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ORIGINAL ARTICLE

Association of *DRB1*11* and *DRB1*12* alleles of the HLA system with the evolution of the Hepatitis B virus infection in Burkina Faso

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Abstract

Background Hepatitis B Virus (HBV) infection affect all social strata of humanity and in the absence of any management, this infection has a different outcome from one infected person to another. This suggests that there are specific individual factors that influence the outcome of the pathology. Sex, immunogenetics and age of contraction of the virus have been cited as factors that influence the evolution of the pathology. In this study, we looked at two alleles of the Human Leucocyte Antigen (HLA) system to measure their possible involvement in the evolution of HBV infection.

Method and results We conducted a cohort study involving 144 individuals spread over 04 distinct stages of infection and then compared allelic frequencies in these populations. A multiplex PCR was conducted and the data obtained was analyzed using R and SPSS software. Our study revealed a predominance of *HLA-DRB1*12* in our study population without, however, showing a significant difference between *HLA-DRB1*11* and *HLA-DRB1*12*. The *HLA-DRB1*12* proportion was significantly higher in chronic hepatitis B (CHB) and resolved hepatitis B (RHB) compared to cirrhosis and hepatocellular carcinoma (HCC) (p-value = 0,002). Carrying *HLA-DRB1*12* has been associated with a low risk of complication of infection (CHB → cirrhosis; OR 0,33 p-value 0,017; RHB → HCC OR 0,13; p-value = 0,00,045) whereas the presence of *HLA-DRB1*11* in the absence of *HLA-DRB1*12* increased the risk of developing severe liver disease. However, a strong interaction of these alleles with the environment could modulate the infection.

Conclusion Our study shown that *HLA-DRB1*12* is the most frequent and it's carriage may be protective in the development of infection.

Keywords Burkina Faso · HCC · Cirrhosis · HLA · *DRB1 · 11 · DRB1 · 12* · HBV

Introduction

Since the discovery of the hepatitis B virus (HBV) in 1965 [1], there has been an increasing amount of research into how to prevent infection with the virus. Despite this, the virus remains widespread throughout the world and the infection it causes is a global public health problem [2]. According to the World Health Organization (WHO), approximately 2 billion people show signs of contact with the virus [3]. WHO estimates that 296 million people were living with chronic

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hepatitis B infection in 2019, with 1.5 million new infections each year. In 2019, hepatitis B resulted in an estimated 820 000 deaths, mostly from cirrhosis and hepatocellular carcinoma (HCC) [4].

With a wide genetic diversity, HBV infection can have several outcomes. The natural history of HBV infection is thus characterized by a variety of clinical profiles ranging from inactive to active carriage that can be complicated by cirrhosis or hepatocellular carcinoma (HCC), [5, 6] while some people manage to eliminate the virus without having shown any clinical signs. This has been attributed not only to the genetic diversity of HBV but also to individual factors such as gender, age of virus contraction, immune status and co-infection with other viruses [7]. Considering the factors intrinsic to susceptibility to infection, the state of the immune system appears to be the main factor in the resolution or complication of HBV infection. Studies have shown that the intensity of the immune response is proportional to the presentation of major histocompatibility complex (MHC) antigens.

The MHC plays a key role in antiviral defense through antigens presented by infected cells and antigen-presenting cells (APCs). Human leukocyte antigens (HLA) are involved in the regulation of the immune response to foreign antigens and are encoded by a series of closely related genetic loci located on chromosome 6 [8].

Given the central role of HLA molecules in the immune system, several studies have been conducted to see the association between specific HLA alleles and susceptibility to HBV infection. As early as 1979, Kew et al. began investigating the association between histocompatibility antigens and HBV infection [9], and since then, further research has demonstrated that highly polymorphic HLA class I and II genes can affect the ability of HLA molecules to elicit immune responses, thus affecting the outcome of HBV infection [2, 10]. Some polymorphisms in HLA class II genes have been shown to be associated with HBV persistence, and others have been shown to affect seroconversion and progression of infection to liver cirrhosis and HCC from chronic HBV infection [10]. Several studies have established associations of specific alleles with the outcome of pathology [6, 11, 12]. The alleles (*HLA-DRB1*11* and *HLA-DRB1*12*) are mainly studied to understand the factors of evolution of the infection towards severe stages of the disease. However, a clear relationship of these polymorphisms with the course of HBV infection has not yet been established due to inconsistent results from different cohorts.

In Burkina Faso, no study has yet been done on the impact of polymorphisms of these genes on the outcome of HBV infection. We are conducting this study not only to provide information on the frequency of carriage of two alleles (*HLA-DRB1*11* and *HLA-DRB1*12*) of the HLA system in the HBV-infected population of Burkina Faso but also to investigate their possible involvement in the course of HBV infection.

Materials and methods

Study population

The study involved 144 individuals, 73 women and 71 men, affected by the hepatitis B virus, grouped into four subgroups according to clinical and biological status (Table 1). All participants were recruited either in the gastroenterology department of the Centre Hospitalier Universitaire Yalgado Ouedraogo (CHU-YO); or in the routine laboratory of the Pietro Annigoni Biomolecular Research Center (CERBA); or in the Regional Center of blood transfusion of Ouagadougou.

Inclusion criteria

Chronic hepatitis B subgroup without cirrhosis and without HCC

This group includes all individuals with only a HBV infection, diagnosed more than 6 months ago with HBsAg positivity and whose ultrasound results reveals no liver pathology.

Chronic hepatitis B subgroup with cirrhosis without HCC

These individuals had HBsAg positivity and para/clinical parameters such as hard liver, stellate angiomas, splenomegaly and thrombocytopenia, presence of oesophageal varices, liver dysmorphia, and signs of portal hypertension.

Table 1 population structure

	CHB n(%)	Cirrhosis n(%)	HCC n(%)	RHB n(%)	Total n(%)
Men	18 (12,5%)	18 (12,5%)	23 (15,97%)	12 (8,33%)	71 (49,31%)
Women	24(16,67%)	21 (14,58%)	18 (12,5%)	10 (6,94%)	73 (59,69%)
Total	42 (29,17)	39 (27,08%)	41 (28,47%)	22 (15,28%)	144 (100%)

n number; (%): proportion; *M*: male; *F*: female; *RHB*: resolved hepatitis B; *CHB*: chronic hepatitis B; *HCC*: hepatocellular carcinoma

Chronic hepatitis B with HCC subgroup

In addition to the criteria listed for cirrhosis, these individuals had encephalopathy with liver failure and elevated alphafetoprotein levels.

Resolved hepatitis B subgroup

All HBsAg-negative and CHBAb-positive individuals with undetectable viral load were considered to have resolved their B viral infection.

Extraction of genetic material

DNA was extracted from blood samples taken from the study subjects. The Genomic Pure Link DNA Extraction Mini Kit (INVITROGEN) was used according to the manufacturer's protocol. Extracts were stored at − 20 °C until used for PCR amplification of target alleles.

PCR amplification

PCR for the detection of *HLA-DRB 1*11* and *HLA-DRB 1*12* alleles was performed using the primers described by Ma et al. (Ma et al. 2015) with a slightly adapted modification. Due to the large number and variability of HLA alleles, a pair of primers targeting the *HGF* gene was included in the amplification reaction in order to validate the PCR in case a given sample did not have any of the alleles studied. A multiplex PCR targeting both alleles and the internal control, the Human Growth Factor (*HGF)* gene, was performed with the GeneAmp PCR System 9700 (Applied Biosystem, USA), with a total reaction volume of 25 µL containing 7 µL of molecular biology water; 10µL of 2X mix (EmeraldAmp GT PCR Master Mix); 0.5 µL of each primer pair (Table 2) at a concentration of 0.2 µM and 5 µL of each DNA extract at 10 ng/µL. The amplification program included an activation phase at 94 °C for 10 min, followed by 35 cycles of denaturation series at 94 °C for 60 s, hybridization at 56 °C for 60 s, elongation at 72 °C for 60 s, and finally extension at 72 °C for 7 min.

Table 2 Primers and amplicon size

Alleles	Primers	Amplicon size (bp)
*DRB1*11*	F: 5′GTTTCTTGGAGTACTACGTC3′	176
	R: 5′CTGGCTGTTCCAGTACTCCT3′	
*DRB1*12*	F: 5′ACTCTACGGGTGAGTGTT3′	244
	R: 5′ACTGTGAAGCTCTCCACAG3′	

HGF F: 5′CAGTGCCTTCCCAACCATTCCCTTA3′432
R: 5′ATCCACTCACGGATTTCTGTTGTGTTTC3′

Electrophoretic migration

PCR products were electrophoretically migrated under non-denaturing conditions in a 2% agarose gel in 1X Tris Borate EDTA (TBE) buffer.

Statistical analysis

The data were entered into the Excel spreadsheet and then analysed using R software version 4.0.2 and SPSS software version 20. The parameters were represented by their numbers and frequencies. The comparison of these frequencies was done using the Chi square and Fisher Test at the 5% threshold.

Ethical consideration

Our study received permission from the Regional Health Department of Ouagadougou (DRSC) and the ethics committee institution of CERBA. In addition, free and informed consent from all participants, or the parents/legal guardians for minor subjects was obtained.

Results

Socio-demographic description of the population

The study population consisted of 144 individuals, 73 (50.69%) of whom were women and 71 (49.31%) men. Their ages ranged from 6 to 76 years with an average of 38.5 ± 13.04 years. The average age of the males was 42.14 ± 12.32 years compared to 34.96 ± 12.82 years for the females.

Allelic frequency in the study population

Statistical analysis of the results of our study showed that the *DRB1*12* allele is the most frequent with a proportion of 47.92% against 36.81% for the *DRB1*11* allele (Table 3). No statistically significant difference was observed between the different allele frequencies (p-value $^{>}0.05$). The proportion of individuals [*DRB1*11/12: (-/-)*] carrying neither of the two alleles studied was 36.80%.

The Table 4 shows the allelic distribution according to sex and clinical status in the study population. The frequency of the *DRB1*11* allele was higher in male individuals (45.1%) than in female individuals (28.8%) (P-value = 0.00028). The *DRB1*12* allele had the same frequency in both sexes (47.9%) (P-value > 0.05). The

Table 3 Allelic distribution in population

		M n(%)	F n(%)	Total
*DRB1*11*	(+)	32 (22,22%)	21 (14,58%)	53 (36,80%)
	(−)	39 (27,08%)	52 (36,11%)	
*DRB1*12*	(+)	34 (23,61%)	35 (24,3%)	69 (47,92%)
	(−)	37 (25,69%)	38 (26,89%)	
*DRB1*11/12*	(+/+)	16 (11,11%)	15 (10,42%)	32 (22,22%)
	(±)	16 (11,11%)	6 (4,17%)	22 (15,28%)
	(−/+)	18 (12,5%)	20 (13,89%)	38 (26,39%)
	(−/−)	21 (14,58%)	32 (22,22%)	53 (36,80%)

n number; *(%)* proportion; *M* male; *F* female; (+): presence; (−): absence

frequency of *DRB1*11* was 46.34%, 30.77%, 28.57% and 45.45% in individuals with HCC, cirrhosis, CHB and RHB respectively. The frequency of the *HLA-DRB1*12* allele was significantly higher in individuals with CHB (57.14%) and resolved hepatitis B (77.27%) compared to individuals with HCC (39.02%) and cirrhosis (30.77%) (p-value = 0.002). In RHB individuals, the frequency of carrying both alleles was significantly higher compared to individuals with HCC, cirrhosis and CHB (p-value = 0.013). The frequency of individuals with only the *HLA-DRB1*12* allele was higher in individuals with a resolved B virus infection. The frequency of the *HLA-DRB1*11* allele was higher in individuals with HCC.

Association of the carriage of both alleles with the progression of the infection to the severe stages

No significant difference was observed between chronic hepatitis B and cirrhosis for *DRB1*11* allele carriage. The *DRB1*12* allele was more observed in CHB than in individuals with cirrhosis (OR = 0.33; 95%CI = 1.20–7.48; p-value = 0.017) (Table 5).

Individuals with chronic hepatitis B and carrying the *DRB1*11* allele in the absence of the *DRB1*12* allele showed an approximately sevenfold increased risk of developing hepatocellular carcinoma as a result of their chronic HBV infection compared to carrying the other allelic combinations. (OR = 7.33; 95%CI = 1.51–31.56; p-Value = 0, 0056).

Association of carrying both alleles with remission of infection

The Table 6 shows the frequency of the *DRB1*11* and *DRB1*12* allelic combinations in the chronic hepatitis population compared to the RHB population with the corresponding Odds Ratios and Confidence Intervals. Individually, no significant difference in the frequency of the two alleles was observed within the populations considered. Similarly, no statistically significant difference was observed for the carriage of a single allele or both (Table 6).

Table 4 Allelic distribution by sex and clinical status

		M(%)	F(%)	p-value
*DRB1*11*	(+)	45,1	28,8	0,00028
	(−)	54,9	71,2	
*DRB1*12*	(+)	47,9	47,9	0,67
	(−)	52,1	52,1	
*DRB1*11/12*	(+/+)	22,5	20,5	0,76
	(±)	22,5	8,2	
	(−/+)	25,4	27,4	
	(−/−)	29,6	43,8	

Clinical status

		HCC *n* (%)	Cirrhosis *n* (%)	CHB *n* (%)	RHB n (%)	p-Value
*DRB1*11*	(+)	19 (46,34)	12 (30,77)	12 (28,57)	10 (45,45)	> 0,05
	(−)	22 (53,66)	27 (69,23)	30 (71,43)	12 (54,55)	
*DRB1*12*	(+)	16 (39,02)	12 (30,77)	24 (57,14)	17 (77,27)	0,002
	(−)	25 (60,98)	27 (69,23)	18 (42,86)	05 (22,73)	
*DRB1*11/12*	(+/+)	08 (19,51)	05 (12,82)	10 (23,81)	08 (36,36)	0,013
	(±)	11 (26,83)	07 (17,95)	02 (4,76)	02 (09,09)	
	(−/+)	08 (19,51)	07 (17,95)	14 (33,33)	09 (40,91)	
	(−/−)	14 (34,15)	20 (51,28)	16 (38,10)	03 (13,64)	

n number; (%): proportion; *M* male; *F* female;(+): presence;(−): absence; *RHB* resolved hepatitis B; *CHB* chronic hepatitis B; *HCC* hepatocellular carcinoma; *OR* odds ratio; *CI* confidence interval

Table 5 Association of DRB1*11 and DRB1*12 allele carriage with negative HBV outcome

		Cirrhosis	CHB	CHB vs Cirrhosis		
		Cas n (%)	Controls n (%)	OR	IC	p-value
*DRB1*11*	(+)	12 (30,77)	12 (28,57)	1,11	0,43–2,88	> 0,05
	(−)	27 (69,23)	30 (71,43)			
*DRB1*12*	(+)	12 (30,78)	24 (57,14)	0,33	0,13–0,87	0,017
	(−)	27 (69,23)	18 (42,86)			
*DRB1*11/12*	(+/+)	05 (12,82)	10 (23,81)	0,47	1,14–1,57	> 0,05
	(±)	07 (17,95)	02 (4,76)	4,37	0,85–22,53	> 0,05
	(−/+)	07 (17,95)	14 (33,33)	0,44	0,15–1,24	> 0,05
	(−/−)	20 (51,28)	16 (38,10)	1,71	0,71–4,14	> 0,05
		HCC	CHB	CHB vs HCC		
		Cas n (%)	Controls n (%)	OR	CI	p-value
*DRB1*11/12*	(+/+)	08 (19,51)	10 (23,81)	0,78	0,27–2,21	> 0,05
	(±)	11 (26,83)	02 (4,76)	7,33	1,51–31,56	0,0056
	(−/+)	08 (19,51)	14 (33,33)	0,48	0,18–1,32	> 0,05
	(−/−)	14 (34,15)	16 (38,10)	0,84	0,34–2,07	> 0,05

n number; (%): proportion; (+): presence; (−): absence; *CHB*: chronic hepatitis B; *HCC* hepatocellular carcinoma; *OR* Odds Ratio; *CI* confidence interval

Table 6 Association of DRB1*11 and DRB1*12 allele carriage with positive HBV outcome

		CHB	RHB	RHB vs CHB		
		Cas n (%)	Controls n (%)	OR	CI	
*DRB1*11*	(+)	12 (28,57)	10 (45,45)	2,08	0,7–6,1	> 0,05
	(−)	30 (71,43)	12 (54,55)			
*DRB1*12*	(+)	24 (57,14)	17 (77,27)	2,55	0,79–8,21	> 0,05
	(−)	18 (42,86)	05 (22,73)			
*DRB1*11/12*	(+/+)	10 (23,81)	08 (36,36)	1,82	0,59–5,61	> 0,05
	(±)	02 (4,76)	02 (09,09)	2	0,26–15,26	> 0,05
	(−/+)	14 (33,33)	09 (40,91)	1,38	0,48–4,02	> 0,05
	(−/−)	16 (38,10)	03 (13,64)	0,26	0,065–1,007	0,042

n number; (%): proportion; (+): presence; (−): absence; *RHB* Resolved Hepatitis B; *CHB* Chronic Hepatitis B; *OR* Odds Ratio; *CI* confidence interval

Association of the carriage of both alleles with the occurrence of cirrhosis and HCC in a resolved B viral infection

The simultaneous absence of the studied alleles in RHB (13.64%) was associated with a 6.67-fold higher risk of progression to cirrhosis (OR = 6.67; 95%IC = 1.69–26-24; p-value = 0.0036). The *DRB1*12* allele was associated with a low susceptibility to progression to *cirrhosis* (OR = 0.13; 95%CI = 0.039–0.44; p-value = 0.00045). The simultaneous presence of *DRB1*11* and *DRB1*12* also appeared to have a protective effect (OR = 0.26; 95%IC = 0.072–0.92; p-value = 0.032) (Table 7).

The presence of the DRB1*12 allele showed a positive association with the evolution of resolved hepatitis. Indeed, individuals carrying this allele were less likely to develop HCC (OR 0.19; 95% 0.06–0.61; p-value 0.0038). Carriers of the *DRB1*11/DRB1*12*$^{+-}$ allele profile were 7.33 times more likely to develop HCC (OR = 7.33 95%IC = 0.73–18.33 p-value = 0.0057) (Table 7).

Probability of progression of HBV infection associated with carriage of *HLA-DRB1*11* and *HLA-DRB1*12* alleles

Figure 1 shows the probabilities of progression of HBV infection in carriers and non-carriers of the *HLA-DRB1*11* and *HLA-DRB1*12* alleles. It shows that in carriers of the

Table 7 Association between DRB1*11 and DRB1*12 allele carriage with the occurrence of cirrhosis and HCC in resolved B viral infection

		Cirrhosis	RHB	Cirrhosis vs. RHB		p-value
		Cases n (%)	Controls n (%)	OR	CI	
*DRB1*11*	(+)	12 (30,77)	10 (45,45)	0,53	0,18–1,57	> 0,05
	(−)	27 (69,23)	12 (54,55)			
*DRB1*12*	(+)	12 (30,78)	17 (77,27)	0,13	0,039–0,44	**0,00045**
	(−)	27 (69,23)	5 (22,73)			
DRB1*11/12	(+/+)	05 (12,82)	08 (36,36)	0,26	0,072–0,92	**0,032**
	(±)	07 (17,95)	02 (09,09)	2,19	0,41–11,59	> 0,05
	(−/+)	07 (17,95)	09 (40,91)	0,31	0,1–1,03	> 0,05
	(−/−)	20 (51,28)	03 (13,64)	6,67	1,69–26,24	**0,0036**
		HCC	RHB	HCC vs RHB		p-value
		Cases n (%)	Controls n(%)	OR	IC	
*DRB1*11*	(+)	19 (46,34)	10 (45,45)	1,04	0,37–2,93	> 0,05
	(−)	22 (53,66)	12 (54,55)			
*DRB1*12*	(+)	16 (39,02)	17 (77,27)	0,19	0,06–0,61	**0,0038**
	(−)	25 (60,92)	5 (22,73)			
DRB1*11/*12	(+/+)	08 (19,51)	08 (6,36)	42	1,51–35,58	> 0,05
	(±)	11 (26,83)	02 (09,09)	7,33	0,73–18,33	**0,0057**
	(−/+)	08 (19,51)	09 (40,91)	0,35	0,11–1,10	> 0,05
	(−/−)	14 (34,15)	03 (13,64)	3,28	0,83–13,03	> 0,05

n: number; (%): proportion; (+): presence;(−): absence; *RHB*: resolved hepatitis B; *HCC*: hepatocellular carcinoma; *OR* odds ratio; *CI* confidence interval

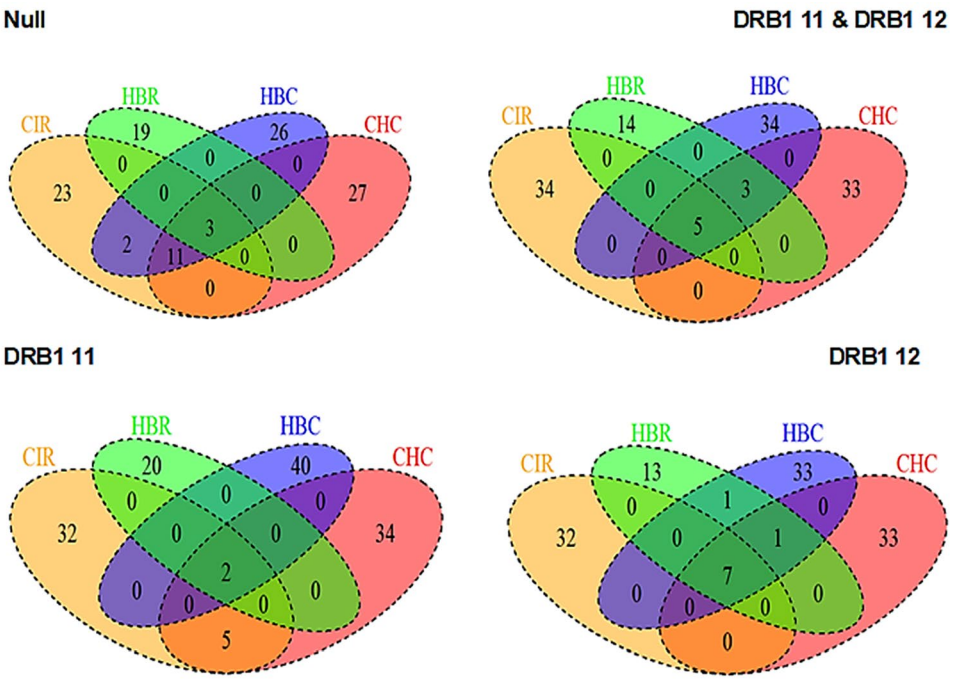

Fig. 1 Venn diagram (probability of progression of HBV infection)

DRB1*11 allele (alone), the probability of an individual with cirrhosis progressing to HCC is 0.06 compared to 0 in the other cases. Carriers of the *DRB1*12* allele with chronic hepatitis B had a 0.016 probability of clearing the virus.

Discussion

Our study involved individuals who are infected with the hepatitis B virus in Burkina Faso and allowed us to estimate the frequency of *DRB1*11* and *DRB1*12* allele carriage in this population. These frequencies were respectively 36.81% and 47.92%. Our results are similar to those of Krishnan et al. (2019) who found a frequency of 41.7% of the *DRB1*12* allele in a Malaysian population. A predominance of this allele was also found by Yang et al., (2007) in a Chinese population (20.8% vs. 16%) [13]. In a study conducted by Ma et al. in 2016 on familial aggregation of hepatocellular carcinoma, the results showed that despite the low frequency of *HLA-DRB1*11* and *HLADRB1*12* alleles in the study population, the frequency of *DBR1*12* (14.58% and 25%) was much higher than that of *DBR1*11* (4.17% and 7.08%) [14].

This study revealed that there was a significant difference in the carriage of the *DRB1*12* allele within the clinical status groups. Carrying this allele was more common in the chronic hepatitis B (57.1%) and resolved hepatitis B (77.3%) groups compared to the other two groups. However, the RHB and CHB groups considered together showed no significant difference. These results corroborate those of Ramezani et al., who showed that there was no significant difference in the *DRB1*12* allele between chronic HBV carriers and cleared individuals in Iran [15].

Persistence or resolution of HBV infection depends on the immune response. Although the mechanism of susceptibility to HBV infection is not well clarified, the results of multiple studies strongly suggest that it is influenced by host immunogenetic factors [16]. Studies to elucidate this phenomenon has shown that the HLA system is involved in the immune response to HBV and that it is an intrinsic factor influencing the course of the infection. HLA genotype is thought to be a genetic factor in predicting the susceptibility of individuals to HBV infection and may be a prognostic factor for disease in certain populations [7]. Furthermore, although the relationship between various clinical manifestations and HLA polymorphic genes has been the subject of several studies, no definite relationship has yet been identified due to inconsistencies in the results; the association being dependent on the populations considered [17]. We characterized the carriage of two alleles (*DRB1*11* and *DRB1*12*) of this system in four distinct population groups (CHB; curved hepatitis B; cirrhosis and HCC) in order to assess their association with the evolution of HBV infection in Burkina Faso.

Our study showed that the *DRB1*12* allele of the HLA system could have a protective effect on the course of HBV infection. The significant difference in the carriage of this allele in curved hepatitis B and CHB compared to the other two groups, which are much more severe stages of infection, suggests a beneficial effect of *HLA-DRB1*12* in the immune management of HBV infection. Furthermore, no significant difference was observed when comparing the frequency of these alleles in CHB and curved hepatitis B. This suggests that the *DRB1*11* and *DRB1*12* alleles have no impact on either viral persistence or clearance in our population. It can therefore be assumed that if *HLA-DRB1*11/*12* carriage is not associated with resolution of the HBV infection in our population, it would at least serve to maintain the infection in a chronic state without any apparent progression to critical stages. Singh et al. in a meta-analysis also established the apparent association of these two alleles with HBV persistence in four racial populations considered (South African, European, Asian, American) [18]. However, these alleles were associated with a clearance of the virus observed in a study carried out on Chinese populations [19]. These differences in the relationship between the alleles and the outcome of the disease could be explained by the relatively small size of our study population on the one hand, and by an epigenetic effect due to the ecological difference between the different study areas on the other.

Comparison of *DRB1*11* and *DRB1*12* frequencies between the CHB population and the cirrhosis and HCC populations revealed that the frequency of *HLA-DRB1*12* was significantly higher in CHBs compared to the other two groups. *DRB1*12* was associated with a low risk of progression to cirrhosis (OR 0.33; p-value 0.017) while no significant association was made with progression from CHB to HCC. This suggests that the *DRB1*12* allele may have a protective effect on the progression of chronic hepatitis to cirrhosis and that individuals carrying the allele are less likely to develop liver cirrhosis. These results are in disagreement with the results found by Chen et al. (2012) who found a significantly higher frequency of cirrhosis (15.05%; p-value 0.036; OR 1.949) and HCC (18.02%; p-value 0.004; OR 2.418) than CHB (8.33%) (Chen 2012) in a Chinese population. Our results were also different from those of Lin et al. who classified *DRB1*12* as a likely genetic candidate for the risk of cirrhosis and HCC in chronic hepatitis B [20]. Several other studies have attributed an elevated risk of HCC to *HLA-DRB1*12* carriage. This variation could be explained by geographical differences and also by the discordance of circulating HBV genotype in the different study areas.

The allelic combination notably *HLA-DRB1*11/DRB1*12*$^{+-}$ has also shown an impact on the evolution

of the pathology. Although the majority of liver cancers develop in cirrhosis, a significant fraction of HBV-related HCC occurs in the context of chronic hepatitis in the absence of cirrhosis [21]. It was associated with a significantly elevated risk of developing HCC from chronic HBV infection (OR 7.33; p-value 0.0056). Comparing the frequencies of the two alleles in the CHB and HCC populations, we found a sevenfold increased risk of developing HCC associated with chronic hepatitis on a non-cirrhotic liver (OR 7.33; 95% CI 1,51–31.56; p-value 0, 0056). This suggests the existence of a factor whose interaction with *HLA-DRB1*11* induces progression from infection to HCC. As the HLA system is polyallelic, this may be due to its association with another allele, but a study of multiple alleles of the system reporting the effect of their interaction is needed to confirm this.

Conclusion

Our study revealed that the *HLA-DRB1*12* allele is more frequent than the *HLA-DRB1*11* allele in the HBV-infected population in Burkina Faso. Carrying this allele was more associated with HBV persistence in our population. There was no association attributable to the effect of the *HLA-DRB1*11* allele. The *HLA-DRB1*12* allele appeared to have a protective effect on the natural history of hepatitis B by maintaining the infection in a chronic state without, however, promoting its progression to severe liver disease. However, *HLA-DRB1*11* carriage in the absence of *HLA-DRB1*12* has been associated with a high risk of developing cirrhosis or HCC. Several factors are involved in the course of HBV infection, and larger sample sizes are needed to better establish the relationship between these alleles and disease outcome. A comparison of HBV genotypes with multiple alleles of the HLA system could be considered.

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Data availability Data will be made available on reasonable request.

Declarations

Conflict of interest The author(s) declare(s) that they have no competing interests.

Ethics approval Our study has received the approval of the Central Regional Direction (DRSC), the national ethics committee in its deliberation number 2022–02-027. In addition, verbal informed consent was obtained from all participants. All the methodology has been performed in accordance with the Declaration of Helsinki.

Consent for publication Not applicable.

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