Research article

Variation of HLA class I (-A and -C) genes in individuals infected with hepatitis B or hepatitis C virus in Cameroon

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ARTICLE INFO

Keywords:
Cell biology
Immunology
Clinical genetics
Genetics
Molecular biology
HLA
HBV
HCV
Association study
Cameroon

ABSTRACT

The Human Leucocyte Antigens (HLA) work in concert with other immune factors to modulate immunity to viral infections. Extensive variation has been reported in the genetic sequences and functions of classical HLA class I genes in many (mostly Western) populations, and several HLA associations with infectious disease outcomes have been reported. Little is known about their role in the susceptibility or resistance to hepatitis viruses in Central African populations. The aim of this study was to determine variants of two HLA class I genes (HLA-A and -C) in adults infected with hepatitis B (HBV)- or -C (HCV) virus in Cameroon.

In this case-control study, a total of 169 unrelated adults comprising 68 HCV-infected, 38 HBV-infected and 63 uninfected (controls) individuals participated. Each consented participant was screened for HBV, HCV, and HIV infections and willingly donated a single blood sample for genomic DNA isolation and some clinical laboratory tests. HLA-A and HLA-C were genotyped using previously described sequence-based techniques (SBT).

A total of 54 HLA alleles were identified in the study population (27 HLA-A and 27 HLA-C). HLA-A*23:01 and HLA-C*07:01 were the most common alleles with genotype frequencies of 31.4% and 29.3%, respectively. Hepatitis individuals were six times more likely to be HLA-A*30:01 carriers than uninfected controls (OR = 6.30, p = 0.020 (HBV); OR = 6.21, p = 0.010 (HCV), respectively). Similarly, carriers of HLA-C*17:01 were over-represented in the HBV-infected compared to the uninfected control group (21.9% vs. 6.4%, respectively) suggesting that this allele could play a role in the susceptibility to HBV infection.

1. Introduction

Globally, infection with the hepatitis B (HBV) and hepatitis C (HCV) viruses are the leading causes of liver-related morbidity and mortality (Mohd Hanafiah et al., 2013; Mortality & Causes of Death, 2016; Rao et al., 2015). In 2015, it was estimated that 257 million and 71 million people were living with chronic HBV and HCV infections, respectively (WHO, 2017), the majority of whom are in resource limited regions such as the sub-Saharan Africa (SSA). Little is known about the burden of these infections in the Central Africa sub region and even less so in Cameroon. However, some recent reports have shown that the prevalence of HBV amongst pregnant women in some regions of Cameroon ranges from 5.7% to 7.7% (Eyong et al., 2019; Fomulu et al., 2013; Torimiro et al., 2006), while that of HCV amongst young adults and the elderly ranges from 0.8% to 6.5% (Bigna et al., 2017; Njouom et al., 2018; Rodgers et al., 2019). Although more than 90% of children in the developing world will become exposed to the hepatitis B virus at some stage of their lives, only about 5% will remain chronically infected in adulthood.

https://doi.org/10.1016/j.heliyon.2020.e05232
Received 1 July 2020; Received in revised form 10 September 2020; Accepted 8 October 2020
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Factors associated with chronicity following HBV infection are not fully understood but available data show that chronic hepatitis B infection can lead to irreversible end organ damage with complications such as cirrhosis and hepatocellular carcinoma, commonly observed among those who acquire infection during childhood (Alward et al., 1985; McMahon et al., 1985). On the other hand, approximately 70–80% of HCV-infected persons develop chronic infection and 15–30% of them are likely to end up with serious debilitating complications including liver fibrosis, cirrhosis, hepatocellular carcinoma (HCC) or liver failure (Amin et al., 2006; Micallef et al., 2006; WHO, 2017). Of the many factors previously implicated with the clearance or chronicity of viral Hepatitis B and C (Aisyah et al., 2018; Akuta et al., 2019; Alric et al., 2016; Bulteel et al., 2016; Chang et al., 1989; Ferreira et al., 2014; Grebely et al., 2007; Isaiguants and Ozeretskaya, 2003; Kong et al., 2014; Micallef et al., 2006; Morsica et al., 2019; O’Brien et al., 2019; Perez-Cano et al., 2002; Singh et al., 2007; Thomas et al., 2009; Wang et al., 2007; Yan and Wang, 2017) and disease progression, the host immunogenetic factors affecting components of the innate and adaptive immune system that modulate host-viral interactions are key players (Alric et al., 2000; Isaiguants and Ozeretskaya, 2003; Kummee et al., 2007; Singh et al., 2007). However, these factors including those of the Human Leucocyte Antigens (HLA) system are yet to be fully elucidated in African cohorts, where both the burden of infection and HLA diversity are greatest.

HLA in humans comprises a complex set of hyper polymorphic genes, located within an approximately 3.6Mbp region of the short arm of human chromosome 6 (6p21.31) (Beck and Trowsdale, 2000) that encodes cell-surface molecules making up part of the innate and adaptive immune response system. The HLA molecules interact with the Killer Cell immunoglobulin-like Receptor (KIR) molecules on the surface of Natural Killer (NK) cells to modulate both innate and adaptive immune responses to self and non-self-peptides (like those derived from microorganisms). They also play a key role in presenting epitope peptides from intracellular organisms to Cytotoxic T lymphocytes (CTL). The HLA genes are divided into three classes – I, II and III – with classes I and II known as the “classical HLA genes” which are naturally highly polymorphic. To date, there are 26,214 (19,031 HLA class I and 7,183 HLA class II) alleles in the Immuno-Polymorphism (IPD-IMGT/HLA) Database (release 3.39.0 of January 20th 2020) (Robinson et al., 2020). The HLA class I region is made up of 19 gene loci but only three are classical genes (HLA – A, -B and –C) with 8 exons each. Exons 2 and 3 are highly polymorphic and encode the peptide binding groove (Shiina et al., 2009).

Recent studies have demonstrated the heterogeneity of HLA class I genes in Cameroonian populations (Ellis et al., 2006; Spinola et al., 2011; Torimiro et al., 2006) consistent with their diverse ethnic backgrounds. Although a number of studies have associated HLA class I genes with both beneficial and deleterious effects on viral infection including HBV and HCV (Khakoo et al., 2004; Singh et al., 2007; Thio et al., 2003; Vanzuela-Ponce et al., 2018; Yindom et al., 2010), there is a paucity of data from African populations with regards to the role of HLA diversity in chronic hepatitis B or C infections. The objectives of this study were to determine and describe the level of HLA-A and -C diversity in a sample of Cameroonian population chronically infected with hepatitis B or C viruses. The authors also wanted to compare the frequency of specific HLA allotype with that observed in the general population recruited in the same setting as the hepatitis cases. The overall aim was to investigate any relationship between HLA alleles and chronic hepatitis caused by HBV and HCV in adult Cameroonians.

2. Materials and methods

In this cross-sectional case-control study, 169 unrelated adults consented to participate and were recruited by convenience sampling from two hospitals in Douala and Yaoundé in Cameroon. Each participant donated a single blood sample that was tested for HBV, HCV and HIV infections and genomic DNA extraction. Those that tested positive for either the HBsAg or HCV Antibodies but negative for HIV were recruited as cases, while those that tested negative for all three viruses accepted to participate as population controls. HIV-positive and hepatitis dually infected individuals were excluded from the study. This study was approved by the Cameroonian National Ethics Committee for Human Health Research. A structured questionnaire was used to collect participants demographic information including age, sex, marital status and profession.

Screening for HIV, HBV and HCV were done using rapid diagnostic test kits [Determine HIV-1/2 SET (Alere Medical Co, Ltd, Japan) and OnSite HBsAg and OnSite HCV Combo kits (CTK BIOTECH, CA, USA)]. Serological detection of the Hepatitis B envelope Antigen and Antibodies (HBsAg and Anti-HBe) was done using a commercial ELISA kit (Bio-merieux Clinical Diagnostics, Geneva, Switzerland).

Plasma load of HBV DNA and HCV RNA were determined using the Abbott Real Time PCR (Abbott Molecular Diagnostics, Wiesbaden, Germany). Genomic DNA was extracted using the QIAamp DNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer’s instructions. HLA-A and HLA-C sequencing was performed using locus specific primers and the Big Dye Terminator Version 3.1 cycle sequencing kit (Applied Biosystems, Foster City, CA) in ABI 3130XL DNA Analyser (Applied Biosystems, Foster City, CA) as previously described (Yindom et al., 2010).

Allele and genotype frequencies were computed using IBM SPSS Statistics for windows, v25 (IBM Corp., Amonk, NY), and Stata, v14.1 (Stata Corp., College Station, TX). Comparisons of allele and genotype frequencies between groups were performed using either Chi -square test, Fisher exact test, or independent samples t-test as may be appropriate and p < 0.05 was considered statistically significant after Bonferroni correction for multiplicity testing. Hardy-Weinberg Equilibrium (HWE) and haplotype analysis were performed using the Arlequin Software version 3.5.2.2 (Excoffier and Schneider, 2005).

3. Results

3.1. Participant characteristics

Table 1 shows the demographic characteristics of the study participants. Thirty-eight participants tested positive for HBsAg and 68 for HCV antibodies and the remainder 63 tested negative for all three viruses (Controls). Males were overrepresented in the HBV infected group 33/38 (86.8%) while the majority of HCV infected participants were females 44/68 (64.7%). In the control group, however, the proportion of male to females was significantly over-represented in the HBV infected and HIV-, HBV- and HCV- uninfected control individuals. The Hardy-Weinberg Equilibrium test was used to classify HBV infected participants according to the American Association for the Study of Liver Diseases (AASLD) as illustrated in Table 2. Eighteen (47.4%) were in the inactive chronic hepatitis phase while 19/38 (50.0%) were in the immune reactivation phase.

3.2. HLA distribution and association with hepatitis B or C virus infections

A total of 54 HLA alleles (27 for each locus) were identified in the study population. The most frequent was HLA-A*23:01 (31.4%) (Table 3), followed by HLA-C*07:01 and HLA-C*04:01 at 29.3% and 28.6%, respectively (Table 4). HLA-A*23:01 was significantly over-represented in people with hepatitis compared to uninfected controls (Figure 1). Interestingly, stratifying analysis by disease status revealed that the proportion of male to female was similar: 33 males (52.4%) and 31 females (47.6%). HCV infected participants were significantly older compared to the HBV-infected and HIV-, HBV- and HCV- uninfected control individuals. Historical data was not available for any of the participants but a combination of routine clinical and laboratory data including Fibro test results was used to classify HBV infected participants according to the American Association for the Study of Liver Diseases (AASLD) as illustrated in Table 2. Eighteen (47.4%) were in the inactive chronic hepatitis phase while 19/38 (50.0%) were in the immune reactivation phase.
in the study population with two (HLA-C*03:02 and -C*03:03) at minor allele frequencies (<5%) (Table 4). HLA-C*03:04, however, was over-
Table 4. HLA-C genotype frequency distribution between cases and controls.

| HLA-C alleles | N = 140 | All (%) | N = 47 | Control (%) | N = 93 | Hepatitis (%) | OR | P | 95% CI |
|---------------|---------|---------|--------|-------------|--------|---------------|----|----|--------|
| C*07:01      | 41      | 29.3    | 15     | 31.9        | 26     | 28.0          | 0.83| 0.628|0.38-1.78|
| C*04:01      | 40      | 28.6    | 12     | 25.5        | 28     | 30.1          | 1.26| 0.573|0.57-2.78|
| C*06:02      | 28      | 20.0    | 9      | 19.1        | 19     | 20.4          | 1.08| 0.859|0.45-2.63|
| C*07:02      | 27      | 19.3    | 6      | 12.8        | 21     | 22.6          | 1.99| 0.166|0.74-5.39|
| C*08:02      | 19      | 13.6    | 5      | 10.6        | 14     | 15.1          | 1.49| 0.473|0.50-4.44|
| C*02:10      | 15      | 10.7    | 7      | 14.9        | 8      | 8.6           | 0.54| 0.257|0.18-1.60|
| C*17:01      | 16      | 11.4    | 3      | 6.4         | 13     | 14.0          | 2.38| 0.184|0.64-8.93|
| C*18:01      | 13      | 9.3     | 6      | 12.8        | 7      | 7.5           | 0.56| 0.315|0.17-1.78|
| C*16:01      | 12      | 8.6     | 2      | 4.3         | 10     | 10.8          | 2.71| 0.196|0.56-13.11|
| C*14:03      | 9       | 6.4     | 3      | 6.4         | 6      | 6.5           | 1.01| 0.988|0.24-4.26|
| C*03:04      | 8       | 5.7     | 6      | 12.8        | 2      | 2.2           | 0.15| 0.011|0.03-0.81|
| C*05:01      | 7       | 5.0     | 2      | 4.3         | 5      | 5.4           | 1.28| 0.775|0.24-6.90|
| C*02:02      | 5       | 3.6     | 2      | 4.3         | 3      | 3.2           | 0.75| 0.757|0.12-4.68|
| C*04:07      | 4       | 2.9     | 1      | 2.1         | 3      | 3.2           | 1.53| 0.714|0.15-15.30|
| C*15:05      | 4       | 2.9     | 1      | 2.1         | 3      | 3.2           | 1.53| 0.714|0.15-15.30|
| C*07:27      | 3       | 2.1     | 1      | 2.1         | 2      | 2.2           | 1.01| 0.993|0.09-11.54|
| C*14:02      | 3       | 2.1     | 1      | 2.1         | 2      | 2.2           | 1.01| 0.993|0.09-11.54|
| C*08:04      | 2       | 1.4     | 0      | 0.0         | 2      | 2.2           | -   | -   |       |
| C*12:03      | 2       | 1.4     | 0      | 0.0         | 2      | 2.2           | -   | -   |       |
| C*01:02      | 1       | 0.7     | 0      | 0.0         | 1      | 1.1           | -   | -   |       |
| C*02:27      | 1       | 0.7     | 1      | 2.1         | 0      | 0.0           | -   | -   |       |
| C*03:02      | 1       | 0.7     | 1      | 2.1         | 0      | 0.0           | -   | -   |       |
| C*03:03      | 1       | 0.7     | 0      | 0.0         | 1      | 1.1           | -   | -   |       |
| C*07:04      | 1       | 0.7     | 1      | 2.1         | 0      | 0.0           | -   | -   |       |
| C*07:05      | 1       | 0.7     | 0      | 0.0         | 1      | 1.1           | -   | -   |       |
| C*14:05      | 1       | 0.7     | 0      | 0.0         | 1      | 1.1           | -   | -   |       |
| C*16:07      | 1       | 0.7     | 0      | 0.0         | 1      | 1.1           | -   | -   |       |

Bold indicates HLA allele with significant difference between groups. N: number of individuals, OR: Odds ratio; P value comparing the control group with the hepatitis group. 95% CI: 95% confidence interval.

Figure 1. HLA-A genotype distribution between cases (participants with hepatitis) and controls (uninfected participants). Only HLA-A alleles present in at least four percent of the study populations are represented. Table 3 shows the distribution of all 27 alleles stratified by disease status.

represented in the uninfected control group compared to individuals with chronic hepatitis B and C (12.8% vs. 2.2%, P = 0.010) suggesting that this allele may be protective against hepatitis. Further analysis revealed that individuals with HLA-C*17:01 were four times more likely to be in this allele may be protective against hepatitis. Further analysis revealed that individuals with HLA-C*17:01 were four times more likely to be in the hepatitis B infected group compared to the uninfected control group (OR = 4.11, P = 0.043, 95% CI: 0.93–18.18, Table 6). This wasn’t the case in the HCV group. Each locus was tested for Hardy-Weinberg equilibrium using Arlequin software version 3.5.2.2. Both loci were in equilibrium (p values: 0.075 and 0.445 for HLA-A and -C loci, respectively) (Table 7). A total number of 128 possible two-loci haplotypes were identified, 24 of which had a frequency of at least 1% in this cohort. A^*23:01–C^*05:01 was the most prevalent haplotype with a frequency of 3.7% followed by A^*23:01–C^*03:04 (3.3%) (Table 8).

4. Discussion

Viral hepatitis caused by HBV and HCV is the main driver of chronic liver diseases including cirrhosis and hepatocellular carcinoma (HCC). The mechanisms of pathogenesis employed by these viruses to evade immune surveillance and establish lifelong persistence in humans are still not fully understood. However, host immunogenetic factors together with viral and environmental factors are key players that modulate progression of most viral diseases. Several studies have implicated HLA class I and II diversity at the population level with clearance or persistence of hepatitis virus infection (reviewed in (Crux and Elahi, 2017; Singh et al., 2007)). The interplay between HLA and other immune regulatory cells and molecules to modulate the outcomes of HBV or HCV infection (viral clearance or persistence) is likely to be multifactorial involving a cascade of immune responses and may also be population specific. In this study, authors sought to determine the diversity of HLA class I molecules focussing on HLA-A and HLA-C loci in a sample of adults living in Cameroon with or without hepatitis B or C virus. Those with dual infection (HBV and HCV) or coinfected with HIV were excluded from the study.

Fifty four (54) HLA alleles were identified (27 HLA-A and 27 HLA-C) in this study population of 169 participants, 106 (62.7%) of whom were infected with either HBV or HCV. The most frequent alleles were HLA-A^*23:01 (31.4%), HLA-C^*07:01 (29.3%) and HLA-C^*04:01 (28.6%). These common HLA types have been previously described in other populations in sub Saharan Africa (SSA), and in Cameroon, HLA-A^*23:01, HLA-C^*04:01 and HLA-C^*07, have been reported to be very
common (Ellis et al., 2000; Shepherd et al., 2015; Spinola et al., 2008; Torimiro et al., 2006; Tshabalala et al., 2018; Yindom et al., 2010). In the present study, the number of individuals carrying either HLA-A*30:01 or HLA-C*17:01 was significantly higher in the groups infected with either
HBV or HCV, respectively, suggesting that these alleles may predispose their carriers to acquiring these hepatitis viruses. In fact, carriers of HLA-A*30:01 had equal risk of acquiring either hepatitis B or hepatitis C viruses while carriers of HLA-C*17:01 were more likely to be infected with HBV and not HCV. Conversely, further analyses suggest that one of three HLA-C*03 subtypes - HLA-C*03:04 - is likely to offer some protection against carriage of hepatitis B virus. Thus, whilst certain HLA alleles may protect from infection with hepatitis viruses, others may actually predispose their carriers to HBV and/or HCV infections.

There is a paucity of data on the association of HLA class I genes, hepatitis infection and liver diseases in Cameroon and several countries in SSA. These results confirm the predominant dominant role of the HLA-A locus in the overall host immune responses against DNA viruses (Hertz et al., 2011; Thio et al., 2003). This study reports for the first time that HLA-A*30:01 may have a significant role to play in the acquisition of both hepatitis viruses (HBV and HCV). Hepatitis B and C patients when compared to healthy participants are six times more likely to be carriers of this allele. In contrast, HLA-C*03:04 was found to be significantly more prevalent in controls compared to cases, showing that it might have a protective effect against viral hepatitis. A growing body of reports have documented that different HLA class I alleles including HLA-A*02, HLA-A*03 and HLA-A*31 are differentially associated with either a good or bad effect in the control of viral hepatitis (Crux and Elahi, 2017).

5. Conclusion

These data support the potential role of HLA-A*30:01 and HLA-C*17:01 in the predisposition to viral hepatitis caused by HBV and HCV in this sample of Cameroonian population. These findings add to the current knowledge of the role of HLA-A and HLA-C loci in the control of HBV and HCV infections in SSA and to the available data on HLA class I (HLA-A and –C) diversity in Cameroon. Although this study is of great importance, the authors acknowledge that it had its own limitations including the fact that information on the ethnicity of the study participants was not collected, the use of healthy (uninfected) individuals as controls and the small sample size. The problem of using healthy control subjects in this type of study is that about 80% of people when exposed to HBV for the first time will develop chronicity while the remainder...
spontaneously clears the virus. To overcome this inconstancy in future studies, participants with spontaneous viral clearance should be compared to those with persistent infection (El-Bendary et al., 2019; Fakhir et al., 2018; Neamatalah et al., 2020). Despite the shortcomings of the present study, the analyses of HLA polymorphisms reported herein will provide valuable guide in the design of future studies to: (1) describe the genomic variation of the HLA class I loci and (2) examine whether variations at those loci are associated with chronicity of hepatitis in this and other populations in the sub region. Future studies should consider using a much larger sample sizes from this and other populations in SSA.

Declarations

Author contribution statement

C. Yengo and L. Yindom: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper. J. Torimiro: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper. M. Kowo, B. Tiedieu, H. Luma, M. Dibassa and S. Rowland-Jones: Contributed reagents, materials, analysis tools or data; Wrote the paper. P. Lebon: Performed the experiments; Wrote the paper.

Funding statement

This work was supported by the Chantal Biya International Reference Centre for Research on Prevention and Management of HIV/AIDS (CIRCB), Cameroon, the HIV Research Trust, and the Nuffield Department of Medicine, University of Oxford, United Kingdom.

Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

The authors thank all the individuals who participated in this study.

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