# Association of HLA-B*5701 Genotypes and Abacavir-Induced Hypersensitivity Reaction: A Systematic Review and Meta-Analysis

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**ABSTRACT - OBJECTIVES:** This study aimed to systematically review and quantitatively synthesize the association between HLA-B*5701 and abacavir-induced hypersensitivity reaction (ABC-HSR). **METHODS:** We searched for studies that investigated the association between HLA-B genotype and ABC-HSR and provided information about the frequency of carriers of HLA-B genotypes among cases and controls. We then performed a meta-analysis with a random-effects model to pool the data and to investigate the sources of heterogeneity. **RESULTS:** From 1,026 articles identified, ten studies were included. Five using clinical manifestation as their diagnostic criteria, 409 and 1,883 subjects were included as cases and controls. Overall OR was 23.6 (95% CI = 15.4 – 36.3). Whereas, the another five studies using confirmed immunologic test as their diagnostic criteria, 110 and 1,968 subjects were included as cases and controls, respectively. The association of ABC-HSR was strong in this populations with HLA-B*5701. Overall OR was 1,056.2 (95% CI = 345.0 – 3,233.3). **CONCLUSIONS:** Using meta-analysis technique, the association between HLA-B*5701 and ABC-HSR is strong in the studies using immunologic confirmation to identify ABC-HSR. These results support the US FDA recommendations for screening HLA-B*5701 allele before initiating abacavir therapy.



## INTRODUCTION

Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI) commonly co-prescribed with other antiretroviral agents in the treatment of HIV infection (1). However, abacavir-induced hypersensitivity reaction (ABC-HSR) is a major problem in abacavir pharmacotherapy (2). Approximately 5-8% of patients initiating abacavir treatment can develop HSR within the first 4-6 weeks (3-5). Symptoms of ABC-HSR are a multi-organ syndrome characterized by two or more clinical signs: fever, rash, gastrointestinal symptoms and respiratory symptoms (5).

HLA-B*5701, a specific human leukocyte antigen (HLA) allele, has been shown to represent the strongest predictor of ABC-HSR (4,6). HLAs are a set of genes that encode major histocompatibility complex (MHC), a group of proteins that have potential roles in the immune system (7,8). Abacavir binds specifically to the HLA-B*5701 protein at its 'F-pocket'. This binding results in the formation of a protein complex recognized as a foreign body, which triggers an autoimmune activation by CD8+T-cells. The outcome of this autoimmune activation is ABC-HSR (9-11).

The association between HLA-B*5701 and ABC-HSR was extensively studied in several epidemiological studies (3,12-15). In 2008, the US Food and Drug Administration recommended a HLA-B*5701 screening test for all patients prior to starting abacavir (5). However, among the published studies, the reported odds ratios showed extreme variation, from 0 to ~7,000 (4,14-17). Such variation might be due to the differences between study populations, methods used to diagnose ABC-HSR, and many other factors.

The present study aimed to use a systematic review and meta-analysis approach to elucidate

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the multiple factors which affect the extent of association between HLA-B*5701 genotype and ABC-HSR.

## METHODS

### Search Strategy and Study Selection

We performed a systematic search in 6 databases [PubMed, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), International Pharmaceutical Abstracts (IPA), Human Genome Epidemiology Network (HuGENet), and Cochrane library] from their inception until September of 2014 using keywords and relevant terms for "HLA-B*5701 genotypes", "abacavir-induced", and "hypersensitivity". There was no restriction on language or study design. We included reports in which (i) the association between the HLA-B*5701 genotype and ABC-HSR was investigated; (ii) all patients in both case and control group had received abacavir; (iii) the use of abacavir was irrelevant to HLA-B*5701 screening, and; (iv) sufficient data for calculating frequency of carriers of the HLA-B*5701 among both cases and controls were reported. Our procedure in the systematic review and meta-analysis is shown in Figure1. If two or more studies shared the same patient population, the study with more complete data or a larger sample size was included. For the studies which met the inclusion criteria but did not provide sufficient data for meta-analysis, the corresponding authors were asked to provide additional information. Studies were also retrieved from the references listed in the selected articles.

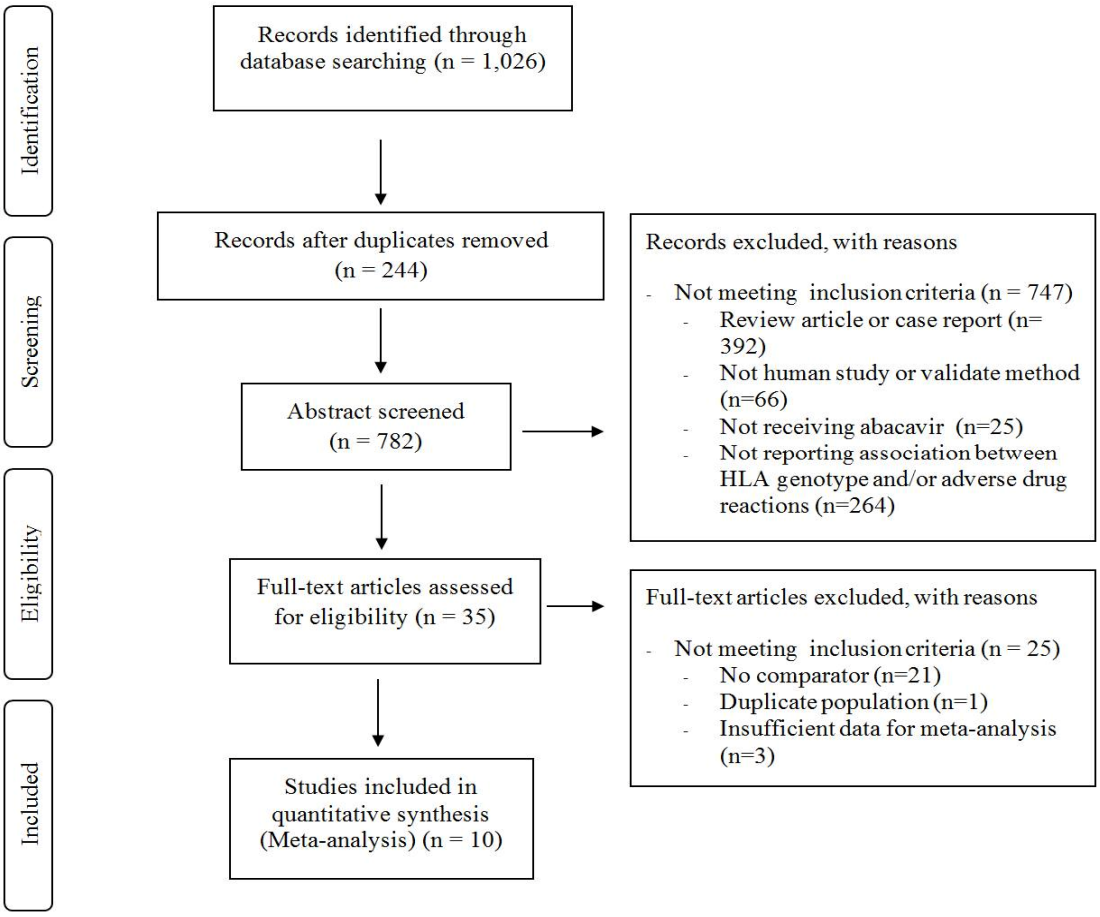


**Figure 1** - Flow diagram of study selection process

### Data Extraction and Quality Assessment

The relevant information from the selected articles was independently extracted as follows: study design, eligibility criteria, definition and diagnostic criteria for the cases and controls, patient demographics, dose and duration of abacavir exposure, method used to diagnose a ABC-HSR (i.e., clinical evaluation with or without confirmatory immunological testing), and the HLA genotyping technique. Genotype

frequencies of HLA-B*5701 were calculated to determine whether the included populations were in Hardy-Weinberg equilibrium (HWE) (18,19). HWE implies that the included individuals are likely to be representative of the population (20,21). The Newcastle-Ottawa scale (NOS) comprising three domains including selection, comparability, and outcome or exposure was used to assess the quality of the included studies (22).

Two reviewers (WT and OL) independently selected the articles, extracted the data, and performed the study quality assessment. Any disagreement was discussed until consensus was reached between both reviewers.

## DATA ANALYSIS

In a routine clinical setting, ABC-HSR is diagnosed by a clinical evaluation with or without immunologic confirmation (skin patch test). However, the diagnostic accuracy of both methods was clearly different. Since the sensitivity of immunologic confirmation was much higher than that of clinical evaluation (0.98 vs. 0.40) the diagnosis when using immunologic confirmation would be more reliable (23). Thus, we performed separate analyses of data sets obtained from the different diagnostic methods. The overall ORs with corresponding 95% confidence intervals (95% CIs) were calculated to determine the association between the presence of at least one HLA-B*5701 and an ABC-HSR. All analyses were performed using the DerSimonian and Laird method under a random-effects model (24). Statistical heterogeneity was assessed using Q-statistic and I-squared tests (25). A p-value of $\leq$ 0.10 indicated heterogeneity between studies. I-squared values of 25%, 50%, 75% denoted a low, moderate, and high of heterogeneity across studies, respectively (26). Subgroup analyses based on ethnicity of the selected studies were performed to explore the sources of heterogeneity. A funnel plot, Begg's test, and Egger's test were used to evaluate publication bias (27,28). All statistical analyses were performed using the STATA software version 11.0 (StataCorp., College Station, TX, USA).

## RESULTS

### Study Selection

Of the 1,026 articles identified, 14 articles met the inclusion criteria (3,4,6,12-17,29-33). The studies of Mallal et.al. (31) and Martin et al. (6) contained the same data, consequently, the former was excluded. Three studies included Hughes et.al. (29), Rauch et.al. (32) and Colombo et.al. (33) did not provide enough information to perform statistical analysis, thus these studies were excluded. Hence ten studies were included in further meta-analysis (3,4,6,12-17,30) (Figure. 1). No additional articles were identified in the bibliographies of the included studies.

### Study Characteristics

Characteristics of the included studies are summarized in Table 1. All studies were case-control studies (3,4,6,12-17,30). Five studies (3,12,14,16,30) used clinical manifestation alone as their diagnostic criteria. Whereas, five studies (4,6,13,15,17) used clinical manifestation and immunological testing to confirm the diagnosis ABC-HSR. Among those studies using clinical manifestations as their diagnostic criteria, 409 and 1,883 subjects were included as cases and controls, respectively (3,4,12-16,30). In studies that used immunological testing to confirm their diagnostic criteria, 110 and 1,968 subjects were included as cases and controls, respectively (4,6,13,15,17). The populations of the included studies were summarized as shown in Table 1. In brief, there were white (8 studies) (3,4,6,12,13,15,17,30), black (5 studies) (3,4,15,16,30), Asian (1 study) (14) and other populations (1 study) (3). The mean ages of the patients were 41.8 and 41.6 years in cases and controls, respectively (3, 6, 12,13,15,17,30). Males comprised 86% of cases (127/148) and 81% of controls (732/899) (3, 6, 12,17,30). In five studies (6,12-15), patients using abacavir for 6-52 weeks without HSR were included in the control group, whereas patients demonstrating the symptoms within 6-10 weeks after commencing the abacavir therapy were classified into the case group (4,6,12,14,15,17). Saag, et al. (15) reported the time to onset of HSR, noting that white patients and black patients demonstrated hypersensitivity within 17 and 32 days, respectively, after the initiation of abacavir therapy. Whereas, Stekler, et al. (13) reported the mean time to onset of ABC-HSR was 9 days. The included studies identified HLA-B*5701 using several distinct techniques: a high resolution DNA-based sequencing method (3,15,16), polymerase chain reaction (PCR) as a sequence based typing technique (14,17), PCR sequence-specific oligonucleotides primers (4,6,13,30), or PCR-restriction fragment length polymorphism (12). No study provided enough information to calculate HWE.

**Association between *HLA-B*5701* and ABC-HSR diagnosed by immunologic confirmation**

The data from 5 studies which identified ABC-HSR by immunological confirmation (4,6,13,15,17) were included. There were 110 cases and 1,938 controls. In these studies, the numbers of patients carrying with at least on allele of HLA-B*5701 were 107 and 41 in cases and controls, respectively. Overall, the OR was 1,056.2 (95% CI = 345.0 – 3,233.3; $I^2$ = 0.00%, p = 0.64). In subgroup analysis based on ethnicity, the summary ORs were 1,113 (95% CI = 319.7-3,875.1; $I^2$ = 0.00%, p = 0.42) for whites (4,6,13,15,17) and 851.6 (95% CI = 67.9 – 10,682.3; $I^2$ = 0.0%, p = 0.00) for blacks (4,15), respectively (Figure 3). There was no apparent publication bias by the Begg test (P =0.29), Egger test (P = 0.72), or funnel plot.

## DISCUSSION

Our results showed a strong association between the HLA-B*5701 and ABC-HSR where ABC-HSR was confirmed by immunological testing. The OR was 1,056.2 (95% CI = 345.0 – 3,233.3). This strong association was similar to the results of the subgroup analyses in black and white population (Figure 3 and Table 2). Whereas, the ORs in the studies using clinical manifestation was 23.6 (95% CI = 15.4 – 36.3). The ORs among ethnicities (i.e. white, black, and Asian) were slightly different (Figure 2 and Table 2).

Our results clearly indicated the superiority of immunological testing for ABC-HSR over clinical manifestation alone and the differing ORs for these groups probably results from the misclassification of ABC-HSR due to false-positive diagnosis. In the Mallal et al. study (4), a skin patch test provided exceptional sensitivity (100%) and specificity (96.9%).

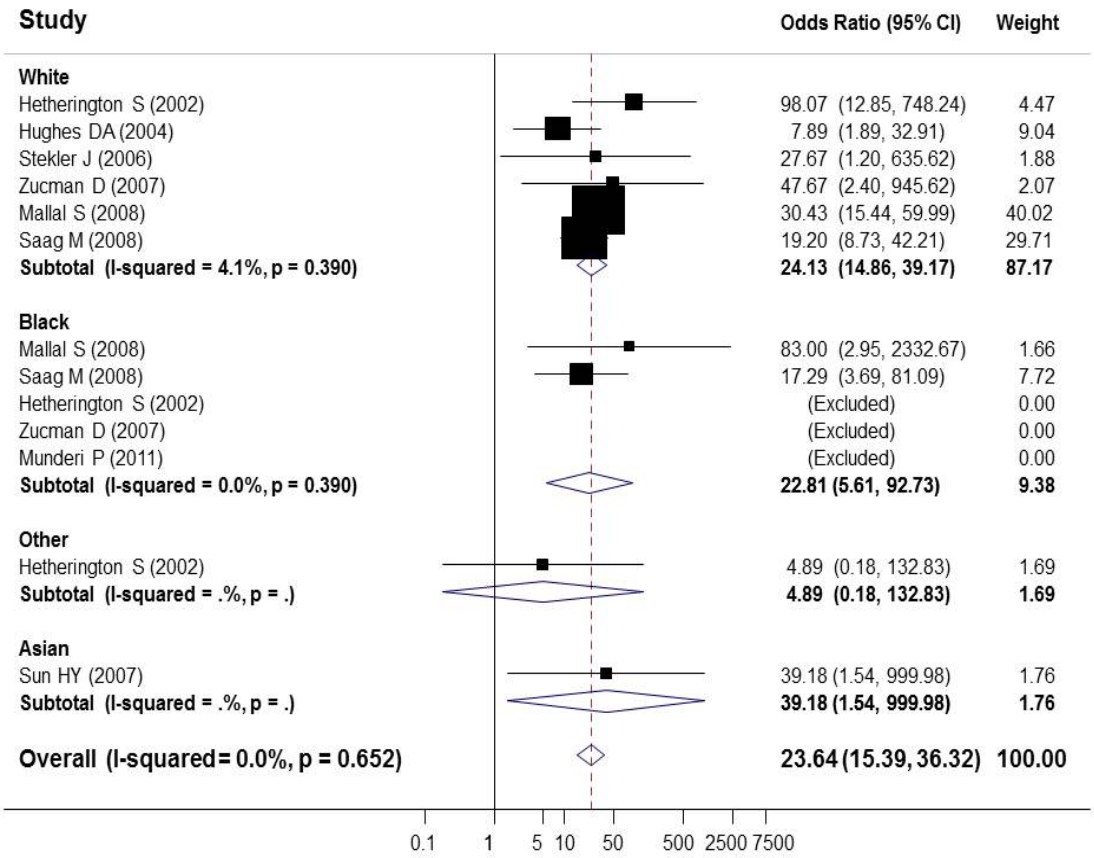


**Figure 2** – Random-effects meta-analysis of clinically diagnosed ABC-HSR among *HLA-B*5701*-positive patients, stratified by ethnicity

Thus, to increases the accuracy of ABC-HSR, immunological testing should supplement any clinical diagnosis of HSR.

In the studies using clinical manifestation, the association between the HLA-B*5701 and ABC-HSR was statistically significant in whites, blacks

and Asians. However, the association for "other" ethnicity group [i.e., mostly Hispanic (Hetherington, et al. study (3)] was not statistically significant (Figure 2 and Table 2). This might be due to 1) a small sample size and 2) less susceptibility to the HSR in the Hispanic population. In studies using immunological confirmation, the association between the HLA-B*5701 and ABC-HSR was strong in whites and blacks (Figure 3).

The Zucman, et al. study (30) was an observational study with 2 prominent objectives: 1) to address the association between HLA-B*5701 and ABC-HSR in a French population, and; 2) to re-evaluate the predictive value of HLA-B*5701 screening. It was divided into 2 parts: part 1) was a retrospective study which tested HLA-B*5701 in patients previously exposed to abacavir; part 2) was a prospective study which pre-screened for HLA-B*5701 in abacavir-naive patients. Thus, our analysis only extracted data from part 1.

The study by Mallal, et al. (4) was a randomized control trial designed to establish the effectiveness of prospective HLA-B*5701 immunological screening to prevent ABC-HSR. Patients in this study were randomly divided into 2 groups. For the first group, all patients received standard abacavir therapy before HLA-B*5701 testing, whereas, subjects in the second group were pretested and those positive for the gene received no abacavir. We only extracted data from the first non-prescreened group and identified as a case-control study. Notably, the 'black' population from Mallal et al. (4) also included American Indians or Alaskan natives (~8%), mixed (~8%) and other ethnicities (~11%).

The results from the Mallal, et al. study (4) showed the incidence of ABC-HSR was significantly lowered in prospective HLA-B*5701 screening group than those in the standard abacavir treatment. However, our results clearly demonstrated the association between HLA-B*5701 and ABC-HSR especially in the studies used immunologic confirmation to identify ABC-HSR (Figure 2 and Table 2).

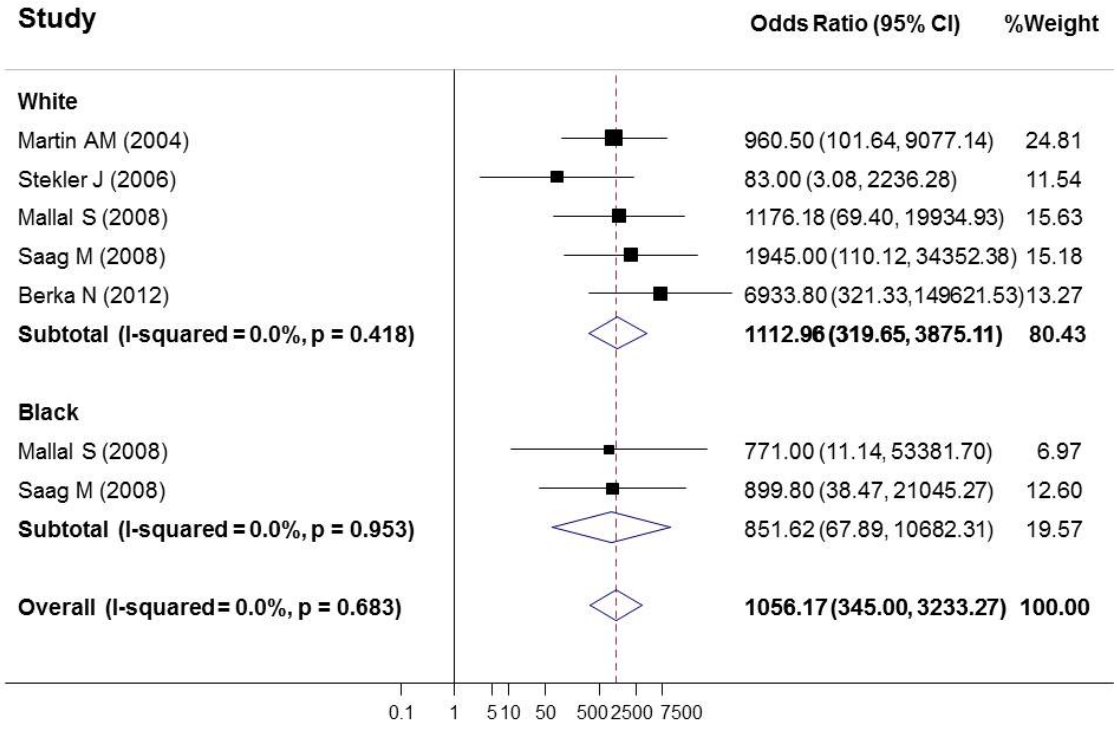


**Figure 3** - Random-effects meta-analysis of immunologic confirmation diagnosed ABC-HSR among *HLA-B*5701*-positive patients, stratified by ethnicity

An emerging mechanism for abacavir action is by its specific steric binding via two unique amino-acid residues in the 'F-pocket' of HLA-B*5701 protein, which results in the protein complexing with self-peptides of which about 20% become recognized as non-self by CD8+T-cells (9-11) and which elicits an ensuing autoimmune activation. A similar modification of HLA-B*1502 also explained carbamazepine-induced hypersensitivities (9). Nevertheless, abacavir-HLA-B*5701 penetrance was not 100%, and we show that the actual abacavir-induced hypersensitivity varied between white, Asian and black HLA-B*5701 carriers and a plausible explanation for this is maybe differing spectrums of self-tolerant peptides in the different populations or more likely different T-cell clonotypes which express a restricted range of the receptors responding to non-self antigens (34). The penetrance of abacavir-induced hypersensitivity in HLA-B*5701 individuals was about 50%, indicating that additional factors determine whether abacavir treatment induces abacavir-induced hypersensitivity (9). Thus, a polymorphism in HLA-B*5701 among the populations is possible. To prove this hypothesis, genetic sequencing studies of this particular gene in each population may be able to provide a better understanding in the difference in the abacavir-induced hypersensitivity reaction.

## CONCLUSION

Using meta-analysis, the association between HLA-B*5701 and ABC-HSR is strong in the studies using immunological confirmation to identify HLA-B*5701 and ABC-HSR. These results support the US FDA recommendations for screening HLA-B*5701 allele before beginning abacavir therapy.

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**Table 1** - Characteristics of included studies.

| Reference | Study design | Country | Population | Case | | Control | | Diagnostic method of ABC-HSR | NOS |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *HLA-B*5701* positive (+) | | negative (-) | | | |
| | | | | + | - | + | - | | |
| (3) | Case-control | UK | White | 36 | 29 | 1 | 79 | Clinical manifestation | 4 |
| | | | Black | 0 | 9 | 0 | 18 | | |
| | | | Other [a] | 1 | 9 | 0 | 15 | | |
| (12) | Case-control | UK | White | 6 | 7 | 5 | 46 | Clinical manifestation | 4 |
| (6) [b] | Case-control | Australia | White | 17 | 1 | 4 | 226 | Immunologic confirmation | 5 |
| (13)[d] | Case-control | United States | White | 2 | 7 | 0 | 41 | Clinical manifestation | 6 |
| | | | | 2 | 2 | 0 | 41 | Immunologic confirmation | |
| (14) | Case-control | Taiwan | Asian | 1 | 16 | 0 | 215 | Clinical manifestation | 4 |
| (30) | Case-control | France | White | 6 | 7 | 0 | 27 | Clinical manifestation | 2 |
| | | | Black | 0 | 3 | 0 | 6 | | |
| (4)[d] | Case-control | Australia | White | 29 | 32 | 19 | 638 | Clinical manifestation | 6 |
| | | | | 22 | 0 | 25 | 666 | Immunologic confirmation | |
| | | | Black [c] | 1 | 4 | 0 | 124 | Clinical manifestation | |
| | | | | 1 | 0 | 0 | 128 | Immunologic confirmation | |
| (15) [d] | Case-control | United States | White | 57 | 72 | 8 | 194 | Clinical manifestation | 6 |
| | | | | 42 | 0 | 8 | 194 | Immunologic confirmation | |
| | | | Black | 10 | 59 | 2 | 204 | Clinical manifestation | |
| | | | | 5 | 0 | 2 | 204 | Immunologic confirmation | |
| (16) | Case-control | Uganda | Black | 0 | 6 | 0 | 241 | Clinical manifestation | 3 |
| (17) | Case-control | Canada | White | 18 | 0 | 2 | 468 | Immunologic confirmation | 5 |

NOS = Newcastle-Ottawa Scale; [a] Including American Hispanic (84%) and other (6%); [b] This study provided only immunologic confirmation data; [c] Including Black (~73%), American Indian or Alaskan native (~8%), Mixed (~8%) and other (~11%); [d] These studied provided both clinical manifestation and immunologic confirmation data. In case group, only some patients were confirmed by immunologic assay.

**Table 2.** Calculated odds ratio of the included studies and summary odds ration categorized by diagnostic methods od detecting hypersensitivity.

| Study | Year | *HLA-B*5701*positive/total | | Odds ratio (OR) | 95% Confidence interval |
|---|---|---|---|---|---|
| | | case | control | | |
| **Clinical manifestation** | | | | | |
| **White** | | | | | |
| (3) | 2002 | 36/65 | 1/80 | 98.07 | 12.85 - 748.24 |
| (12) | 2004 | 6/13 | 5/51 | 7.89 | 1.89 - 32.91 |
| (13) | 2006 | 2/9 | 0/41 | 27.67 | 1.20 - 635.62 |
| (30) | 2007 | 6/13 | 0/27 | 47.67 | 2.40 - 945.62 |
| (4) | 2008 | 29/61 | 19/657 | 30.43 | 15.44 - 59.99 |
| (15) | 2008 | 57/129 | 8/202 | 19.20 | 8.73 - 42.21 |
| **Sub-total, I-squared = 4.1%, *p* = 0.390)** | | | | **24.31** | **14.86 – 39.17** |
| **Black** | | | | | |
| (4) | 2008 | 1/5 | 0/124 | 83.00 | 2.95 - 23,332.67 |
| (15) | 2008 | 10/69 | 2/206 | 17.29 | 3.69 - 81.09 |
| (30) | 2007 | 0/3 | 0/6 | NA | NA |
| (3) | 2002 | 0/9 | 0/18 | NA | NA |
| (16) | 2011 | 0/6 | 0/241 | NA | NA |
| **Sub-total, I-squared = 0.0%, p = 0.390** | | | | **22.81** | **5.61 - 92.73** |
| **Asian** | | | | | |
| (14) | 2007 | 1/17 | 0/215 | 39.18 | 1.54 - 999.98 |
| **Other** | | | | | |
| (3) | 2002 | 1/10 | 0/15 | 4.89 | 0.18 - 132.83 |
| **Summary OR, I-squared = 0.0%, *p*= 0.6520** | | | | **23.64** | **15.39 - 36.32** |
| **Immunologic confirmation** | | | | | |
| **White** | | | | | |
| (6) | 2004 | 17/18 | 4/230 | 960.50 | 101.64 - 9,077.14 |
| (13) | 2006 | 2/4 | 0/41 | 83.00 | 3.08 - 2,236.28 |
| (4) | 2008 | 22/22 | 25/691 | 1,176.18 | 69.40 - 19,934.93 |
| (15) | 2008 | 42/42 | 8/202 | 1,945.00 | 110.12 - 34,352.38 |
| (17) | 2012 | 18/18 | 2/470 | 6,933.80 | 321.33 - 149,621.53 |
| **Sub-total, I-squared=0.00%, *p*=0.418** | | | | **1,112.96** | **319.65 - 3,875.11** |
| **Black** | | | | | |
| (4) | 2008 | 1/1 | 0/128 | 771.00 | 11.14 - 53,381.70 |
| (15) | 2008 | 5/5 | 8/206 | 899.80 | 38.47 - 21,045.27 |
| **Sub-total, I-squared=0.00%, *p*=0.953** | | | | **851.62** | **67.89 - 10,682.31** |
| **Summary OR, I-squared=0.00%, *p*=0.638** | | | | **1,056.17** | **345.00 - 3,233.27** |