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The Heterozygous GT Genotype of SNP rs3754217 in the Extracellular Matrix Protein 1 (ECM1) Gene Could Be a Protective Factor against HBV-Related Cirrhosis

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Abstract

Introduction: Hepatitis B virus (HBV) infection remains a major public health problem despite the introduction of a universal HBV vaccination several years ago. Thus, the high endemicity, observed especially in developing countries, particularly in Togo, underlines the urgent need for further research into the mechanisms explaining the diversity of clinical outcomes of HBV in this region. The analysis of genetic factors appears particularly relevant for identifying prognostic markers and for better understanding the progression of this infection to severe forms. This study characterized these extracellular matrix protein 1 (ECM1) gene polymorphisms rs3834087 and rs3754217 and their association with the progression of HBV in Togo. **Methodology:** Genotyping of the ECM1 gene polymorphisms rs3834087 and rs3754217 were performed on 141 participants, including 90 cases (25 with chronic hepatitis B, 41 with cirrhosis, and 24 with hepatocellular carcinoma) and 51 healthy controls, using real-time PCR with the QuantStudio™ 5 Real-Time PCR system. Allelic

discrimination was performed using TaqMan software Genotyper. **Results:** The frequencies of the GAG/GAG, GAG/-, and -/- genotypes of the ECM1 gene polymorphism rs3834087 were 5.67%, 7.80%, and 86.52%, respectively. Furthermore, the frequency of the wild-type GAG allele was 9.57%, while that of the mutated allele was 90.42%. The rs3754217 gene polymorphism exhibited GG, GT, and TT genotype frequencies of 31.91%, 58.86%, and 9.21%, respectively. Its wild-type G allele was 61.34%, while that of the mutated T allele was 38.65%. The results show that a potential protective effect against the progression of a severe infection was associated with the GT genotype of rs3754217 in the subgroup of chronic HBV towards severe forms, including hepatic cirrhosis, with an OR of 0.33 and a 95% CI of 0.10 - 1.03, p = 0.04. **Conclusion:** The present study is the first investigation conducted in Togo to evaluate the association between the ECM1 gene polymorphisms rs3834087 and rs3754217 and the progression of HBV infection. It showed that the GT heterozygous genotype of rs3754217 is associated with protection against the progression of chronic hepatitis B to cirrhosis.

Keywords

HBV, ECM1, Polymorphisms, Liver Cancer, Togo

1. Introduction

Hepatitis B is a viral disease characterized by potentially fatal inflammation of the liver. The hepatitis B virus (HBV) is an enveloped, DNA virus belonging to the *Hepadnaviridae* family [1]. The virus is responsible for its most often acute or even fulminant inflammations, which can either resolve or become chronic. It is a highly endemic disease that poses a major public health problem worldwide: a leading cause of mortality and morbidity [2] [3]. According to the WHO 2020, approximately 296 million people suffer from chronic hepatitis B infection [4]; approximately 820,000 people die each year, primarily from liver cirrhosis or hepatocellular carcinoma (*i.e.*, primary liver cancer) [5].

Chronic hepatitis B infection increases the risk of developing a liver tumor tenfold, thus constituting one of the main risk factors for the occurrence of HCC [6], [7]. In Africa, particularly in sub-Saharan Africa, the prevalence rate of HBV is between 8% and 18%, and it constitutes an area of high endemicity [8]. The prevalence of HBV in the general population in Togo varies between 13% and 16% according to the Global Alliance for Vaccines and Immunization [9]. Bitty-Anderson *et al.* found a prevalence of 9.9% in a study conducted in Lomé [10]. This prevalence was further estimated at 8.76% by Dossim *et al.* in Kara, a city located in the northern region of the country [11].

These findings underscore the high endemicity of the virus in the country [12] despite the implementation, since 2008, of a universal HBV vaccination as part of the Expanded Program on Immunization (EPI). These data highlight the urgent

need to further investigate the mechanisms explaining the diversity of clinical outcomes of HBV in this region. In this context, the analysis of genetic factors appears particularly relevant for identifying prognostic markers and for better understanding the progression of the infection [13]. Studies have revealed that numerous human genes can confer protection or promote the progression of the infection to severe forms of the disease, specifically the *p*53, *RB*1 [14] [15], *GST* [7], [16], *ECM*1 [17], and interleukins (IL6 and IL10) [18].

Indeed, during HBV infection, an infiltration of immune cells occurs, leading to hepatocyte damage [19] [20] and cause extracellular matrix (ECM) deposition, which increases liver tissue damage [21]. The ECM1 protein (85 kDa glycoprotein) exists in two forms (interstitial and basal) and regulates extracellular matrix bonds. Its decrease exacerbates liver fibrosis [22] [23]. Massive remodeling of the interstitial extracellular membrane generally promotes tumor progression, notably by inducing biochemical and biophysical changes affecting cell signaling, cell migration, tumor progression, and extracellular matrix stiffness [24]. The *ECM*1 gene controls tissue remodeling and liver homeostasis, inhibiting fibrogenesis by regulating stellate hepatocytes. These polymorphisms (e.g., rs3754217 and rs3834087) could alter their function, modulating the risk of liver complications in patients with hepatitis B [25]. The rs3834087 gene involves a three-base insertion/deletion (GAG) in ECM1. The rs3754217 gene results from the substitution of guanine (G) for thymine (T) on chromosome 1 [22]. In Togo, the correlation between the *ECM*1 gene polymorphisms (rs3834087 and rs3754217) and the progression of HBV infection remains unexplored. The present research activities aim to investigate the correlation between the ECM1 gene polymorphisms rs3834087 and rs3754217 and HBV progression.

2. Methods

2.1. Period, Type, and Study Population

2.1.1. Type and Period of the Study

This study was conducted at the Laboratory of Molecular Biology and Genetics (LABIOGENE) at Joseph KI-ZERBO University in Ouagadougou, Burkina Faso. Of the 141 participants, 90 were cases and 51 were healthy controls. Samples were collected in Togo, specifically at the University Hospital Center Campus (CHU Campus) for the cases and at the Togolese National Blood Transfusion Center (CNTS) for the controls in Lomé.

This was an analytical case-control study that evaluated the role of the *ECM*1 gene polymorphisms rs3754217 and rs3834087 in the progression of HBV infection. The study took place over a 21-month period, including the data collection period (from February 2024 to October 2025).

2.1.2. Study Population

The study population consisted of patients with chronic hepatitis B, liver cirrhosis B, hepatocellular carcinoma due to hepatitis B who came for a consultation or treatment at the CHU Campus of Lomé and controls were sampled from blood donation at the CNTS. It comprised two distinct cohorts: cases and controls. The

case cohort consisted of individuals diagnosed with chronic hepatitis B (HCB), hepatitis B viral cirrhosis, and hepatocellular carcinoma attributed to HBV infection. Conversely, the control cohort included individuals who tested negative for HBsAg, anti-HCV antibodies, and HIV.

2.2. Inclusion and Exclusion Criteria

- **Inclusion Criteria**
  - **Chronic hepatitis B:** Participants in this group had a confirmed HBV infection for over six months, evidenced by HBsAg positivity, and ultrasound results showing no significant liver abnormalities;
  - **Cirrhosis:** Participants in this category had a clinically confirmed cirrhotic liver condition, with HBV being the sole etiological agent;
  - **Hepatocellular carcinoma:** Enrollment was based on alpha-fetoprotein (AFP) assay results, CT scan findings, and/or histological liver examination. Only individuals with HBV as the sole exposure factor were considered.
  - **Control group:** Participants who tested negative for HBsAg, anti-HCV, and HIV during a blood donation.
- **Non-Inclusion Criteria**

Exclusions encompassed HBV-negative cases, HCV-positive cases, HIV-positive cases, HBV-positive and/or HIV-positive controls, and individuals unwilling to partake in the study. Also excluded were individuals who did not provide explicit informed written consent.

2.3. Sample Collection

Sampling began with interviews of patients using a structured questionnaire, collecting sociodemographic data, dietary habits, and history of liver disease. Following the interview, whole blood was collected and divided into two labeled tubes (EDTA and dry) for subsequent serological and molecular analysis. After centrifugation, the samples were decanted and stored at −20˚C pending analysis.

2.4. DNA Extraction and Quantification

Genomic DNA extraction was performed using the Rapid Salting-Out technique from whole blood [7] [26]. The principle is based on cell lysis, protein digestion and precipitation, impurity washing, and DNA elution. DNA concentration and purity were measured using a Biodrop spectrophotometer.

2.5. Genotyping of the rs3754217 and rs3834087 Polymorphisms of the *ECM*1 Gene

Genotyping of ECM1 gene polymorphisms was performed using real-time PCR with the Quant Studio™ 5 Real-Time instrument [22].

25 µL reaction mixture contained 6.5 µL of pure water, 2 µL of HOT FIREPol® Probe Universal qPCR Mix 5X, 1 µL of probe 1, and 1 µL of probe 2 of the TaqMan® SNP Genotyping Assays were diluted 1/10, with 1 µL of the forward primer,

1 µL of the reverse primer diluted 1/10, and 2.5 µL of DNA. The amplification program consisted of an initial denaturation step at 95˚C for 10 minutes, followed by 40 cycles of denaturation at 95˚C for 15 seconds, hybridization/elongation at 60˚C for 1 minute, and a final elongation at 60˚C for 30 seconds. The specific primers used for amplification, coupled with Minor Groove Binder (MGB) probes with non-fluorescent quenchers (NFQs), are listed in Table 1.

Table 1. Primer and probe sequences.

Polymorphisms			Primers and Probes
rs 3754217	Primers	F	5'-ACGTTTGGATGGGGACTGATTAGAGGAGAAC-3'
		R	5'-ACGTTTGGATGAACTGAGGCACAAACTAGGG-3'
	Probes		5'-VIC-AGGGGCTCAAACACCTCTTGCTCCT-MGB-NFQ-3'
			5'-FAM-GATTCTCTGAATCAGTTTCTCTTGA-MGB-NFQ-3'
rs 3834087	Primers	F	5'-ACGTTGGATGAGACCTAGATGGAATCAGCC-3'
		R	5'-ACGTTGGATGTGAAAAAGGGAGCATGGCAG-3
	Probes		5'-VIC-ATGGAATCAGCCCTAAGGGATGAG-MGB-NFQ-3'
			5'-FAM-AAAGGCCTTAGGGAGAAATTCTG-MGB-NFQ-3'

2.6. Statistical Analysis

Data were entered into Excel 2019 and analyzed using SPSS version 20 and EPI Info 7.2.5.0. The odds ratio (OR) was calculated for comparisons with a 95% confidence interval. The difference was considered statistically significant for a p-value < 0.05.

2.7. Ethical Considerations

Competent Authorities

This study received approval from the Togolese Bioethics Committee for Health Research (Reference: Opinion No. 054/2023/CBRS of 22/11/2023). In the field, healthcare personnel at the study sites were informed of all aspects of the study, and participation was voluntary.

Participant Consent

Each participant signed an informed consent form presented to them by the research team. For participants unable to read the form, a translation of its content was provided in the local language in the presence of a witness. Prior to the signing, each participant or witness was informed of the study's purpose by reviewing a study information sheet.

Management of Personal Data

A unique inclusion code was assigned to each participant by the investigator and recorded in a confidential register (Excel file). This document constitutes the sole identification key linking personal data (surname/first name) to inclusion numbers, kept and secured by the investigators; it guarantees the irreversible anonymization of the study data.

3. Results

3.1. Description of the Study Population

➢ **Depending on age and sex**

The study population comprised a total of 141 participants, divided into 54 women (38.29%) and 87 men (61.70%). The age of the subjects ranged from 17 to 84 years, with a mean of 41.13 ± 14.29 years. Analysis by sex shows that women had a mean age of 41.76 ± 14.094 years, slightly higher than that of men (40.76 ± 14.485 years). Considering the clinical subgroups, the mean age was 35.57 ± 12.153 years in the controls, 33.48 ± 11.087 years in patients with chronic hepatitis B (HCB), 45.54 ± 12.754 years in cirrhotic patients, and 53.37 ± 13.723 years in patients with hepatocellular carcinoma (HCC). These values reflect a trend towards increasing age with disease severity, suggesting that progression to advanced forms of HBV is more common in older subjects.

➢ **According to clinical status**

Our study population consisted of 90 cases (HBC = 25; Cirrhosis = 41 and HCC = 24) and 51 controls. Figure 1 shows the proportions of the subgroups of chronic hepatitis (17.73%), cirrhosis (29.08%), HCC (17.02%) and controls (36.17%) (Figure 1).

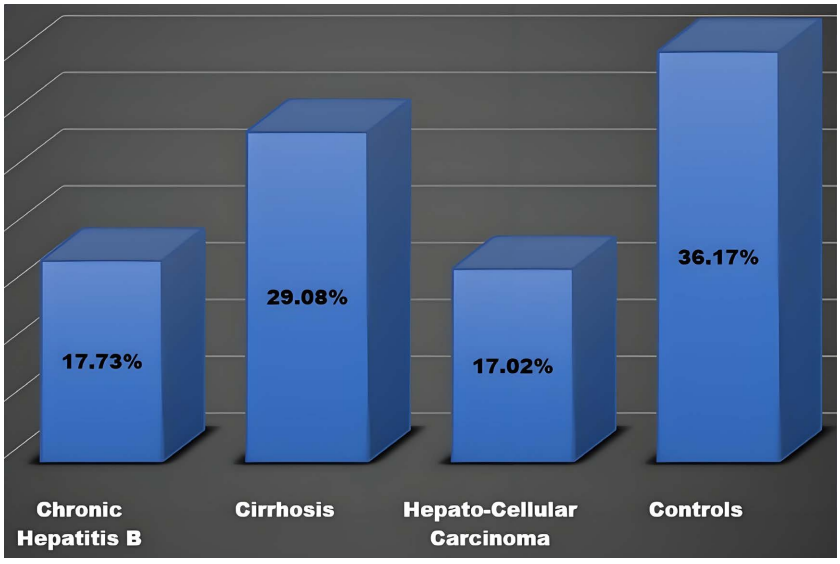

Figure 1. Distribution of study population by clinical status.

3.2. Genotypic and Allelic Frequencies of the ECM1 Gene Polymorphisms rs3834087 and rs3754217 Stratified by Sex

- **rs3834087**

To assess the risk of progression to severe forms of hepatitis B virus infection, the GAG/GAG genotype and the GAG allele were taken as a reference.

Among women infected with the hepatitis B virus, the distribution of genotypes reveals a clear predominance of the homozygous mutated form (-/-), observed in 90.24% of cases compared to 92.30% of controls. The heterozygous form (GAG/-)

represents 7.32% of cases, while none were reported in the control group. As for the homozygous wild-type form (GAG/GAG), the frequency remains low, estimated at 2.43% in cases compared to 7.69% in controls. Allelic analysis also highlights an important representation of the mutated allele, present in 93.90% of infected women compared to 92.30% in controls. This difference was not statistically significant ($p > 0.05$) (Table 2).

In males, the distribution of genotypes shows a predominance of the homozygous mutated profile (-/-), found in 87.5% of cases compared to 79.48% of controls. Heterozygous genotypes (GAG/-) represent 6.25% and 12.82%, respectively, while the wild-type form (GAG/GAG) is observed in 6.25% of cases and 7.69% of controls. The mutated allele has a high frequency in the case group (90.62%) compared to the control group (85.89%), which is not a statistically significant difference ($p > 0.05$) (Table 2).

- **For the rs3754217**

The GG genotype and the G allele were taken as a reference. In the female population, among cases, the genotypic frequencies were 39.02% for homozygous GG, 46.34% for heterozygous GT, and 14.63% for homozygous TT mutants. Among controls, the genotypic frequencies were 23.07% for homozygous GG, 69.23% for heterozygous GT, and 7.69% for homozygous TT mutants. The frequency of mutated alleles was 37.8% in cases and 42.30% in controls. This difference was not significant ($p > 0.05$). In the male population, among cases, the genotypic frequencies were 26.53% for homozygous GG, 69.38% for heterozygous GT, and 4.08% for homozygous TT mutants. Among controls, the genotypic frequencies were 34.21% for homozygous GG, 55.26% for heterozygous GT, and 10.52% for homozygous TT mutants. The frequency of mutated alleles was 38.77% in cases and 38.15% in controls, with no significant difference ($p > 0.05$) (Table 2).

Table 2. Distribution of genotypic and allelic frequencies of the ECM1 gene polymorphisms rs3834087 and rs3754217 according to sex.

		Women				Men			
		Case N = 41 (%)	Controls N = 13 (%)	OR (95% CI)	p-value	Case N = 49 (%)	Controls N = 38 (%)	OR (95% CI)	p-value
rs 3834087									
Genotype	GAG/GAG	1 (2.43)	1 (7.69)	**Reference**		3 (6.12)	3 (7.89)	**Reference**	
	GAG/-	3 (7.32)	0 (0)	NA	0.40	3 (6.12)	5 (13.15)	0.6 (0.07 - 5.13)	0.52
	-/-	37 (90.24)	12 (92.30)	3.08 (0.17 - 53.16)	0.44	43 (87.75)	30 (78.94)	1.43 (0.27 - 7.59)	0.49
Allele	GAG	5 (6.09)	2 (7.69)	**Reference**		9 (9.18)	11 (14.47)	**Reference**	
	mutated allele	77 (93.90)	24 (92.30)	1.28 (0.23 - 7.04)	0.53	89 (90.81)	65 (85.52)	1.67 (0.65 - 4.27)	0.27
rs 3754217									
Genotype	GG	16 (39.02)	3 (23.07)	**Reference**		13 (26.53)	13 (34.21)	**Reference**	
	GT	19 (46.342)	9 (69.23)	0.39 (0.09 - 1.71)	0.17	34 (69.38)	21 (55.26)	1.61 (0.63 - 4.15)	0.31
	TT	6 (14.63)	1 (07.69)	1.12 (0.09 - 13.03)	0.71	02 (04.08)	4 (10.52)	0.50 (0.07 - 3.22)	0.39
Allele	G	51 (62.19)	15 (57.69)	**Reference**		60 (61.22)	47 (61.84)	**Reference**	
	T	31 (37.80)	11 (42.30)	0.82 (0.33 - 2.03)	0.68	38 (38.77)	29 (38.15)	1.02 (0.55 - 1.90)	0.93

OR = Odds Ratio; CI = Confidence Interval; NA = Not Applicable.

3.3. Distribution of Genotypic and Allelic Frequencies of the ECM1 Gene Polymorphisms rs3834087 and rs3754217 According to Clinical Status

Analysis of the distribution of genotypes and alleles of the two polymorphisms, according to the different clinical statuses of the studied population, namely chronic hepatitis B (HBC), cirrhosis, hepatocellular carcinoma (HCC) and controls, revealed no specific profile nor any correlation with either of the clinical groups ($p > 0.05$).

Following this analysis, the rs3834087 polymorphism reveals a tendency towards association between genotypes, alleles and progression to severe forms of HBV infection. Although this association is not statistically significant overall ($p > 0.05$).

As for the rs3754217 polymorphism, the genotypes and alleles reveal a protective tendency against severe forms of HBV infection. Although this association is not statistically significant overall ($p > 0.05$) (Table 3).

Table 3. Genotypic and allelic frequencies according to clinical status.

			Total Pop N = 141 (%)	Controls N = 51 (%)	HBC N = 25 (%)	Cirrhosis N = 41 (%)	HCC N = 24 (%)	OR (95% CI)	p-value
rs 3834087	Genotype	GAG/GAG	8 (5.67)	4 (7.84)	1 (4)	2 (4.87)	1 (4.16)	**Reference**	
		GAG/-	11 (7.80)	5 (9.80)	2 (8)	4 (9.75)	0 (0)	1.2 (0.19 - 7.44)	0.60
		-/-	122 (86.52)	42 (82.35)	22 (88)	35 (85.36)	23 (95.83)	1.90 (0.45 - 8.00)	0.29
	Allele	GAG	27 (9.57)	13 (12.74)	4 (8)	8 (9.75)	2 (4.16)	**Reference**	
		mutated allele	255 (90.42)	89 (87.25)	46 (92)	74 (90.24)	46 (95.83)	1.73 (0.78 - 3.84)	0.17
rs 3754217	Genotype	GG	45 (31.91)	16 (31.37)	7 (28.00)	13 (31.70)	9 (37.50)	**Reference**	
		GT	83 (58.86)	30 (58.82)	15 (60.00)	24 (58.53)	14 (58.33)	0.97 (0.45 - 2.07)	0.94
		TT	13 (09.21)	5 (09.80)	3 (12.00)	4 (09.75)	1 (4.16)	0.88 (0.24 - 3.15)	0.84
	Allele	G	173 (61.34)	62 (60.78)	29 (58.00)	50 (60.97)	32 (66.66)	**Reference**	
		T	109 (38.65)	40 (39.21)	21 (42.00)	32 (39.02)	16 (33.33)	0.96 (0.58 - 1.58)	0.88

OR: Odds ratio, **CI**: Confidence interval.

3.4. Comparison of Genotypic and Allelic Frequencies of the rs3834087 Polymorphism of the ECM1 Gene between the Different Clinical Subgroups.

Analysis of the genotypic and allelic frequencies of the rs3834087 and rs3754217 polymorphisms of the ECM1 gene with the clinical subgroups revealed interesting results.

HBC and cirrhosis: for both polymorphisms, although no significant association ($p > 0.05$) was identified, analysis of the genotypes and alleles of the two rs variants appeared to confer a reduced risk of progression to cirrhosis. Only the GT heterozygote of the rs3754217 polymorphism showed a statistically significant protective effect with an OR of 0.33 and a CI of 0.10 - 1.03, $p = 0.04$.

The controls towards HBC: Genotypic and allelic analysis of the two polymorphisms of the ECM1 gene of the evolution of healthy subjects towards probable hepatitis B infection reveals a non-significant increased probability of progression towards severe forms of infection, therefore a risk factor (OR > 1; p > 0.05).

From healthy subjects, to HBC, to cirrhosis, to HCC: This analysis suggests that the rs3834087 polymorphism confers a non-statistically significant positive risk across all its genotypes and alleles, and a non-significant positive risk of progression from cirrhosis to HCC in healthy individuals or those with hepatitis B (OR > 1; p > 0.05). Conversely, the rs3754217 polymorphism reveals a lower risk, thus a non-significant protective effect, on the progression from cirrhosis in healthy individuals or those with hepatitis B to HCC (OR < 1; p > 0.05).

It should be noted that the mutated allele of the ECM1 rs3834087 gene, with an OR of 3.35 and a CI of 0.72 to 15.52, is particularly associated with a three times higher risk of progression from healthy individuals to HCC near the threshold of significance (p = 0.08).

These observations, presented in Table 4, highlight the importance of understanding genetic factors in the progression of HBV infections and their potential implications for prognosis.

Table 4. Genotypic and allelic frequencies of the rs3834087 polymorphism of the ECM1 gene between the different clinical subgroups.

Genotypic and allelic frequencies in HBC and cirrhosis						
			HBC N = 25 (%)	Cirrhosis N= 41 (%)	OR (95% CI)	p-value
rs 3834087	Genotype	GAG/GAG	1 (4)	2 (4.87)	**Reference**	
		GAG/-	2 (8)	4 (9.75)	1.00 (0.05 - 18.91)	0.76
		-/-	22 (88)	35(85.36)	0.79 (0.06 - 9.30)	0.67
	Allele	GAG	4 (8)	8 (9.75)	**Reference**	
		mutated allele	46 (92)	74 (90.24)	0.80 (0.22 - 2.82)	0.49
rs 3754217	Genotype	GG	7 (28.00)	13 (31.70)	**Reference**	
		GT	15 (60.00)	24 (58.53)	0.33 (0.10 - 1.03)	0.04
		TT	3 (12.00)	4 (09.75)	0.71 (0.12 - 4.15)	0.52
	Allele	G	29 (58.00)	50 (60.97)	**Reference**	
		T	21 (42.00)	32 (39.02)	0.88 (0.43 - 1.80)	0.73
Genotypic and allelic frequencies in HBC and controls						
			HBC N = 25 (%)	Controls N = 51 (%)	OR (95% CI)	p-value
rs 3834087	Genotype	GAG/GAG	1 (4)	4 (7.84)	**Reference**	
		GAG/-	2 (8)	5 (9.80)	1.60 (0.10 - 24.70)	0.63
		-/-	22 (88)	42(82.35)	2.09 (0.22 - 19.90)	0.45
	Allele	GAG	4 (8)	13 (12.74)	**Reference**	
		mutated allele	46 (92)	89 (87.25)	1.67 (0.51 - 5.44)	0.28

Continued

rs 3754217	Genotype	GG	7 (28.00)	16 (31.37)	**Reference**	
		GT	15 (60.00)	30 (58.82)	1.14 (0.38 - 3.37)	0.80
		TT	3 (12.00)	5 (09.80)	1.37 (0.25 - 7.39)	0.51
	Allele	G	29 (58.00)	62 (60.78)	**Reference**	
		T	21 (42.00)	40 (39.21)	1.12 (0.56 - 2.23)	0.74
Genotypic and allelic frequencies in HCC and cirrhosis						
			HCC N = 24 (%)	Cirrhosis N= 41 (%)	OR (95% CI)	p-value
rs 3834087	Genotype	GAG/GAG	1 (4.16)	2 (4.87)	**Reference**	
		GAG/-	0 (0)	4 (9.75)	N/A	0.42
		-/-	23 (95.83)	35(85.36)	1.31 (0.11 - 15.34)	0.66
	Allele	GAG	2 (4.16)	8 (9.75)	**Reference**	
		mutated allele	46 (95.83)	74 (90.24)	2.48 (0.50 - 12.22)	0.21
rs 3754217	Genotype	GG	9 (37.50)	13 (31.70)	**Reference**	
		GT	14 (58.33)	24 (58.53)	0.84 (0.28 - 2.47)	0.75
		TT	1 (4.16)	4 (09.75)	0.36 (0.03 - 3.78)	0.37
	Allele	G	32 (66.66)	50 (60.97)	**Reference**	
		T	16 (33.33)	32 (39.02)	0.78 (0.37 - 1.64)	0.51
Genotypic and allelic frequencies in HBC and HCC						
			HBC N = 25 (%)	HCC N = 24 (%)	OR (95% CI)	p-value
rs 3834087	Genotype	GAG/GAG	1 (4)	1 (4.16)	**Reference**	
		GAG/-	2 (8)	0 (0)	N/A	0.50
		-/-	22 (88)	23 (96)	1.04 (0.06 - 17.76)	0.74
	Allele	GAG	4 (8)	2 (4.16)	**Reference**	
		mutated allele	46 (92)	46 (95.83)	2.00 (0.34 - 11.46)	0.35
rs 3754217	Genotype	GG	7 (28.00)	9 (37.50)	**Reference**	
		GT	15 (60.00)	14 (58.33)	0.72 (0.21 - 2.47)	0.60
		TT	3 (12.00)	1 (4.16)	0.25 (0.02 - 3.06)	0.29
	Allele	G	29 (58.00)	32 (66.66)	**Reference**	
		T	21 (42.00)	16 (33.33)	0.69 (0.30 - 1.57)	0.37
Genotypic and allelic frequencies in HCC and Controls						
			HCC N = 24 (%)	Controls N = 51 (%)	OR (95% CI)	p-value
rs 3834087	Genotype	GAG/GAG	1 (4.16)	4 (7.84)	**Reference**	
		GAG/-	0 (0)	5 (9.80)	N/A	0.5
		-/-	23 (95.83)	42 (82.35)	2.19 (0.23 - 20.77)	0.43
	Allele	GAG	2 (4.16)	13 (12.74)	**Reference**	
		mutated allele	46 (95.83)	89 (87.25)	3.35 (0.72 - 15.52)	0.08

Continued

rs 3754217	Genotype	GG	9 (37.50)	16 (31.37)	**Reference**	
		GT	14 (58.33)	30 (58.82)	0.82 (0.29 - 2.33)	0.72
		TT	1 (4.16)	5 (09.80)	0.35 (0.03 - 3.53)	0.35
	Allele	G	32 (66.66)	62 (60.78)	**Reference**	
		T	16 (33.33)	40 (39.21)	0.77 (0.37 - 1.59)	0.48
Genotypic and allelic frequencies in cirrhosis and control groups						
			Cirrhosis N= 41 (%)	Controls N = 51 (%)	OR (95% CI)	p-value
rs 3834087	Genotype	GAG/GAG	2 (4.87)	4 (7.84)	**Reference**	
		GAG/-	4(9.75)	5 (9.80)	1.60 (0.1869 - 13.69)	0.54
		-/-	35(85.36)	42 (82.35)	1.66 (0.2880 - 9.64)	0.44
	Allele	GAG	8 (9.75)	13 (12.74)	**Reference**	
		mutated allele	74 (90.24)	89 (87.25)	1.35 (0.53 - 3.43)	0.52
rs 3754217	Genotype	GG	13 (31.70)	16 (31.37)	**Reference**	
		GT	24 (58.53)	30 (58.82)	0.98 (0.39 - 2.44)	0.97
		TT	4 (09.75)	5 (09.80)	0.98 (0.21 - 4.43)	0.64
	Allele	G	50 (60.97)	62 (60.78)	**Reference**	
		T	32 (39.02)	40 (39.21)	0.99 (0.54 - 1.79)	0.97

OR: Odds ratio, **CI**: Confidence interval.

4. Discussion

This study, conducted in Togo, included participants comprising both healthy HBV carriers (controls) and patients with various clinical forms of the infection, including chronic hepatitis B (HBC), cirrhosis, and hepatocellular carcinoma (HCC). It allowed us not only to estimate the allelic and genotypic frequencies of the ECM1 gene polymorphisms rs3834087 and rs3754217 within this population, but also to assess their impact on the progression of HBV infection in Togo.

In the cohort, the mean age increased with the severity of clinical forms: 33.48 years for Chronic Hepatitis B (HBC), 45.54 years for cirrhotic patients, and 53.37 years for hepatocellular carcinoma (HCC). Individually, for example, the mean age of patients with cirrhosis was 45.54 ± 12.75 years. The present results are similar to previous studies conducted in Burkina Faso, which found mean ages of cirrhosis patients of 46.5 and 46.9 years in 2002 and 2020, respectively [27] [28]. However, our results differ from those of a study conducted in America, where the mean age was approximately 60 years [29]. These figures show that our patients were younger, compared to those in developed countries. The age difference observed between our West African population (predominance of viral liver infections) and the American population (predominance of the risk factor alcohol) could be explained by the etiology of cirrhosis (the same applies to the average age of patients with HCC in our study population, compared to that of developed countries).

Analysis of the data for the two ECM1 gene polymorphisms in the general pop-

ulation of our study reveals highly relevant results. For rs3834087, we found that the GAG/GAG, GAG/-, and -/- genotypes had respective frequencies of 5.67%, 7.80%, and 86.52%. Furthermore, the frequency of the wild-type GAG allele was 9.57%, while that of the mutated allele was 90.42%. Our results highlight the predominance of the homozygous -/- and the mutated allele. These results differ from those found by Traore *et al.*, who found the predominance of the heterozygous GAG/- and the wild-type GAG allele in Burkina Faso in 2024 [22]. These two studies also differ from that conducted by He *et al.* in China, where the wild-type GAG/GAG genotype and the GAG allele were predominant [30]. By examining the polymorphisms of the rs3754217 gene, we found that the GG, GT, and TT genotypes had frequencies of 31.91%, 58.86%, and 9.21%, respectively. Furthermore, the frequency of the wild-type G allele was 61.34%, while that of the mutated T allele was 38.65%. Our results, and those of Traore *et al.*, highlight the predominance of the heterozygous GT genotype over the other genotypes, where they had found a GT predominance of 70.1% [22]. Our results corroborate those of He *et al.*, who showed that the wild-type GG and heterozygous GT genotypes were more prevalent, with frequencies of approximately 45% - 50%, and that the mutated genotype represented about 6% [30]. Furthermore, the wild-type G allele was found to be predominant compared to the mutated allele. Such disparities highlight the influence of geographic and racial factors, climatic exposures, and occupational factors on genetic variability.

Examining our polymorphisms according to sex revealed that the T mutation of the rs3754217 gene appears to confer a non-significant risk of progression of viral hepatitis B to severe forms in men (OR = 1.02, CI = 0.55 to 1.90; p = 0.93) but seems to show protection in women (OR = 0.82, CI = 0.33 to 2.03; p = 0.68). This coincides with the analysis performed by Traore *et al.* The mutated GAG allele of the rs3834087 polymorphism appears to increase the risk of severe viral hepatitis B in both sexes, but more pronounced in men (OR = 1.67, CI = 0.65 to 4.27; p = 0.27). These two analyses suggest that men have a genetic predisposition to developing severe forms of hepatitis B infection. This could be explained by the role of sex hormones in chronic HBsAg carriage and the severity of the infection. Indeed, according to some studies, the virus's genome contains a specific DNA sequence that interacts with the androgen receptor. This could explain why men infected with the virus are more likely to develop severe forms of the infection [22] [25] [31].

Analysis of our data according to clinical subgroups revealed some very intriguing trends. It emerged that a potentially significant protective effect against the progression of severe infection was associated with the GT genotype of rs3754217 in the subgroup of chronic HBV to severe forms, particularly liver cirrhosis, with an OR of 0.33 and a CI of 0.10 - 1.03, p = 0.04. Our results corroborate the findings of He *et al.* in China, who found that the GT genotype of rs3754217 was significantly associated with a reduced risk of progression in all patients with chronic HBV infection (OR = 0.75, 95% CI: 0.56 - 1.00) [30]. Our results differ from those found by Traore *et al.* in 2024 in Burkina Faso [22]. This protection against severe forms of

the infection could be explained by the fact that a mutation in the ECM1 gene leads to an increase in the ECM1 protein. Indeed, ECM1 has been shown to be systematically downregulated during liver damage, and strategies for ECM1 re-expression in hepatocytes could be used to treat liver fibrosis [22] [30]. Similarly, research conducted by Fan *et al.* on liver fibrosis in mouse models confirmed this hypothesis by showing that liver damage reduced ECM1 production levels during fibrogenic activity, and ECM1 re-expression prevented the progression of liver fibrosis [17].

Following analysis of the other subgroups, no significant association was found between the two polymorphisms regarding the progression or protection of chronic hepatitis B towards cirrhosis and HCC. Our results are similar to those found by He *et al.*, but show some differences compared to the results of Traore *et al.*, who found some associations between chronic carriers and controls with the mutated allele that conferred a low risk of progression to severity. Based on the associations observed within our study groups and the discrepancies with the results of Traore *et al.* and He *et al.*, we can speculate on the influence of regional epigenetic differences or environmental determinants. Our study was conducted in Togo, and the observed differences in genotypic and allelic frequencies could be due to regional epigenetic differences or differences in environmental exposure. These could include dietary exposures, lifestyles, and environmental factors specific to Togo that may have influenced ECM1 gene expression. Given these findings, further research could be undertaken to explore the potential influence of these factors on ECM1 gene expression. This research could provide valuable insights into the underlying mechanisms contributing to the observed differences in genotypic and allelic frequencies and could help explain discrepancies with the results of other researchers. It could also contribute to the development of personalized interventions and treatments tailored to specific populations based on their unique genetic and environmental profiles.

5. Study Limitations

The main limitation of our study lies in the sampling process. Due to a lack of information or awareness, almost all patients are admitted to the hepato-gastro-enterology department at very advanced stages of the disease (with death occurring within a maximum of 24 hours of admission). Secondly, the frequency of cases was relatively low (barely three patients per week, and even then, inclusion and exclusion criteria had to be applied). Finally, a lack of financial resources prevented us from considering alternative sample collection strategies, such as visiting all hospitals in Togo with hepato-gastro-enterology departments.

6. Conclusions

Our study was the first to examine the association between the ECM1 gene polymorphisms rs3834087 and rs3754217 and the occurrence of severe forms of HBV infection in the Togolese population. From a genetic standpoint, the frequencies of the GAG/GAG, GAG/-, and -/- genotypes of the ECM1 gene polymorphism

rs3834087 were 5.67%, 7.80%, and 86.52%, respectively. Furthermore, the frequency of the wild-type GAG allele was 9.57%, while that of the mutated allele was 90.42%. The rs3754217 gene polymorphism exhibited GG, GT, and TT genotype frequencies of 31.91%, 58.86%, and 9.21%, respectively. Its wild-type allele G was 61.34%, while that of the mutated allele T was 38.65%. This study showed that a potential protective effect against the progression of severe infection might be associated with the GT genotype of rs3754217 in the chronic HBV subgroup towards severe forms, including liver cirrhosis. However, no association was observed between these two polymorphisms and the development of cirrhosis or its progression to HCC.

It is possible that an interaction between several factors could better explain the emergence of severe forms of HBV infection in Togo. Therefore, it is important to conduct further research to better understand and identify other factors that may contribute to the development of these severe forms. This would help identify new therapeutic targets, promote the development of new anti-hepatitis drugs and liver biomarkers, and guide clinicians in the management of severe cases, particularly in high-prevalence regions like Togo.

Declaration

The data used and/or analyzed during this study are available from the corresponding author upon reasonable request.

Ethical Statement

This study has received approval from the Togolese Bioethics Committee for Health Research (Reference: Opinion No. 054/2023/CBRS of 22/11/2023).

Consent

Our study complies with the Declaration of Helsinki, adopted by the World Medical Association (WMA), on the ethical principles governing medical research involving human subjects. Participants gave their free and informed consent. Every effort was made to preserve not only the privacy, but also the confidentiality, dignity, and honor of the patients.

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Author Contributions

Concept and design of the study: **LT**, **KSD**, **FWD** and **JS**.

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The corresponding author states that the manuscript has been read and approved by all the named authors and that the order of authorship in the manuscript has been approved by all of us.

Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this article.

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Abbreviations

CHB	Chronic Hepatitis B
DNA	Deoxyribonucleic Acid
ECM1	Extracellular Matrix Protein 1
HBsAg	HBs Antigen
HBV	Hepatitis B Virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HSC	Hepatic stellate cells
KIR	Killer cell immunoglobulin-like receptor
WHO	World Health Organization
p53	Tumor protein 53
RB1	Retinoblastoma 1
rs	SNP reference
SNP	Single nucleotide polymorphism
TGF β1	Transforming growth factor beta 1.