674 | 35.76 | 0.000 | 83.2 | R | 1.23 (0.50–3.05) | 0.45 | 0.649 | 0.786 (0.764) |
| 1001    | 6            | 20/401  | 36/612  | 5.71  | 0.336 | 12.4 | F | 0.81 (0.46–1.43) | 0.73 | 0.466 | 0.085 (1.000) |
| 1401    | 4            | 20/264  | 18/326  | 1.97  | 0.578 | 0.0 | F | 1.20 (0.60–2.41) | 0.51 | 0.608 | 0.868 (0.734) |

**Results**

**Characteristics of studies**

We finally identified 24 studies, including 2346 cases and 5506 controls [9–12,19–38]. The retrieval process is presented in Figure 1. The characteristics of each study are shown in Table 1. Thirteen studies were conducted in whites and 12 studies were conducted in Asians. Nine studies were conducted in children. We also extracted the number of DRB1 alleles for each study.

**Meta-analysis of HLA-DRB1 alleles and risk of asthma**

We took 19 HLA-DRB1 alleles into consideration, including 13 HLA-DRB1 allele families and 6 HLA-DRB1-specific alleles. The detailed results of the association between HLA-DRB1 alleles and asthma are presented in Table 2.

Among the allele families, significant associations were found in HLA-DRB1*03 and HLA-DRB1*15 alleles (DRB1*03: OR=1.51, 95%CI=1.27–1.80; DRB1*15: OR=0.63, 95%CI=0.42–0.93). HLA-DRB1*03 was significantly increased the risk of asthma and HLA-DRB1*15 was associated with significantly decreased risk of asthma. No evidence of correlations was found in other allele families. Heterogeneity was observed in DRB1*04, DRB1*07, DRB1*11, DRB1*14, and DRB1*15 (P<0.10 or I²<50%). Thus, the random-effect model was used to analyze these alleles. Begg’s and Egger’s tests were carried out to estimate the publication bias, and the results showed that there was no publication bias among any of the allele families (P>0.05). There was no significant difference between asthma and the specific alleles (DRB1*0101, DRB1*0301, DRB1*0701, DRB1*0901, DRB1*1001, DRB1*1401). Among these specific alleles, heterogeneity was observed in DRB1*0101 and DRB1*0301 (P>0.10 or I²<50%). Publication bias was found in DRB1*0101 (P<0.05).

Subgroup analysis by ethnicity and age were carried out among allele families. For ethnicity (categorized as whites and Asians),
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Table 3. Meta-analysis stratified by ethnicity and age.

| Alleles | Ethnicity   | OR (95%CI) | P (%) | Ethnicity | OR (95%CI) | P (%) | Ethnicity | OR (95%CI) | P (%) | Ethnicity | OR (95%CI) | P (%) |
|---------|-------------|------------|-------|-----------|------------|-------|-----------|------------|-------|-----------|------------|-------|
|         | Whites      |            |       | Asians    |            |       | Children  |            |       | Not       |            |       |
| 01      | 42.7        | 1.10 (0.88–1.38) | 0.05 | 40.5 | 0.73 (0.42–1.26) | 0.25 | 52.5 | 1.11 (0.84–1.45) | 0.31 | 31.3       | 0.95 (0.69–1.32) | 0.01 |
| 03      | 24.2        | 1.54 (1.28–1.84) | 0.05 | 20.9 | 1.13 (0.56–2.30) | 0.37 | 27.2 | 1.71 (1.37–2.14) | 0.0  | 12.5       | 0.94 (0.94–1.65) | 0.0  |
| 04      | 50.6        | 1.22 (0.95–1.57) | 0.05 | 80.2 | 0.82 (0.34–1.95) | 0.56 | 53.5 | 1.38 (1.01–1.87) | 0.26 | 77.3       | 0.70 (0.39–1.24) | 0.0  |
| 07      | 12.9        | 1.01 (0.82–1.23) | 0.05 | 63.6 | 2.82 (1.13–7.09) | 0.0  | 0.0  | 1.18 (0.92–1.50) | 0.56 | 82.2       | 1.54 (0.77–3.05) | 0.0  |
| 08      | 0.0         | 1.42 (0.88–2.31) | 0.05 | 40.5 | 0.77 (0.50–1.20) | 0.12 | 30.9 | 0.82 (0.52–1.29) | 0.0  | 0.0        | 1.29 (0.81–2.05) | 0.0  |
| 09      | 0.0         | 0.98 (0.37–2.57) | 0.05 | 17.6 | 1.50 (0.96–2.36) | 0.0  | 0.0  | 1.88 (1.08–3.27) | 0.0  | 0.0        | 0.97 (0.52–1.79) | 0.0  |
| 10      | 0.0         | 0.93 (0.52–1.67) | 0.05 | 0.0  | 1.82 (0.91–3.62) | 0.16 | 17.8 | 1.30 (0.78–2.15) | 0.28 | 25.8       | 1.04 (0.42–2.60) | 0.0  |
| 11      | 63.8        | 1.21 (0.87–1.67) | 0.05 | 0.0  | 1.01 (0.49–2.05) | 0.98 | 38.6 | 1.16 (0.80–1.68) | 0.60 | 66.8       | 1.20 (0.71–2.00) | 0.0  |
| 12      | 22.4        | 1.30 (0.83–2.02) | 0.05 | 0.0  | 1.08 (0.70–1.66) | 0.56 | 37.0 | 1.34 (0.93–1.95) | 0.0  | 0.0        | 0.87 (0.49–1.54) | 0.0  |
| 13      | 23.0        | 0.91 (0.75–1.10) | 0.05 | 54.1 | 1.09 (0.62–1.90) | 0.0  | 0.0  | 0.97 (0.76–1.23) | 0.0  | 60.6       | 0.88 (0.68–1.15) | 0.0  |
| 14      | 0.0         | 1.35 (0.98–1.86) | 0.05 | 52.5 | 0.38 (0.15–0.96) | 0.35 | 48.5 | 0.70 (0.20–2.50) | 0.67 | 71.6       | 0.98 (0.54–1.79) | 0.0  |
| 15      | 34.6        | 0.68 (0.50–0.93) | 0.05 | 83.8 | 0.41 (0.06–2.68) | 0.0  | 56.4 | 0.57 (0.37–0.87) | 0.0  | 1.01       | 0.56 (1.82) | 0.0  |
| 16      | 0.0         | 0.70 (0.44–1.12) | 0.05 |      | 0.94 (0.36–2.45) | 0.0  | 0.0  | 0.71 (0.44–1.15) | 0.0  | 0.84       | 0.36–1.97 | 0.0  |

DRB1*03 significantly increased the risk of asthma and DRB1*15 significantly decreased the risk of asthma in whites. DRB1*07 significantly increased the risk of asthma and DRB1*14 significantly decreased the risk of asthma in Asians. For age (categorized as children or not), DRB1*03, DRB1*04, and DRB1*09 suggested the risk-enhancing role and DRB1*15 suggested a protective role. The detailed information of the subgroup analysis is presented in Table 3.

Discussion

Asthma is a complex heterogeneous respiratory disease. The pathogenesis of asthma involves many different cells. IgE and an imbalance between T helper cell 1 (Th1) and T helper cell 2 (Th2) are thought to play a key role in the pathogenesis of asthma [39–41]. The human major histocompatibility complex (MHC) is localized to chromosome 6p21 and is thought to play a role in regulating inflammation on T helper cells [7,42,43]. For the past 2 decades, many studies have focused on the relationship between HLA-DRB1 alleles and asthma, which may help to disclose the pathogenesis of asthma [44–48]. Use of meta-analysis could resolve the inconsistent results, which have harmful effect on false-positive and false-negative associations [49]. Thus, we performed this meta-analysis to clarify the association between HLA-DRB1 alleles and asthma.

Two alleles (DRB1*03 and DRB1*15) were found have statistically significant associations with risk of asthma among 13 HLA-DRB1 allele families. The results showed that individuals who carry HLA DRB1*03 have a 51% higher risk of asthma compared with those who do not carry this allele. Similar conclusions were reported in other studies. A study by Juhn et al. [28] found that the 12-year cumulative incidence of asthma by age among children who carry HLA DRB1*03 was 33%, compared to 24.2% among those who did not carry this allele. Lama et al. [10] demonstrated a significantly higher frequency of HLA-DRB1*03 in asthmatics than in controls. HLA DRB1 may have an effect on asthma through regulating Th1 vs. Th2 immune response. Murray et al. [43] showed that the interaction between T cell receptor, peptide, and major histocompatibility complex (MHC) can determine Th1/Th2 dominance through a differential T cell receptor affinity and ligand density between different MHC genes. In this study, we also found that DRB1*15 was a protective factor for asthma. A similar protective role of DRB1*15 was reported in other studies [30,37]. Although the precise mechanism of this effect is still unknown, we hypothesis that HLA-DRB1 alleles have different effects on asthma. In addition, we also examined the association between HLA-DRB1 specific alleles and asthma, but no significant difference was found between them. Because of the limited number of studies, we only chose 6 HLA-DRB1-specific alleles in this meta-analysis. These results of specific alleles still require evaluation by further studies.
Considering ethnicity and age, we performed subgroup analysis in HLA-DRB1 allele families. DRB1*03 significantly increased the risk of asthma and DRB1*15 significantly decreased the risk of asthma in whites. DRB1*07 significantly increased the risk of asthma and DRB1*14 significantly decreased the risk of asthma in Asians. For age, DRB1*03, DRB1*04, and DRB1*09 were suggested to affect risk and DRB1*15 was suggested to have a protective role. Publication bias is another factor to consider in meta-analysis. In this meta-analysis, the Begg’s rank correlation method and the Egger’s linear regression method showed that there was no publication bias in any alleles except DRB1*010.

There are some limitations to the present study that should be addressed. First, we only chose some of the HLA-DRB1-specific alleles in this study due to the scarcity of data in the literature. Second, the relationship between the HLA-DRB1 alleles and asthma did not consider confounding factors such as sex, lifestyle factors, and other risk factors. It is best to adjust these factors when conducting the studies. Third, asthma is the result of the interaction of genetic and environmental factors, but we could not extract sufficient data on these factors from the primary publications. Thus, this meta-analysis could not elucidate gene-gene and gene-environment interactions. More studies should be designed to analyze these associations in the future. Results of the present study must be interpreted cautiously in light of its limitations.

Conclusions

Despite these limitations, this meta-analysis suggests that DRB1*03 is positively associated with asthma risk and DRB1*15 is negatively associated with asthma risk. Additional studies on the association between DRB1-specific alleles and asthma are required.

Conflict of interest

The authors declare no conflict of interest.

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