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Meta-analysis of correlationship 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 = 0.68–1.29; 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.[1] 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.[2–4] 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.[5]

The HLA-G gene is located on chromosome 6p21.3, and comprises 7 introns and 8 exons.[6] 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.[7,8] 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.[9–12] Other studies indicated that there is no association between HLA-G 14-bp Ins/Del polymorphism and virus infections.[13–18] 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.

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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.[19] $I^2 > 25\%$ indicated heterogeneity among the included studies. When I^2 statistic was $> 25\%$, the random-effect DerSimonian–Laird method was used[19]; otherwise, the fixed-effect Mantel–Haenszel method was used.[20] 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),[11,15,16] HTLV-1,[9,10] human papillomavirus (HPV),[17,18] HCMV,[12] hepatitis C virus (HCV),[13] and human immunodeficiency virus (HIV).[14]

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;

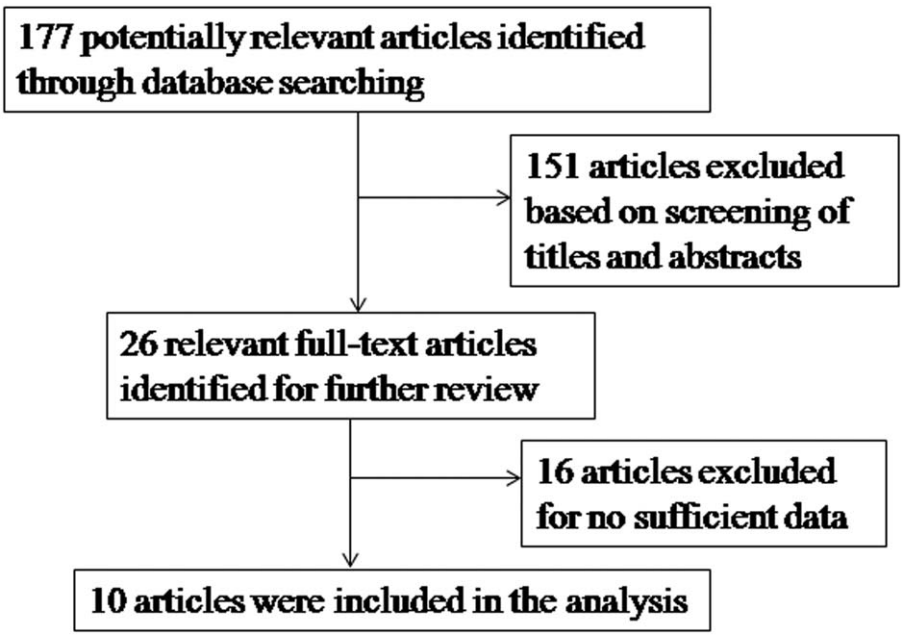

Figure 1. XXX.

Table 1

Genotype and allele distribution of the HLA-G 14-bp Ins/Del polymorphism in patients with virus infection diseases and controls.

First author[Ref]	Year	Virus type	Concurrent disease	Ethnicity	Case			Control			Case		Control		HWE*
					Ins/Ins	Ins/Del	Del/Del	Ins/Ins	Ins/Del	Del/Del	Ins	Del	Ins	Del	
Ferreira[13]	2017	HBV		Mixed	32	99	66	45	87	70	163	231	177	227	0.08
Laaribi[10]	2014	HBV		Africa	87	109	67	63	113	70	283	243	239	253	0.21
Jiang[6]	2011	HBV	HCC	Asian	12	66	144	68	208	263	90	354	344	734	0.01
Haddad[5]	2011	HTLV-1		Mixed	18	82	38	29	67	54	118	158	125	175	0.32
Ciliao Alves[4]	2016	HTLV-1		Mixed	13	48	21	29	64	60	74	90	122	184	0.11
Xu[12]	2014	HPV		Asian	15	92	72	7	64	72	122	236	78	208	0.13
Simoes[11]	2009	HPV	SIL	Mixed	24	37	36	12	23	24	85	109	47	71	0.15
Zheng[7]	2009	HCMV		Asian	6	14	34	28	81	56	26	82	137	193	0.89
da Silva[9]	2014	HIV	HCV	Mixed	101	292	189	104	298	226	494	670	506	750	0.73
Cordero[8]	2009	HCV	SCD	Mixed	4	14	3	11	34	27	22	20	56	88	0.96

HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HPV = human papillomavirus, HTLV-1 = human T-lymphotropic virus type 1, Ins/Del = insert/delete, SCD = sickle cell disease, SIL = squamous intraepithelial lesions.

* Hardy–Weinberg Equilibrium in control.

allele: OR = 1.01, 95% CI = 0.81–1.25, Fig. 2D). However, subgroup analysis based on virus type showed that the polymorphism was significantly associated with HTLV-1 infection in the dominant model (OR = 0.61, 95% CI = 0.42–0.90, $P < .05$) (Table 2). Similarly, there was significant association between HLA-G 14-bp Ins/Del polymorphism and Mixed population in ethnicity-based subgroup analysis in the dominant model (OR = 0.79, 95% CI = 0.67–0.94, $P < .01$).

3.3. Tests for sensitivity and publication bias

Among the included literatures, one did not meet the HWE; however, sensitivity analysis showed that there was no significant change to the pooled OR (data was not shown). This suggested that our analyses are comparatively stable and reliable. We obtained Begg's funnel plots in all 4 models (Fig. 3). Harbord's tests demonstrated no evidence of publication bias in the 4 models ($P > .1$)

4. Discussions

HLA-G is known as an important immune regulatory molecule that facilitates virus infection, and mediates tumor cell escape from host immunological surveillance by inhibiting immune cells functions.[18] Polymorphism of HLA-G 14-bp Ins/Del was shown to be associated with mRNA stability and splicing patterns, which may have an impact on the expression of HLA-G protein.[7,8]

To date, few studies have been able to conduct systematic research on this issue. The current study systemically reviewed the relationship between HLA-G 14-bp Ins/Del and virus susceptibility. We carried out this meta-analysis with 10 articles, which included 1835 cases and 2357 controls. The results implied that HLA-G 14- bp Ins/Del polymorphism may not have a significant effect on virus susceptibility in any comparison models. Further stratification analyses based on virus type and ethnicity revealed no significant associations between HBV, HPV, and other viruses in Asian and African population. However, we found evidence of significant association between HTLV-1 and Mixed population in a dominant model. It is possible that the non-allelic interaction and host genes may be associated with persistence of virus infection. Xu et al[18] showed that the relationship between 14-bp Ins/+3142G haplotype and HPV18 infection risk was prominent in a previous study. In addition, higher frequency of the 14-bp Ins /+3142G haplotype was observed in African-derived HIV positive patients when compared with that in controls.[14]

Table 2

Meta-analysis of the associations between the HLA-G 14-bp polymorphism and virus susceptibility in 4 genetic models.

Variables	Dominant model			Recessive model			DD vs II			D vs I		
	P†OR	OR (95%CI)	I^2 (%)‡	P†OR	OR (95%CI)	I^2 (%)‡	P†OR	OR (95%CI)	I^2 (%)‡	P†OR	OR (95%CI)	I^2 (%)‡
Total	0.68	0.93 (0.68–1.29)	80.2	0.29	1.12 (0.84–1.48)	28.8	0.88	1.03 (0.71–1.49)	64.9	0.95	1.01 (0.81–1.25)	79
Virus type												
HBV	0.55	1.18 (0.69–2.01)	83.7	0.46	0.86 (0.58–1.28)	39.3	0.45	1.39 (0.60–3.22)	85.6	0.50	1.18 (0.73–1.91)	90
HTLV-1	0.01	0.61 (0.42–0.90)*	0	0.36	0.78 (0.46–1.33)	9	0.90	0.97 (0.56–1.66)	0	0.36	0.89 (0.69–1.14)	0
HPV	0.08	0.72 (0.50–1.04)	0	0.20	1.39 (0.84–2.29)	0	0.12	0.60 (0.32–1.14)	0	0.06	0.77 (0.58–1.01)	0
Other virus	0.96	1.03 (0.34–3.16)	89.3	0.17	0.56 (0.25–1.28)	56	0.95	1.03 (0.39–2.76)	71.1	0.82	1.08 (0.56–2.08)	85.4
Ethnicity												
Mixed	0.008	0.79 (0.67–0.94)*	13.0	0.41	1.09 (0.88–1.35)	0	0.52	0.92 (0.73–1.17)	0	0.18	0.92 (0.82–1.04)	0
Asian	0.29	1.59 (0.68–3.73)	90.6	0.47	1.38 (0.57–3.36)	71	0.40	1.64 (0.51–5.26)	82.1	0.3	1.43 (0.72–2.81)	90.9
Africa	0.45	0.86 (0.58–1.27)	0	0.07	0.70 (0.47–1.02)	0	0.12	0.69 (0.44–1.11)	0	0.10	0.81 (0.63–1.04)	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.

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

‡ No statistical significance was found by the heterogeneity test, then the fixed-effects model was adopted here, otherwise, random-effect will be employed.

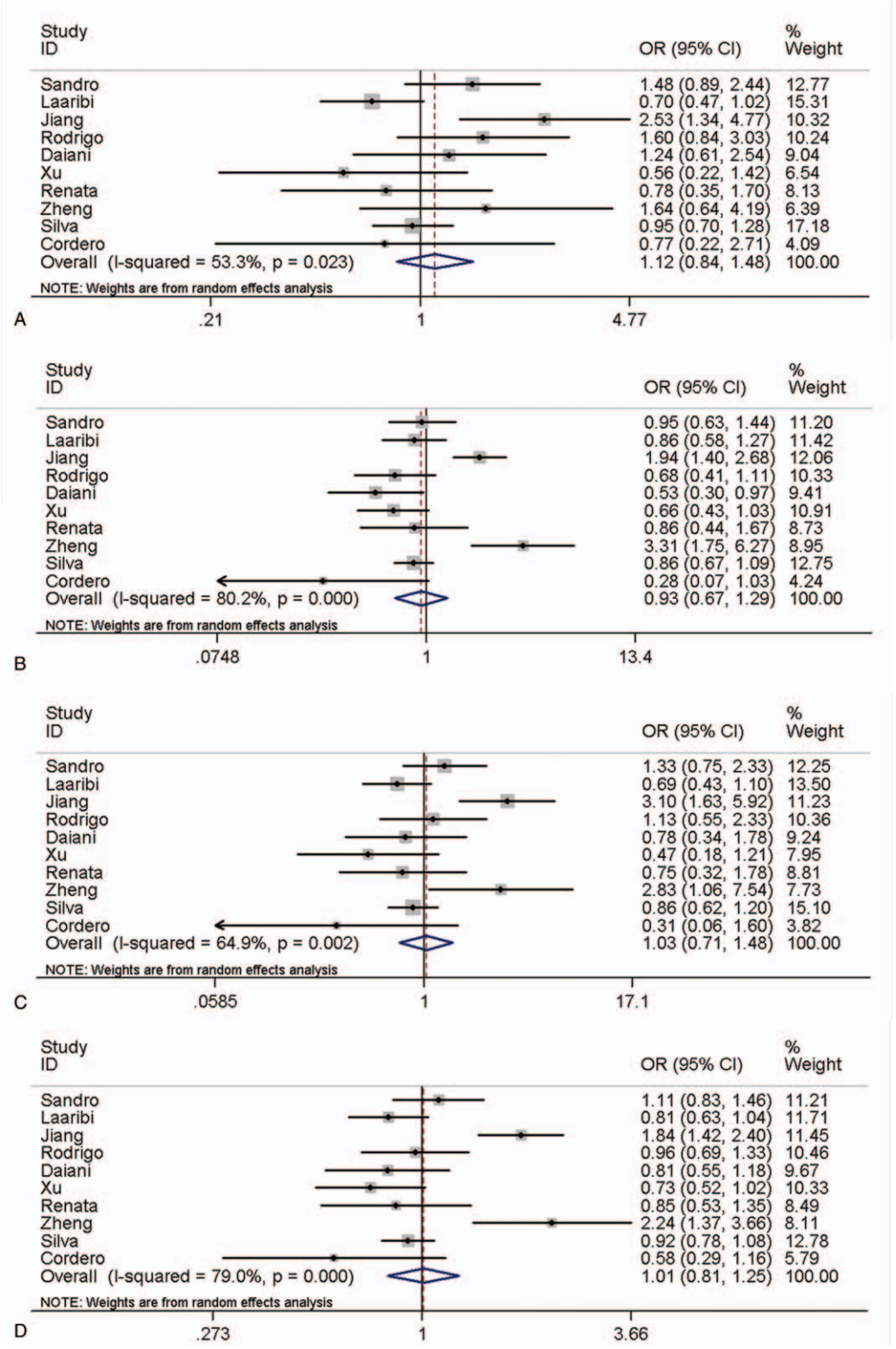

Figure 2. XXX.

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

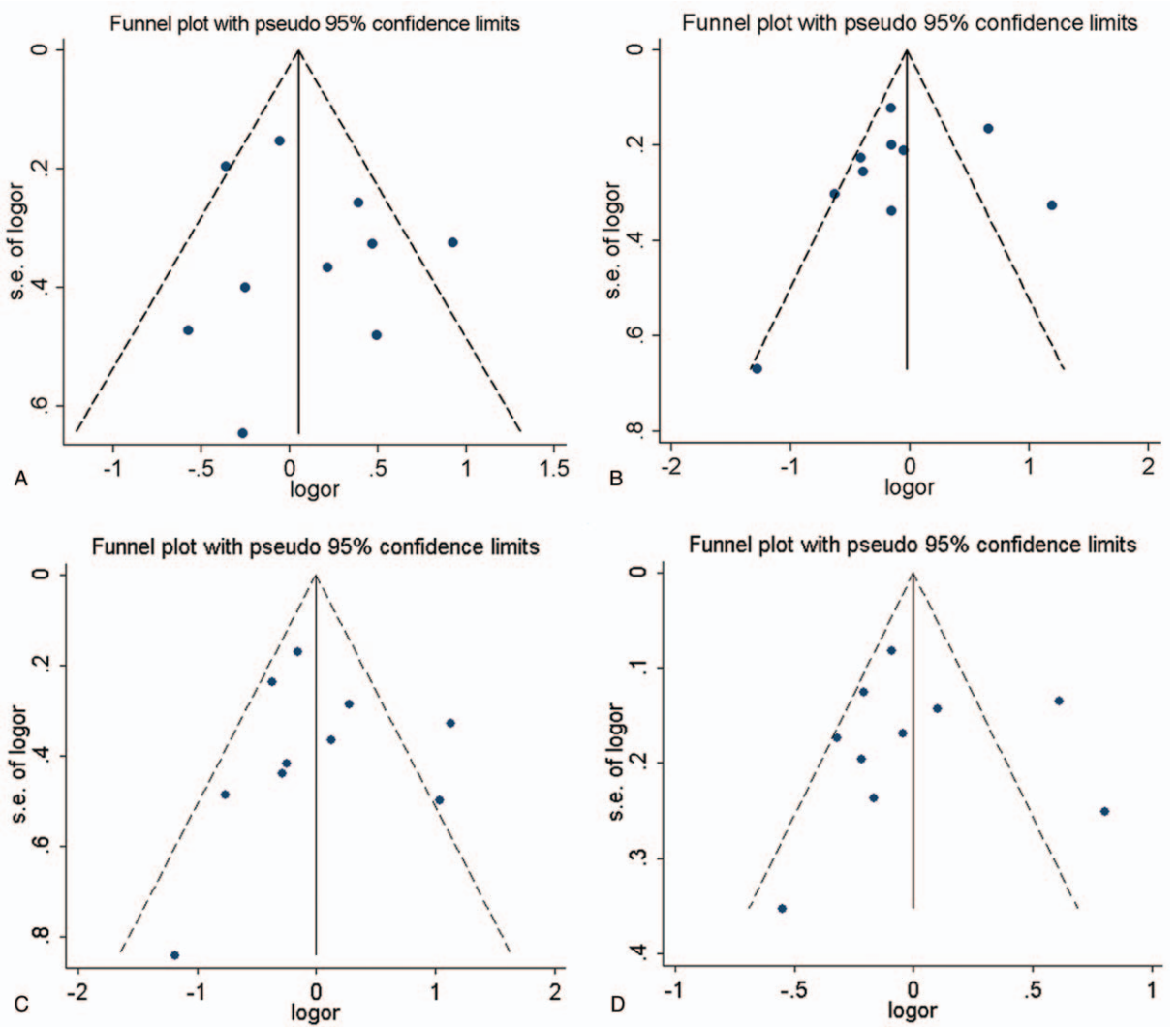

Figure 3. XXX.

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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References

[1] Kovats S, Main EK, Librach C, et al. A class I antigen, HLA-G, expressed in human trophoblasts. Science 1990;248:220–3.
[2] LeBouder F, Khoufache K, Menier C, et al. Immunosuppressive HLA-G molecule is upregulated in alveolar epithelial cells after influenza A virus infection. Hum Immunol 2009;70:1016–9.
[3] Lozano JM, Gonzalez R, Kindelan JM, et al. Monocytes and T lymphocytes in HIV-1-positive patients express HLA-G molecule. AIDS 2002;16:347–51.
[4] Rizzo R, Hviid TV, Govoni M, et al. HLA-G genotype and HLA-G expression in systemic lupus erythematosus: HLA-G as a putative susceptibility gene in systemic lupus erythematosus. Tissue Antigens 2008;71:520–9.
[5] LeMaoult J, Rouas-Freiss N, Carosella ED. Immuno-tolerogenic functions of HLA-G: relevance in transplantation and oncology. Autoimmun Rev 2005;4:503–9.
[6] Carosella ED, Moreau P, Lemaoult J, et al. HLA-G: from biology to clinical benefits. Trends Immunol 2008;29:125–32.

[7] Hviid TV, Hylenius S, Rorbye C, et al. HLA-G allelic variants are associated with differences in the HLA-G mRNA isoform profile and HLA-G mRNA levels. Immunogenetics 2003;55:63–79.
[8] Rousseau P, Le Discorde M, Mouillot G, et al. The 14 bp deletion-insertion polymorphism in the 3' UT region of the HLA-G gene influences HLA-G mRNA stability. Hum Immunol 2003;64:1005–10.
[9] Ciliao Alves DC, Haddad R, Rocha-Junior MC, et al. HLA-G 3'-untranslated region polymorphisms are associated with HTLV-1 infection, proviral load and HTLV-associated myelopathy/tropical spastic paraparesis development. J General Virol 2016;97:2742–52.
[10] Haddad R, Ciliao Alves DC, Rocha-Junior MC, et al. HLA-G 14-bp insertion/deletion polymorphism is a risk factor for HTLV-1 infection. AIDS Res Hum Retroviruses 2011;27:283–8.
[11] Jiang Y, Chen S, Jia S, et al. Association of HLA-G 3' UTR 14-bp insertion/deletion polymorphism with hepatocellular carcinoma susceptibility in a Chinese population. DNA Cell Biol 2011;30:1027–32.
[12] Zheng XQ, Zhu F, Shi WW, et al. The HLA-G 14 bp insertion/deletion polymorphism is a putative susceptible factor for active human cytomegalovirus infection in children. Tissue Antigens 2009;74:317–21.
[13] Cordero EA, Veit TD, da Silva MA, et al. HLA-G polymorphism influences the susceptibility to HCV infection in sickle cell disease patients. Tissue Antigens 2009;74:308–13.
[14] da Silva GK, Vianna P, Veit TD, et al. Influence of HLA-G polymorphisms in human immunodeficiency virus infection and hepatitis C virus co-infection in Brazilian and Italian individuals. Infect Genet Evol 2014;21:418–23.
[15] Ferreira SD, Chacha SG, Souza FF, et al. The HLA-G 14-base pair deletion allele and the deletion/deletion genotype are associated with persistent HBe antigenemia in chronic hepatis B infection. Hum Immunol 2017;78:166–71.
[16] Laaribi AB, Zidi I, Hannachi N, et al. Association of an HLA-G 14-bp Insertion/Deletion polymorphism with high HBV replication in chronic hepatitis. J Viral Hepat 2015;22:835–41.
[17] Simoes RT, Goncalves MA, Castelli EC, et al. HLA-G polymorphisms in women with squamous intraepithelial lesions harboring human papillomavirus. Mod Pathol 2009;22:1075–82.
[18] Xu HH, Shi WW, Lin A, et al. HLA-G 3' untranslated region polymorphisms influence the susceptibility for human papillomavirus infection. Tissue Antigens 2014;84:216–22.
[19] DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clin Trials 1986;7:177–88.
[20] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22:719–48.