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Research Article

APOBEC3G Polymorphisms and Implications for a Population with Chronic Hepatitis B Virus in Burkina Faso

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Host factors such as APOBEC3G were associated with hypermutation, which might interfere with HBV replication. The need to assess the impact of APOBEC3G polymorphisms on a hepatitis B-infected population is highlighted by a previous study. Thus, our study aimed to characterize two APOBEC3G single nucleotide polymorphisms and evaluate their association among chronic carriers of hepatitis B in Burkina Faso. Three hundred forty-five (345) individuals were recruited, including 106 HBsAg positive and 239 HBsAg negative. APOBEC3G polymorphisms rs6001417 and rs8177832 DNA genotyping were characterized by TaqMan allelic discrimination. The minor allele G of rs600417 frequency was higher among participants with chronic hepatitis B. Furthermore, rs600417 was associated with the dominant model ($p < 0.05$). Multivariate analysis for chronic hepatitis B risk factors shows that the risk of chronic hepatitis B for genotype CG and GG of rs6001417 seem to be significantly reduced and are, respectively, OR = 0.25 (95% CI 0.09–0.72, $p \leq 0.01$) and OR = 0.08 (95% CI 0.02–0.31, $p \leq 0.001$). In the analysis, the GG genotype of rs8177832 seems to increase the risk of chronic hepatitis B by more than six (6) times, and it was statistically significant OR = 6.41(95% CI 1.74–23.55, $p \leq 0.01$). This study shows that APOBEC3G may be a susceptibility gene for chronic hepatitis B virus carriage in our context. The locus could contribute to the mediation of host native resistance to HBV infection.

1. Introduction

Hepatitis virus infection is a significant public health concern. More than 296 million persons are living with chronic hepatitis B infection. Furthermore, worldwide, there are more than 820,000 deaths resulting from cirrhosis and hepatocellular carcinoma (primary liver cancer) [1]. In Burkina Faso, about 10–14% of the general population is infected with hepatitis B [2]. It is known that HBV is the leading cause of HCC in Africa. About 40% of men and 15% of women who have acquired HBV perinatally have a high risk of dying from liver cirrhosis or hepatocellular carcinoma. Sub-Saharan African countries are paying the highest toll, as hepatocellular carcinoma patients have a younger profile and are potential drivers of the countries' economy and development [3, 4]. The clinical outcome of hepatitis B infection depends on the complex interplay between viral replication and host immune response. Host genetic, viral, and environmental factors are also thought to control disease development, progressions, or regression [5–7]. APOBEC3G (apolipoprotein B messenger-RNA-editing enzyme, catalytic peptide-like 3G) from the APOBEC3

family is a host restriction factor and a single-stranded DNA deaminase that inhibits the replication of viruses having a step of reverse transcription [8]. It was shown that APOBEC3G, 3B, 3C, and 3F could inhibit hepatitis B virus (HBV) replication soon after the discovery of HIV-1 replication inhibition by the same proteins [9–11]. HBV is a double-stranded DNA virus with a reverse transcription step during its replication; APOBEC3G would interact with HBV by deaminating the new negative DNA strand [12, 13]. Furthermore, APOBEC3G was associated with hypermutation, which might interfere with HBV replication [14]. APOBEC3G single nucleotide polymorphisms (SNPs) investigated in this study, rs6001417, and rs8177832, had minor allele G frequencies of 0.37 and 0.34, respectively, among Africans [15]. In Burkina Faso, APOBEC3G polymorphisms such as H186R (rs8177832) and rs6001417 were associated with susceptibility to HIV and coinfection HIV/hepatitis B [16, 17]. The latter study highlighted the need to assess the impact of APOBEC3G polymorphisms on hepatitis B-infected populations. Thus, our study aimed to evaluate the association of two polymorphisms (SNPs) of APOBEC3G among chronic carriers of hepatitis B.

2. Methods

2.1. Participants. This transversal study was conducted on 345 individuals, including 106 HBsAg positive and 239 HBsAg negative recruited between 2012 and 2015 at the St Camille Hospital (HOSCO) and the Pietro Annigoni Biomolecular Research Center (CERBA) in Ouagadougou. Chronicity was determined based on showing a six-month-old record of HBsAg positive test [18].

2.2. Sample collection, HBV serological testing, HCV/HBV/HIV testing, and HBV plasma viral load quantification. Blood samples were obtained by venipuncture and centrifuged to isolate serum from dry tubes and plasma from EDTA-coated tubes. The sera were firstly screened for HBsAg carriage using the ABON RDT test. Secondly, to screen for HIV-1, HBV, and HCV, DNA and RNA were extracted from serum using a Genomic Column DNA Express kit (Sacace Biotechnologies, Como, Italy) according to the manufacturer's instructions. We then used the HCV/HBV/HIV Real-Time PCR kit (Sacace Biotechnologies, Como, Italy), which detects the presence of the three viruses. Hepatitis B viral load was then quantified for the sample that tested positive for HBV thirdly, using the genesig HBV Real-Time Quantitative kit (Primerdesign, Southampton, United Kingdom).

2.3. DNA Extraction and APOBEC3G Polymorphism Genotyping. To genotype for APOBEC3G polymorphisms rs6001417 and rs8177832, genomic DNA was extracted from the whole blood cells using the « DNA Rapid Salting-Out » technic described by Miller et al. [19].

TaqMan SNP assays (ABI, Foster City, CA) were used to determine the different genotypes of rs6001417 and rs8177832 according to the manufacturer's instruction on the 7500 fast Real-Time PCR (Life Technologies, California, USA). Real-time PCR was realized in a total reaction volume of 25 μL which contains 5 μL of DNA (4 ng/μL), 12.5 μL of TaqMan Universal PCR Master Mix (2X), 6.25 μL nuclease-free water and 1.25 μL of SNP mix (40X). The PCR amplification conditions were: one cycle at 95° for 10 minutes and forty cycles of 92° for 15 seconds and 60 for 1 minute. The different polymorphisms for each single nucleotide polymorphism rs8177832 and rs6001417 genotypes are AA (with mutations in A⟶G) and CC (C⟶G), respectively.

Table 1: Baseline characteristics.

		HBsAg positive ($n = 106$)		HBsAg negative ($n = 239$)	
		n	%	*n*	%
Sex	M	57	53.77	56	23.43
	F	49	46.23	183	76.57
Age	≤30 years	81	76.40	139	58.2
	>31 years	25	23.60	100	41.8

2.4. Ethical Considerations. Informed consent forms were obtained from all study participants. The study protocol was approved by the Ethical Committee for Health Research in Burkina Faso (deliberation number 2014-7-086). Participants and participants' guardians gave their free, informed consent. The information collected was anonymous and confidential.

2.5. Statistical Analysis. The Hardy–Weinberg equilibrium was determined using the Power Marker software version 3.25. The SPSS17.0 statistical software (SPSS, Chicago, IL, United States) was used for the data analysis. The mean HBV viral load was calculated among the HBV-positive persons. The baseline characteristics of the study population in terms of sex and age range were determined. We performed a chi-squared test to find significant differences between HBsAg-positive and -negative persons. Furthermore, it was also used to determine the best inheritance model. Binary logistic regression analysis adjusted with the estimates for potential confounders, including age and gender, was carried out. Data were statistically significant when $p \leq 0.05$.

2.6. Results. The study population comprised 232 females and 113 males. The mean age was 29.68 ± 9.18; the age group younger than 30 years was the most representative among HBsAg positive and negative, with 76.40% and 58.2% (Table 1).

The mean HBV viral load reported among chronic hepatitis B carriers is 4.9 10^6 UI/mL. The two single nucleotide polymorphisms are in Hardy–Weinberg equilibrium, as shown in Table 2. The SNPs genotypes frequencies were combined with the results from the logistic regression in Table 2. The genotypes of both polymorphisms rs6001417 and rs8177832 were sought in our study population: for rs6001417, 23.2% of wild-type genotype CC, 50.1% of

Table 2: APOBEC3G genotypic frequencies according to chronic HBsAg status.

SNPs	Genotypes	HBsAg positive $n = 106$ (%)	HBsAg negative $n = 239$ (%)	Crude OR	95% CI	p value
rs6001417	CC	16 (15.10)	64 (26.80)	**1**	—	—
	CG	59 (55.70)	114 (47.70)	**2.07**	**1.10–3.89**	**0.02**
	GG	31 (29.24)	61 (25.52)	**2.03**	**1.01–4.08**	**0.05**
	C	91	242	**1**	—	—
	G	121 (57.07)	236 (49.37)	1.36	0.98–1.89	0.06
	HWEa	0.37	0.78	—	—	—
rs8177832	AA	26 (24.52)	69 (28.90)	**1**	—	—
	AG	59 (55.70)	111 (46.44)	1.41	0.81–2.45	0.22
	GG	21 (19.81)	59 (24.70)	0.94	0.48–1.85	0.87
	A	111	249	**1**	—	—
	G	101 (47.6)	229 (47.91)	0.99	0.72–1.37	0.95
	HWEa	0.49	0.56	—	—	—

HBsAg: hepatitis B virus surface antigen; OR: odds ratio; CI: confidence interval; CC, CG, GG: genotypes of d variant rs6001417; AA, AG, GG: genotypes of variant rs8177832. Bold values highlight statistically significant values, i.e., p-values less or equal to 0.05.

heterozygous CG, and 26.7% of GG genotypes; regarding rs8177832, 27.5% of wild-type genotypes AA, 49.3% of heterozygous AG, and 23.2% of minor allele genotypes GG.

The minor G allele of the polymorphism rs6001417 frequency was higher among HBsAg-positive persons (57.07%) compared to HBsAg-negative persons (49.37%), but it was not statistically significant, OR = 1.36 (95% CI = 0.98–1.89; $p = 0.06$). The heterozygous individuals with CG genotype frequency are higher among HBsAg positive (55.70%) than HBsAg negative (47.70%). The association between the genotype and chronic hepatitis B carriage was statistically significant OR = 2.07 (95% CI = 1.10–3.89; $p = 0.02$). Furthermore, the homozygous individuals for the genotype GG frequency are also higher among HBsAg-positive persons (29.24%) when compared to HBsAg negative persons, and the association between genotype GG and chronic hepatitis B was significant OR = 2.03 (95% CI = 1.01–4.08; $p = 0.05$) (Table 2).

The minor allele G of the polymorphism rs8177832 frequency among HBsAg-positive persons (47.60%) was almost similar to that among HBsAg-negative persons (47.91%). There was no association between the minor allele G and chronic hepatitis B carriage when comparing the two groups, OR $a = 0.99$ (95% CI = 0.72–1.37; $p = 0.95$) (Table 2).

Our results seemed to show that for the association between 2 single nucleotide polymorphisms and HBsAg status, based on the additive, dominant, and recessive models, the most significant genotype inheritance model for rs6001417 was the dominant model: OR = 2.06 (95% CI = 1.12–3.76, $p = 0.02$) (Table 3). No model seems significant for rs8177832.

Multivariate analysis for chronic hepatitis B risk factors shows that individuals over 30 years have almost three times the risk of having chronic hepatitis B, OR $a = 2.91$(95% CI 1.62–5.23, $p \leq 0.001$). Furthermore, it shows that males have a reduced risk of having chronic hepatitis, OR = 0.22 (95% CI 0.13–0 0.37, $p \leq 0.001$). Additionally, the risk of chronic hepatitis B for genotypes CG and GG of rs6001417 seem to be significantly reduced and are, respectively, OR = 0.25 (95% CI 0.09–0.72, $p \leq 0.01$) and OR = 0.08 (95% CI 0.02–0.31, $p \leq 0.001$). In the analysis, AG and GG genotypes of rs8177832 seem to increase the risk of chronic hepatitis B. It was statistically significant for the latter, and respectively OR = 1.33 (95% CI 0.52–3.38, $p \leq 0.55$) and OR = 6.41(95% CI 1.74–23.55, $p \leq 0.01$) (Table 4).

3. Discussion

We report that APOBEC3G is a susceptibility gene for chronic hepatitis B virus carriage, one of the first studies on APOBEC3G in HBV infection in West Africa. The mean age of our study population was 29.68 years, which is similar to the mean age found in the chronic hepatitis B carriers in Wongjarupong et al.'s studies in Burkina Faso [20, 21]. Studies also an important HBV transmission perinatally and during childhood in sub-Saharan Africa and especially in Burkina Faso, which can explain the high number of HBV chronic carriers [18, 20, 22, 23].

The GG genotypes of rs6001417 in the adjusted model reduce the risk of chronic hepatitis B carriage significantly. The polymorphism was most present among the HBV-positive group. This result was comparable to that of Compaore et al. on HIV/HBV coinfected individuals, where mainly the GG genotype was protective [16].

Heterozygous individuals for rs6001417 with genotype CG seemed to have their risk of carriage of chronic hepatitis B increased by two (2) times in the crude model. Still, when adjusted for age and sex, CG seemed to have a protective effect, and the association between genotype a and chronic hepatitis B insignificative OR = 0.25 (95% CI 0.09–0.72, $p \leq 0.01$). Although, in the literature, Qaisar et al. [24] have found a protective effect for the CG genotype on noncarriers of a virus with a retro-transcription step, such as HIV [24].

In this study, which evaluated the associated two polymorphisms (SNP) of APOBEC3G with chronic carriage of hepatitis B, females were the most represented in the population. These results are different than that of Ezzikouri et al. [25], who found in a study on APOBEC3G polymorphisms modulating hepatitis B chronicity in 395 persons in Morocco men. This difference can be explained by the fact

Table 3: Association between APOBEC3G SNPs and status according to the recessive, dominant, and recessive model.

Marker	Model	OR	95% CI	p value
rs6001417	C/G and G/G vs. C/C dominant	**2.06**	**1.12–3.76**	**0.02**
	C/G and C/C vs. G/G recessive	1.21	0.72–2.01	0.47
rs8177832	A/A vs. A/G and G/G dominant	1.25	0.74–2.11	0.40
	A/A and A/G vs. G/G recessive	0.75	0.43–1.32	0.32

OR: odds ratio; CI: confidence interval; CC, CG, GG: genotypes of d variant rs6001417; AA, AG, GG: genotypes of variant rs8177832. Bold values highlight statistically significant values, i.e., p-values less or equal to 0.05.

Table 4: Multivariate analysis of chronic hepatitis B risk factors.

	Category	Adjusted OR	95% CI	p value
Age (years)	**≤30**	—	—	—
	>30	**2.91**	**1.62–5.23**	**≤0.001**
Sex	Female	—	—	
	Male	**0.22**	**0.13–0.37**	**≤0.001**
rs6001417	CC	Reference	—	—
	CG	**0.25**	**0.09–0.72**	**≤0.01**
	GG	**0.08**	**0.02–0.31**	**≤0.001**
rs8177832	AA	Reference	—	—
	AG	1.33	0.52 – 3.38	0.55
	GG	**6.41**	**1.74–23.55**	**<0.01**

Adjusted OR: adjusted odds ratio; CI: confidence interval; CC, CG, GG: genotypes of d variant rs6001417; AA, AG, GG: genotypes of variant rs8177832. Bold values highlight statistically significant values, i.e., p-values less or equal to 0.05.

that women are widespread in health centers in our context especially due to prenatal tests including HBV.

Our results showed that the dominant model was based on the association between 2 single loci and HBV status. The dominant model was the most significant genotype for rs6001417, with G being the minor allele. One copy of an allele G is then enough to produce an effect [26].

When the association of the SNP genotypes is evaluated in an adjusted model for age and sex, the association's orientation changes from an increased risk to a reduced risk of chronic hepatitis. In the case of rs8177832 genotypes in the adjusted model, they increased the risk of chronic hepatitis up to six (6) times. It was statistically significant, although there appeared to be no association when it was evaluated. From these results, age and sex could be confounding factors in our study. Hu et al. also found an inverse association when adjusting for some factors in their research [27]. Unlike the study by He et al., the rs8177832 polymorphism seems to be associated with an increased risk of chronic hepatitis B [28]. This could be due to the difference between the population genetics [29, 30].

Our study has limitations, such as the low number of participants and sex-related parameters. However, it allowed us to see some differences between the two groups of APOBEC3G polymorphism implications in chronic hepatitis B carriage studied, but we could not carry out haplotype analyses. We did not find an association between rs8177832 and HBV chronic carriage in the crude association model. Though, it was found in the adjusted model. These findings may impact the research on APOBEC3G relative to hepatitis B infection.

4. Conclusion

This study shows that APOBEC3G gene polymorphisms might influence chronic hepatitis B virus carriage in our context. The locus could contribute to the mediation of host native resistance to HBV infection. The findings might be used to fight against the evolution of hepatitis B infection to the chronic carriage state, and thus, hepatocellular carcinoma.

Data Availability

The data supporting this study's findings are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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