Meta-analysis of correlation between HLA-G 3’ UTR 14-bp Ins/Del polymorphism and virus susceptibility

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Abstract

Background: There is a considerable amount of literature on the potential relationship between human leukocyte antigen-G 14-bp Ins/Del polymorphism and virus infection; however, results from these studies were inconclusive.

Objectives: A meta-analysis was carried out to determine whether the 14-bp Ins/Del polymorphism is a susceptible factor for virus infection.

Methods: Data were extracted from PubMed and Web of Science databases, and included 10 case-control studies (1835 patients and 2357 controls).

Results: A total of 177 records from 10 studies were retrieved. Overall, no significant correlation was found between HLA-G 14-bp Ins/Del polymorphism and total viruses under all genetic models (dominant model: OR = 0.93, 95% CI = 0.88–1.29; recessive model: OR = 1.12, 95% CI = 0.84–1.48; deletion/deletion (DD) vs insertion/insertion (II): OR = 1.03, 95% CI = 0.71–1.49; deletion (D) vs insertion (I): OR = 1.01, 95% CI = 0.81–1.25). However, further subgroup analyses by virus type and ethnicity revealed that HLA-G 14-bp Ins/Del polymorphism was significantly associated with HTLV-1 infection in mixed population under the dominant model.

Conclusions: Our study demonstrated that HLA-G 14-bp Ins/Del polymorphism may not have any effect on susceptibility to viruses.

Abbreviations: CI = confidence interval, HBV = hepatitis B virus, HCMV = human cytomegalovirus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, HLA-G = human leukocyte antigen-G, HPV = human papillomavirus, HTLV-1 = human T-lymphotropic virus type 1, HWE = Hardy-Weinberg equilibrium, Ins/Del = insert/delete, OR = odds ratio, UTR = untranslated regions.

Keywords: HLA-G, meta-analysis, polymorphism, virus infection

1. Introduction

Human leukocyte antigen (HLA)-G was first reported to be a key player in maintaining maternal-fetal immune tolerance. It has been shown that expression level of HLA-G increases significantly during pathological states, such as in tumors, autoimmune diseases, and infectious diseases. HLA-G has been implicated in viral infections, as its tolerogenic function mediates escape of the virus from host immune defenses. The immune suppressive mechanism of HLA-G includes inhibition of cytotoxic activity of natural killer and cytotoxic T cells, CD4+ T cell alloproliferative response, and dendritic cells maturation.

The HLA-G gene is located on chromosome 6p21.3, and comprises 7 introns and 8 exons. A 14-base pairs (14-bp) insertion/deletion (Ins/Del) polymorphism (rs66554220) in the 3’ untranslated region (UTR) of the HLA-G gene has been associated with mRNA stability and splicing patterns, which has an impact on protein levels. To date, there has been little agreement on the association between HLA-G 14-bp Ins/Del polymorphism and susceptibility to viral infections. Some studies have linked HLA-G 14-bp Ins/Del polymorphism with human cytomegalovirus (HCMV) and human T-lymphotropic virus type 1 (HTLV-1) infections. Other studies indicated that there is no association between HLA-G 14-bp Ins/Del polymorphism and virus infections. Since these results were inconclusive, we decided to perform a systematic review to assess the relationship between HLA-G 14-bp Ins/Del polymorphism and virus infections.

2. Materials and methods

2.1. Ethical considerations

All analyses were based on previous published studies; thus no ethical approval and patient consent are required.

2.2. Search strategy

We searched for relevant literatures using the PubMed and Web of Science databases; the search terms used were: “HLA-G OR human leukocyte antigen-G” AND “polymorphism OR variant OR mutation” AND “virus OR viruses”; no language restriction was applied.
2.3. Study selection criteria

Inclusion criteria for the studies were as follows: studies that investigated the correlation between the 14-bp Ins/Del polymorphism and virus infection; results included sufficient genotype data to determine the odds ratio (OR) and 95% CI; (3) study design was case controlled. Exclusion criteria were as follows: letters, reviews; duplicated data.

2.4. Data extraction

Two researchers extracted qualified data; extracted information included the first authors’ names, year of publication, ethnicity, virus type, the number of cases and controls, and evidence of Hardy–Weinberg equilibrium (HWE) in controls. We resolved discrepancies through discussions.

2.5. Statistics

Based on the raw information, we calculated the HWE of HLA-G 14-bp Ins/Del polymorphism in the control group via the Chi-square test. The STATA version 12.0 software was used to perform the meta-analysis. An odds ratio with 95% CI was used to evaluate the significance of association between HLA-G 14-bp Ins/Del and susceptibility to viral infections. A random-effect or fixed-effect model was used, depending on the degree of heterogeneity. The pooled OR with the corresponding 95% CI were calculated in a recessive model (Ins/Ins vs Ins/Del + Del/Del), a dominant model (Ins/Ins + Ins/Del vs Del/Del), homozygote comparison (Del/Del vs Ins/Ins), and allele comparison (Ins vs Del). Subgroup analyses were performed according to virus type (only one study would be incorporated into the “other virus” group) and ethnicity (categorized as Asian, Africa, and Mixed population).

The $I^2$ test was used to assess the effects of heterogeneity. $I^2 > 25\%$ indicated heterogeneity among the included studies. When $I^2$ statistic was $> 25\%$, the random-effect DerSimonian–Laird method was used; otherwise, the fixed-effect Mantel–Haenszel method was used. To evaluate the significance of the pooled OR, the Z test was carried out, and $P < .05$ was considered to be statistically significant.

Furthermore, sensitivity analysis was conducted to determine the effects of individual studies on the pooled susceptibility to virus by consecutively excluding single studies. Lastly, funnel plots and asymmetrical tests were performed to assess publication bias.

3. Results

3.1. Characteristics of eligible studies

A total of 177 publications were screened from databases. Figure 1 shows the study selection procedure; 10 articles, including 1835 patients and 2357 controls were ultimately selected. The specific characteristics of the qualified reports are presented in Table 1. The included focused on the following virus types: hepatitis B virus (HBV), HTLV-1, human papillomavirus (HPV), HCMV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV).

3.2. Meta-analysis of HLA-G 14-bp Ins/Del polymorphism and virus infection

Results of the meta-analysis are shown in Table 2. The $I^2$ test demonstrated distinct heterogeneity in the selected studies in 4 genetic models. Therefore, the random effect model was applied to generate a larger pool of studies with 95% CI. As shown in Figure 2, no apparent association between HLA-G 14-bp Ins/Del polymorphism and virus infection was detected under the genetic models (recessive model: OR = 1.12, 95% CI = 0.84–1.48, Fig. 2A; dominant model: OR = 0.93, 95% CI = 0.68–1.29, Fig. 2B; homozygote: OR = 1.03, 95% CI = 0.71–1.49, Fig. 2C;
Meta-analysis of the associations between the HLA-G 14-bp Ins/Del polymorphism and virus susceptibility in 4 genetic models.

| Variables | Dominant model | Recessive model |
|-----------|----------------|-----------------|
|           | P OR (95%CI) P (%) | P OR (95%CI) P (%) | P OR (95%CI) P (%) | P OR (95%CI) P (%) |
| Total     | 0.68 (0.68–1.29) | 80.2 0.29 (0.84–1.46) 28.8 | 0.88 (0.71–1.49) 64.9 | 0.95 (0.81–1.25) 79 |
| Virus type |                 |                 |                 |                 |
| HBV       | 0.55 (0.69–2.01) | 83.7 0.46 (0.59–1.28) 39.3 | 0.45 (0.60–3.22) 85.6 | 0.50 (0.73–1.91) 90 |
| HTLV-1    | 0.01 (0.42–0.90) * | 0 0.36 (0.46–1.33) 9 | 0.90 (0.56–1.66) 0 | 0.36 (0.69–1.14) 0 |
| HIV       | 0.08 (0.50–1.04) | 0 0.20 (0.84–2.29) 0 | 0.12 (0.32–1.14) 0 | 0.06 (0.58–1.01) 0 |
| Other virus | 0.96 (0.34–3.16) | 89.3 0.17 (0.25–1.28) 56 | 0.95 (0.39–2.70) 71.1 | 0.82 (0.56–2.08) 85.4 |
| Ethnicity |                 |                 |                 |                 |
| Mixed     | 0.008 (0.76–0.94) * | 13.0 0.41 (0.88–3.13) 0 | 0.52 (0.73–1.17) 0 | 0.18 (0.82–1.04) 0 |
| Asian     | 0.29 (0.58–0.68) | 70.6 0.47 (0.57–3.36) 71 | 0.40 (0.51–2.56) 82.1 | 0.31 (0.72–2.81) 90.9 |
| Africa    | 0.45 (0.58–0.12) | 0 0.07 (0.47–1.02) 0 | 0.12 (0.44–1.11) 0 | 0.10 (0.81–6.33–1.04) 0 |

OR odds ratio, 95% CI 95% confidence interval.

HBV = hepatitis B virus, HPV = human papillomavirus, HTLV-1 = human T-lymphotropic virus type 1.

* A significant result.

1 The statistical significance of the pooled OR was determined by the Z test.

2 No statistical significance was found by the heterogeneity test, then the fixed-effects model was adopted here, otherwise, random-effect will be employed.
To apply the interpretations obtained from the current meta-analysis, certain limitations should be considered. First, the number of included studies was not big enough, which set a limit to perform further subgroup analyses. Second, aside from disease susceptibility, polymorphism at HLA-G 14-bp may be associated with clinical features. Due to a lack of adequate data, we were unable to analyze possible confounding factors, such as age, sex, virological, immunological, or environmental variables, which may have an effect on the progression of the disease. Third, although no evidence of publication bias was observed in...
Harbord’s test, publication bias is unavoidable in meta-analyses. There were only total 10 studies on viral infection included in this meta-analysis; 3 studies on HBV, 2 studies on HPV, 2 studies on HTLV-1, and a single study on each of HCMV, HIV, and HCV.

5. Conclusion

Overall, our study demonstrated that HLA-G 14-bp Ins/Del polymorphism may exert no influence on susceptibility to viruses. However, due to the limited number of studies examined, some results from the current meta-analysis are limited. In the future, larger eligible studies are required to investigate the gene-gene and gene-environment interactions on HLA-G gene polymorphism in viral diseases. This may provide a more comprehensive and reliable foundation for etiological research, and promote clinical prevention of virus infection.

Author contributions

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