**HLA-G genetic variants and hepatocellular carcinoma: a meta-analysis**

A.V.C. Coelho¹, R.R. Moura¹, S. Crovella¹ and F. Celsi²

¹Departamento de Genética, Universidade Federal de Pernambuco, Recife, PE, Brasil  
²Institute for Maternal and Child Health, Scientific Institute for Research, Hospitalization and Care Burlo Garofolo, Trieste, Itália

Corresponding author: A.V.C. Coelho  
E-mail: antonio.victor@ufpe.br

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**ABSTRACT.** Human leukocyte antigen (HLA)-G is a key tolerogenic molecule mainly expressed in the placenta and is crucial for implantation of the embryo and immunological tolerance of the fetus during pregnancy. However, under pathological conditions, such as cancer or viral infections, HLA-G can be expressed in other tissues. The gene coding for HLA-G (HLA-G, chromosome 6p21.3) presents numerous polymorphisms, some of them influencing its expression. One of the most studied, is the 14 bp ins/del (rs371194629) situated at the 3'-UTR of the gene. The insertion is thought to stabilize HLA-G mRNA. Different studies have analyzed the role of rs371194629 in hepatic injury, with either hepatotropic virus infection (i.e., HBV or HCV) or hepatocellular carcinoma (also induced by viral infection). Results from these studies are heterogeneous, differing with ethnicity and population age, and the role of rs371194629 is unclear. For these reasons, we decided to perform a meta-analysis of these results,
concluding that the 14-bp ins/del polymorphism does not significantly contribute to hepatic injury.

**Key words:** MHC class I; HLA-G; Liver neoplasms; Genetic polymorphism; Association studies

**INTRODUCTION**

*HLA-G* is a non-classical human leukocyte antigen (HLA) class Ib gene, located at chromosome 6 at position 6p21.3 (Geraghty et al., 1987). The protein possesses immunomodulatory functions that promote tolerance to the semi-allogenic fetus during pregnancy. HLA-G inhibits proliferation and the cytolytic function of cytotoxic T lymphocytes and natural killer cells (Rouas-Freiss et al., 1997; Riteau et al., 1999; Bahri et al., 2006; Caumartin et al., 2007). Furthermore, it can induce apoptosis via Fas/FasL (Fons et al., 2006) and differentiation of CD4+ regulatory cells (LeMaoult et al., 2007).

Under physiological conditions, HLA-G is expressed only in few cell types: trophoblasts (Kovats et al., 1990), cornea cells (Le Discorde et al., 2003), and erythroid and endothelial cells (Menier et al., 2004). Under pathological conditions, tumors (Urosevic and Dummer, 2003) and tissues affected by autoimmune diseases (Rosado et al., 2008) and viral infections (Lozano et al., 2002) may express HLA-G.

*HLA-G* mRNA levels are finely regulated by its complex promoter and terminal regions. Therefore, sequence variations in both areas could modify gene expression. For example, the single nucleotide polymorphism (SNP) rs1233334 (-725C/G/T) is located at the end of an interferon-sensitive response element motif and the -725 G allele creates a CpG site, which when methylated can inhibit transcription. Moreover, at the 3'-UTR, a 14-bp ins/del has been widely reported as causing mRNA instability (rs371194629) (Rousseau et al., 2003). The presence of a G allele at rs1063320 (3142C>G) is known to increase the site affinity for microRNA, favoring mRNA degradation (Tan et al., 2007). Being upstream of an AU-rich motif involved in mRNA degradation, the A allele at rs9380142 (3187A>G) decreases HLA-G expression (Yie et al., 2008). Specifically, the 14-bp ins/del has been the subject of numerous studies, first in spontaneous abortion investigations (Yan et al., 2006; Xue et al., 2007) then in autoimmune disease (Lee et al., 2015), viral infections (da Silva et al., 2014) and cancer (Li et al., 2015). Since HLA-G function is quite pleiotropic, the role of the 14-bp ins/del varies and depends on the pathology under scrutiny.

Viruses have been the subject of evolutionary pressure to avoid host immune system responses. One of the mechanisms that have been developed is increasing expression of HLA-G, either directly or indirectly by inflammatory milieu caused by viral infection. HLA-G expression has been analyzed in different chronic viral infections: human immunodeficiency virus, human papillomavirus, human cytomegalovirus, and hepatitis B/C virus (HBV/HCV) (Catamo et al., 2014). Specifically, the latter two viruses are involved in chronic liver injury that could be followed by malignant transformation (hepatocellular carcinoma). Increased expression of HLA-G has been associated either with HBV infection, via increased viral load (Souto et al., 2011), or HCV infection (Weng et al., 2011). Moreover, in early stages of HCV-associated liver infection, both soluble and membrane bound HLA-G protein production are increased (de Oliveira Crispim et al., 2012; Amiot et al., 2014). It is also possible that the presence of HLA-G expression in the context of HBV and HCV infections could favor virus
spread, but in early phases of chronic injury, it could have a protective effect.

Given the different studies on the role of HLA-G and HLA-G genetic variations in chronic hepatitis and HBV/HCV infection, we decided to perform a meta-analysis on the role of a 14-bp ins/del polymorphism (the most studied HLA-G genetic variations as reported in the literature) in hepatitis and hepatocellular carcinoma.

**MATERIAL AND METHODS**

**Literature search strategy and study selection**

We searched hepatitis and hepatocellular carcinoma (HCC) literature, paying special attention to genetic association studies analyzing the HLA-G 3'-UTR 14-bp indel polymorphism. Full texts were searched through the PubMed database (www.ncbi.nlm.nih.gov/pubmed) using these key words: “hla-g polymorphisms hepatitis” or “hla-g polymorphism hcc”. After full-text retrieval, we incorporated in the analysis all the studies attending to the following inclusion criteria: be an observational genetic association study that includes patients with HCC or chronic hepatitis due to viral infections. We excluded reviews and studies that analyzed genetic variations in more than one non-classical HLA (to avoid confounding effects).

Data about each study are summarized in Table 1, including country of origin of the sampled individuals and ethnicity, study sample size, male/female ratio in cases, mean age, type of infection (HBV or HCV), and concurrent diseases prevailing in the sampled individuals.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Sample size</th>
<th>Male/Female ratio in cases</th>
<th>Mean age (SD)</th>
<th>Type of infection</th>
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<td>Cordero et al., 2009</td>
<td>Brazil</td>
<td>21</td>
<td>72</td>
<td>1/1</td>
<td>27.3</td>
<td>HCV</td>
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<td>China</td>
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<td>Kim et al., 2013</td>
<td>Korea</td>
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<td>da Silva et al., 2014</td>
<td>Brazil and Italy</td>
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*Standard deviation (SD). *Both cases and controls present sickle-cell disease. *Not reported (NR) by the authors. *HCC present only on cases. *HCC present in both HBV-infected and HCV-infected patients. *Brazilian individuals with European-descendant ethnicity. *Brazilian individuals with African-descendant ethnicity. *Italian individuals. The listed studies were included in a random-effect model meta-analysis.

**Statistical analysis**

The adherence of allelic frequencies to the Hardy-Weinberg equilibrium for the case and control groups was assessed by χ² tests. Odds ratios (OR) were calculated for each genetic association study included in the analysis through 2 x 2-contingency tables, which distributed 3'-UTR 14-bp indel allelic counts in cases (individuals with hepatitis or HCC) versus controls (individuals with no hepatitis or HCC).

A meta-analysis was performed with all included data to obtain a pooled OR representing the overall measure of association of HLA-G indel alleles with hepatitis or HCC. The meta-analysis was performed by using the R software version 3.1.1.
Heterogeneity between studies was quantified by the I² measure, which is a transformation of the τ² statistic and estimated by the DerSimonian and Laird method (DerSimonian and Kacker, 2007). The Cochran’s Q-test with n-1 degrees of freedom (in which n is the number of studies included) was used to assess if heterogeneity was significantly different from zero. For this test only, significance level was set at 0.10 (α = 0.10), as recommended by the literature, since this test is prone to yield false-negative conclusions (Higgins et al., 2003). For all remaining analysis, a significance level of 0.05 (α = 0.05) was assumed. If heterogeneity was to be deemed significantly different from zero, a random-effect model was assumed (OR pooling by inverse variance weighting). A fixed-effect model was chosen if no heterogeneity was detected (OR pooling by Mantel-Haenszel method) (Mantel and Haenszel, 1959). Ninety-five percent confidence intervals (95%CI) were calculated for each included OR and the final pooled OR. The t-test was used to calculate the associated P value for the pooled OR. Presence of publication bias, commonly defined as disproportional preference for positive association results over no association reports (Rothstein et al., 2006), was assessed using the Egger test.

HLA-G 14-bp indel polymorphism across populations

As a side analysis, we evaluated HLA-G 14-bp indel polymorphism frequency distribution across selected populations from the 1000 Genomes database (1000 Genomes Project Consortium et al., 2012) to assess if different genetic backgrounds could influence the results of genetic association studies performed in diverse populations.

We downloaded HLA-G 14-bp indel polymorphism (rs371194629) genotypes from eight populations deposited in the 1000 Genomes database. These populations came from similar geographic backgrounds to the samples included in the meta-analysis. Two came from East Asia (Han Chinese in Beijing, China - CHB and Japanese in Tokyo, Japan - JPT), one from European descendants [Utah (USA) residents (CEPH) with Northwestern European Ancestry - CEU], one from Africa (Yoruba in Ibadan, Nigeria - YRI), and four admixed populations from Latin America (Colombians from Medellin, Colombia - CLM; Mexican ancestry from Los Angeles, USA - MXL; Peruvians from Lima, Peru - PEL; and Puerto Ricans from Puerto Rico - PUR). Then, we calculated allele frequencies in the control samples and the 1000 Genomes reference populations through direct genotype counting and compared the populations’ diversity through pairwise Wright’s fixation index (FST) computed with a locally developed algorithm. We assumed FST values lower than 0.05 to represent low genetic divergence; values between 0.05 and 0.15 indicated moderate divergence; values between 0.15 and 0.25 indicated large divergence; and values greater than 0.25 meant very large divergence (Wright, 1951).

RESULTS

The literature search produced six genetic association studies evaluating HLA-G 3’-UTR 14-bp indel polymorphism association with hepatitis. Cordero et al. (2009) recruited HCV-infected individuals with sickle-cell disease from Brazil; Jiang et al. (2011) sampled HBV-infected subjects with HCC from China; Kim et al. (2013) sampled Korean individuals with chronic HBV infection and HCC; Teixeira et al. (2013) sampled both HBV- and HCV-infected Brazilian patients; da Silva et al. (2014) sampled HIV-HCV co-infected Brazilian and Italian subjects; and Laaribi et al. (2015) recruited HBV-infected Tunisian subjects. Since the
study of da Silva et al. (2014) sampled three distinct ethnic groups, we considered them as three independent sampling events, so they were stratified and included in the meta-analysis separately.

The meta-analysis included a total of 1114 cases and 1644 controls. No deviations from Hardy-Weinberg equilibrium were observed for HLA-G 3'-UTR 14-bp indel allelic frequencies in both cases and controls. Table 1 summarizes the study characteristics as reported by the authors.

The heterogeneity estimated by the DerSimonian and Laird method was significantly different from zero, as suggested by the Cochran’s Q-test result ($I^2 = 72.4%$; $Q = 25.3$ with degrees of freedom = 7 and $P = 0.0007$). Thus, a random-effect model was assumed. The individual ORs from all genetic association studies included in the meta-analysis were pooled, resulting in a summary OR. The $t$-test suggested that the 14-bp insertion allele might not influence susceptibility to hepatitis or hepatocellular cancer occurrences (pooled OR = 1.05; 95%CI = 0.76-1.43; $t = 0.34$ and $P = 0.75$). The Egger test showed no evidence for publication bias (test statistic = 0.89, $P = 0.37$). The meta-analysis results, including OR and 95%CIs from each study, are summarized in Figure 1. The sensitivity analysis revealed no bias by removing any study from analysis or from sampling stratification, as detailed above.

The $F_{ST}$ analysis indicates an overall genetic uniformity across worldwide populations, with the possible exception of Asian-origin samples. The Asian populations had the lowest minor allele frequencies (MAF) of the 14-bp ins allele. The Chinese sample (Jiang et al., 2011) had an MAF = 0.29, whereas the Korean (Kim et al., 2013) had an MAF = 0.18. The 1000 Genomes JPT reference sample had an MAF = 0.25. In contrast, all the remaining non-Asian samples had MAF > 0.30, with a mean frequency of 0.40 (whereas the Asian samples had a mean of 0.24) and a range between 0.33 in CLM and YRI to 0.49 in the Tunisian sample (Laaribi et al., 2015) (Table 2).

![Figure 1](image.png)

**Figure 1.** Forest plot of individual odds ratios (OR), individual 95% confidence intervals (95%CI), and pooled ORs from a random-effect model meta-analysis involving association studies examining the 14-bp ins/del polymorphism (rs371194629) in the 3'-UTR of HLA-G and its relation to hepatocellular carcinoma.
### Table 2. Pairwise comparison of HLA-G 3’-UTR ins/del polymorphism (rs371194629) 14-bp ins allele in the studies selected for meta-analysis (control samples only) and in reference populations from 1000 Genomes database.

<table>
<thead>
<tr>
<th>MAF (14-bp ins allele)</th>
<th>Cordoro et al., 2009</th>
<th>Jung et al., 2011</th>
<th>Kam et al., 2013</th>
<th>Teneva et al., 2013</th>
<th>da Silva et al., 2014 (1)</th>
<th>da Silva et al., 2014 (2)</th>
<th>da Silva et al., 2014 (3)</th>
<th>Laaribi et al., 2015</th>
<th>CEU</th>
<th>CHB</th>
<th>JPT</th>
<th>YRI</th>
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CEU = Utah Residents (CEPH) with Northern Western European Ancestry; CHB = Han Chinese in Beijing, China; JPT = Japanese in Tokyo, Japan; YRI = Yoruba in Ibadan, Nigeria; CLM = Colombians from Medellin, Colombia; MXL = Mexican Ancestry from Los Angeles, USA; PEL = Peruvians from Lima, Peru; PUR = Puerto Ricans from Puerto Rico. $F_{ST}$ values lower than 0.05, low genetic divergence; values between 0.05 and 0.15, moderate divergence; values between 0.15 and 0.25, large divergence; and values greater than 0.25, very large divergence. Bold italic values represent $F_{ST}$ values >0.05.
Therefore, the $F_{ST}$ indexes revealed a small but significant ($0.05 > F_{ST} > 0.09$) presence of genetic diversity when comparing the Korean (Kim et al., 2013) sample to some of the other non-Asian admixed samples, namely the reference MXL sample and Brazilian samples (Cordero et al., 2009; Teixeira et al., 2013; da Silva et al., 2014). In contrast, all non-Asian samples and the Chinese sample (Jiang et al., 2011) had very low pairwise $F_{ST}$ indexes ($F_{ST} < 0.05$) when compared (Table 2).

These results may point to true non-classical major histocompatibility complex differences in some Asian populations in relation to other populations (namely lower frequencies of the 14-bp ins allele), but since we are analyzing a single HLA-G locus, we cannot speculate any further. However, the observed overall diversities were very small.

**DISCUSSION**

The meta-analysis data presented here argue against a possible role of rs371194629 (14-bp ins/del) in chronic hepatic injury or HCC. Indeed, the association studies examined in this analysis did not provide a very strong correlation between the 14-bp ins/del and hepatitis or HCC. Moreover, in some cases, the 14-bp ins allele appeared to be protective, while in other cases, this allele was associated with risk. Our analysis demonstrates that the 14-bp ins/del polymorphism and whichever allele is present do not provoke any significant overall effect. It is possible that the functional effect of the rs371194629 SNP depends on ethnicity; however, our analysis suggests that there is little variation in rs371194629 locus distribution among non-Asian populations. This reinforces our conclusions that the allele has little influence over hepatitis or HCC, since the meta-analysis would not be biased by ethnicity in this case.

Regarding Asian populations, a study published in 2014 found a significant association between the presence of the ins/ins genotype and breast cancer susceptibility in this demographic (Ge et al., 2014). HLA-G pathological expression is well correlated to HCC. As an example, Cai et al. (2009) found that HLA-G expression was negatively associated with patient survival and time between relapses, suggesting that HLA-G could worsen the HCC outcome. This study was subsequently confirmed and extended by two studies in the following years (Lin et al., 2010; Wang et al., 2011), confirming once more that increased HLA-G levels appear to be detrimental towards patient survival. Thus, the role of HLA-G in HCC appears to be important albeit unrelated to the 14-bp ins/del allele, and much more research has to be done to better elucidate how HLA-G could influence survival in cancer. The 14-bp ins allele generates a more stable HLA-G mRNA (Rousseau et al., 2003) it could be hypothesized that this polymorphism has a role in HCC. However, our analysis shows that this is not the case; other mechanisms are probably taking place, such as promoter strength through epigenetic modulation or mRNA stability regulated by miRNA (Catamo et al., 2014).

In conclusion, our meta-analysis demonstrates that the 14-bp ins/del probably has no role in chronic hepatitis or HCC, and stimulates other research towards different HLA-G polymorphisms or even other genetic factors, which could lead to the discovery of markers with more impact and better diagnostic potential. Further association analysis and review are needed to pinpoint such genetic variants, potentially revealing data that could be useful for diagnostic procedures.

**Conflicts of interest**

The authors declare no conflict of interest.

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