



# Hepatitis B virus preCore/Core region variability in pregnant women in the Republic of Guinea

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## Abstract

**Introduction.** The vertical route of hepatitis B virus (HBV) transmission is a significant problem in African countries, which is characterized by late diagnosis of the disease and high mortality. The high prevalence of hepatocellular carcinoma (HCC) in Africa may be due to variability in the HBV preCore/Core region, mutations in which contribute to disease progression. Molecular genetic characterization of strains circulating among pregnant women may reflect the overall mutational profile of the pathogen in the population.

**The objective** of this study was to analyze the variability of the HBV preCore/Core region circulating among pregnant women in the Republic of Guinea.

**Materials and methods.** The study material included 480 plasma samples obtained from HBV-positive pregnant women from the Republic of Guinea. For all samples, the nucleotide sequences of the preCore/Core region of the HBV genome were sequenced and analyzed.

**Results.** Amino acid variability in the preCore region was determined in 211 (43.96%), and in the Core region in 473 (98.54%) patients. 12 polymorphic sites of the preCore region were identified in which amino acid substitutions occurred, including 8, 2 and 5 positions identified for genotypes E, A and D, respectively. In the Core region, 67 substitution positions were identified, including 46 in samples of genotype E, 23 in HBV genotype A and 26 in genotype D. It was shown that the distribution of substitutions in the preCore and Core regions in HBV genotypes E, A and D differs significantly with a predominance in mutations among HBV genotype E —  $p < 0.0001$ . Individual characteristic mutations have been identified for each genotype. The most common clinically significant mutations in the preCore/Core region in the study group were identified, including pc-H5D (27,08%), pc-W28\* (35,21%), c-E64D (33,54%), c-L116I/V/G (91,46%), c-T146N (73,13%). The double mutation A1762T/G1764A in the basal core promoter was shown in 74 samples of HBV genotype E, which accounted for 15.42% of the total group and 16.59% of patients with HBV genotype E.

**Conclusion.** The frequency of clinically significant preCore/Core mutations among pregnant women in the Republic of Guinea was determined. The data obtained reflect their prevalence in the general population and can be used to predict the progression of chronic HBV among the region's population.

**Keywords:** hepatitis B virus, occult hepatitis B, HBV variability, genotypes, clinically significant mutations, preCore/Core, laboratory diagnostics

**Ethics approval.** The study was conducted with the informed consent of the patients. The research protocol was approved by the National Ethics Committee of the Ministry of Health of the Republic of Guinea (protocol No. 129/CNERS/16, August 31, 2015).

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## Вариабельность preCore/Core-региона вируса гепатита В у беременных женщин в Гвинейской Республике

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### Аннотация

**Актуальность.** Вертикальный путь передачи вируса гепатита В (ВГВ) является одним из наиболее значимых в странах Африки, для которых характерны позднее выявление заболевания и высокая смертность. Причиной высокой распространённости гепатоцеллюлярной карциномы в Африке может быть вариативность preCore/Core-региона ВГВ, мутации в котором способствуют прогрессированию заболевания. Молекулярно-генетическая характеристика штаммов, циркулирующих среди беременных женщин, может отражать общий мутационный профиль патогена в популяции.

**Целью** нашей работы был анализ вариабельности preCore/Core-региона ВГВ, циркулирующего среди беременных женщин в Гвинейской Республике.

**Материалы и методы.** Исследовали 480 образцов плазмы, полученных от ВГВ-положительных беременных женщин из Гвинейской Республики. Для всех образцов проводили секвенирование и анализ нуклеотидных последовательностей preCore/Core-региона генома ВГВ.

**Результаты.** Аминокислотная изменчивость в preCore-регионе определена у 211 (43,96%) пациенток, в Core-регионе — у 473 (98,54%). Выявлены 12 полиморфных участков preCore-региона, в которых происходили аминокислотные замены, в том числе для генотипов E, A и D определены 8, 2 и 5 позиций соответственно. В Core-регионе определены 67 позиций замен, в том числе 46 в образцах генотипа E, 23 — генотипа A, 26 — генотипа D. Распределение замен в preCore- и Core-регионах у ВГВ-генотипов E, A и D значительно отличается с преобладанием мутаций среди генотипа E ( $p < 0,0001$ ). Для каждого генотипа определены индивидуальные характерные мутации. Выявлены наиболее распространённые клинически значимые мутации в preCore/Core-регионе в обследуемой группе, в том числе pс-H5D (27,08%), pс-W28\* (35,21%), с-E64D (33,54%), с-L116I/V/G (91,46%), с-T146N (73,13%). Двойная мутация A1762T/G1764A в базальном ядерном промоторе показана в 74 образцах генотипа E, что составило 15,42% от общей группы и 16,59% от пациентов с генотипом E.

**Заключение.** Определена частота встречаемости клинически значимых мутаций preCore/Core среди беременных женщин Гвинейской Республики. Полученные данные отражают их распространённость в общей популяции и могут быть использованы для прогноза прогрессирования хронического гепатита В среди населения данного региона.

**Ключевые слова:** вирус гепатита В, скрытый гепатит В, вариабельность ВГВ, генотипы, клинически значимые мутации, preCore/Core, лабораторная диагностика

**Этическое утверждение.** Исследование проводилось при добровольном информированном согласии пациентов. На проведение данного этапа работы было получено согласие Национального комитета по этике Министерства здравоохранения Гвинейской Республики (протокол № 129/CNERS/16 от 31.08.2015).

**Источник финансирования.** Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

**Конфликт интересов.** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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## Introduction

Hepatitis B virus (HBV), which is capable of causing both acute and chronic liver disease and is the seventh leading cause of death worldwide, remains a serious public health problem despite all measures taken for its elimination. According to various researchers, the number of patients chronically infected with HBV in the world amounts to 360 million people<sup>1</sup>. More than 75 million of them live in sub-Saharan Africa, where the population prevalence of the HBV surface antigen (HBsAg), the main laboratory diagnostic marker, exceeds 8% and in some regions it could even reach 25% [1]. Natural routes of transmission include sexual (direct sexual contact), vertical (from mother to fetus during or after childbirth), as well as prenatal (transplacental) infection, and transmission due to household contacts, including direct and indirect, including sharing hygiene items and similar methods of contact with an infected person. One of the most significant routes of HBV transmission in Africa is vertical transmission [2]. Without therapeutic intervention, the incidence of mother-to-child transmission exceeds 31% [3]. The particular importance of early infection is due to the fact that when infected before the age of 5 years, the vast majority of cases develop chronic HBV [4]. Furthermore, early HBV infection is one of the most significant risk factors for liver cirrhosis (LC) and hepatocellular carcinoma (HCC) development [5]. Another reason for the huge number of HCC patients and the high mortality rate in Africa is the late diagnosis of the disease and the consequent late referral of patients to health facilities [6]. The most affected country is Gambia, followed by the Republic of Guinea, Liberia and Sierra Leone [7]. This is due to both insufficient coverage with diagnostics and very low public awareness of viral hepatitis, routes of transmission and the consequences of infection. In addition to social factors, viral factors can influence the progression of the disease. Thus, a high viral load and active viral replication as a result of that increases the risk of LC and HCC, but even a viral load of less than 200 IU/ml does not exclude disease progression [8]. The high heterogeneity of the virus, for which 10 genotypes and more than 40 sub-genotypes are currently described, also has an impact on disease progression [9, 10]. For example, HBV subgenotype C2 is characterized by more frequent chronicity and severe disease course, including the development of HCC, than B2, and viruses of genotypes A and B are more sensitive to therapy than D and C [11].

However, the genotypic factor is not the only parameter contributing to disease progression; natural and selective viral mutations also play a major role. With the exception of rare deletions, most mutations in the preCore/Core region are point mutations, mainly asso-

ciated with decreased HBeAg levels and/or decreased viral load. Moreover, in the Core region, mutations are localized mainly in the immunogenic regions (MHC classes I + II) and thus may influence disease progression. For example, mutations in the preCore region (*G1896A*) and in the basal core promoter (BCP) — *T1753C*, *A1762T/G1764A*, amino acid substitutions in the Core region — *F24Y*, *E64D*, *E77Q*, *A80I/T/V*, *L116I*, *E180A* — are known to be associated with a severe course of liver disease and development of HCC [12]. Molecular genetic variation in viruses may show links to spatial and temporal variation, i.e. evolution over time, spread in geographic regions, at-risk groups, key populations, changes in transmission routes [13]. Therefore, dynamic monitoring of circulating virus variants in population groups reflecting the situation in the population and potentially capable of spreading the pathogen is quite important for predicting the epidemiological situation. Pregnant women are a group which fit that category, as they demonstrate the epidemiological profile of the sexually mature heterosexual population of a particular geographical region under study.

The Republic of Guinea, a country of more than 13.6 million people on the Atlantic coast of West Africa, is one of the poorest countries in the world<sup>2</sup>, where medicine remains the least publicly funded area. Thus, in 2019, the country's GDP contribution to the health and social work sectors did not exceed 3.2%<sup>3</sup>. Prevention of vertical transmission of HIV, a key factor in improving maternal and child health, has been significantly reduced, and the average number of visits to antenatal care clinics has decreased [14, 15]. At the same time, the prevalence of HBV in the country is extremely high: unlike HIV, testing for viral hepatitis markers is rarely performed, even during antenatal check-ups of pregnant women, so most patients are not diagnosed with the disease. Since there is no screening for viral hepatitis, there is no prevention of vertical transmission of HBV. The incidence of HBV DNA is 22.36% among conventionally healthy individuals [16], 30.4% among blood donors [17], and 26.5 % among pregnant women in some regions of the country [18, 19]. It was previously shown that almost all HBsAg-positive women who gave birth naturally transmitted the virus to the child [20].

Despite the implementation of HBV vaccination in the country in 2006, the vaccination coverage currently does not exceed 47% of the population, which is due to the lack of a well-established infrastructure for storage and transport of vaccines that require compliance with the cold chain, as well as to the socio-cultural

<sup>1</sup> WHO. Hepatitis B: Fact sheet. 2023. URL: <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b>

<sup>2</sup> Countrymeters. Guinea Population. URL: <http://countrymeters.info/en/guinea> (дата обращения: 09.03.2023).

<sup>3</sup> INS GUINÉE. Annuaire Statistique; 2019. URL: [https://www.stat-guinee.org/images/Documents/Publications/INS/annuelles/annuaire/ANNUAIRE\\_STATISTIQUE\\_AGRICOLE\\_2019\\_INS\\_FINALISE.pdf](https://www.stat-guinee.org/images/Documents/Publications/INS/annuelles/annuaire/ANNUAIRE_STATISTIQUE_AGRICOLE_2019_INS_FINALISE.pdf) (дата обращения: 20.12.2022).

peculiarities of the population, distrust of local residents in medical personnel [21].

There are relatively few data on the molecular genetic features of the virus circulating in the Republic of Guinea, and the characterization of the preCore/Core region is very limited in the literature [22].

**The objective** of this study was to analyze the variability of preCore/Core region of HBV strains circulating among pregnant women in the Republic of Guinea.

### Materials and methods

Blood plasma samples obtained from 480 HBV-infected pregnant women living in the Republic of Guinea were used in this study [19]. Laboratory studies were conducted at the Russian-Guinean Scientific Research Centre for Epidemiology and Prevention of Infectious Diseases, located at the Institute of Applied Biology of Guinea in the prefecture of Kindia. The consent of the Ethical Committee of Guinea was obtained for this stage of work (protocol No. 129/CNERS/16 of 31.08.2015). All subjects gave written informed consent to participate in the experiment.

HBV DNA in blood plasma was determined by real-time PCR with hybridization-fluorescence detection using a method developed at the St. Petersburg Pasteur Research Institute of Epidemiology and Microbiology, which allows detection of HBV DNA at low viral load. The sensitivity of the method is 10 IU/ml when extracted from 100 µl of plasma [23]. Nucleotide sequences of complete HBV genomes were obtained using nested PCR based on overlapping primer pairs followed by Sanger sequencing [22]. The obtained HBV sequences were analyzed to identify mutations in the studied region of the HBV genome relative to the consensus sequence of the Mart-B47 virus (HE974377.1, genotype D) [23] to ensure uniformity in the designation of substitution positions and to identify substitutions characteristic of some genotypes but poorly (or not at all) represented in others. Furthermore, all sequences of genotypes A, D and E were analyzed relative to the reference sequences of the corresponding genotypes (GenBank international database numbers AY128092.1, NC\_003977.2 and AB032431.1, respectively). The online database tool Geno2Pheno HBV<sup>4</sup>, as well as Hepatitis B Virus Phylogenetic Typing Tool<sup>5</sup> were used, where AY128092.1, NC\_003977.2 and AB032431.1 were also selected as reference strains from the proposed strains.

Statistical data processing was performed using the programs MS Excel, Prizm 5.0 (GraphPad Software Inc.), Statistica 8.0 (StatSoft Inc.). The Clopper-Pearson exact interval was used to assess statistical error. The results are presented with 95% confidence interval (95% CI). To assess the reliability of differences be-

tween data obtained in pairwise comparisons, the Fisher's exact test or the  $\chi^2$  test with Yates correction was used, depending on the characteristics of the samples. A probability value of  $p < 0.05$  was determined as the threshold for the reliability of differences.

### Results

The age of the subjects ranged from 13 to 55 years and averaged 25.8 years. The number of HBsAg-negative cases was 188 (39.17%; 95% CI 34.77-43.69%). HBV genotypes determined on the basis of phylogenetic analysis are presented in **Table 1** [19].

The nucleotide sequences of the viral genome of each sample were analyzed to study the preCore/Core region variability of HBV in the study group. The amino acid variability of the preCore region was determined in 211 individuals (43.96%; 95% CI 39.46-48.53%) and that of the Core-region in 473 individuals (98.54%; 95% CI 97.02-99.41%). Analysis of the preCore region revealed 12 polymorphic sites in which amino acid substitutions occurred, including 8 positions identified for genotype E, 5 for genotype D, and 2 for genotype A. The occurrence of amino acid substitutions in the pre-Core region is shown in **Fig. 1**.

During the comparative analysis, the distribution of mutations among HBV genotypes E, A and D was found to be significantly different ( $p < 0.0001$ ). For genotype E, *H5D*, *L8Q*, and *C12R* substitutions, among others, were identified, which are not represented among isolates of genotypes A and D. In turn, the *V17L/I* mutation was shown only for HBV genotype A, and substitutions *A19T*, *S20F*, *L27V* were detected only in HBV genotype D. When analyzing the distribution of amino acid substitutions present in at least 2 genotypic groups, significant differences were also identified with a predominance of mutations among HBV genotype E:  $\chi^2 = 16.206$ ;  $df = 8$ ;  $p = 0.0395$ .

In the Core region, 67 positions of amino acid substitutions were identified, including 46 for genotype E, 23 for genotype A, and 26 for genotype D. The most common amino acid substitutions occurrence in the Core region is presented in **Fig. 2**.

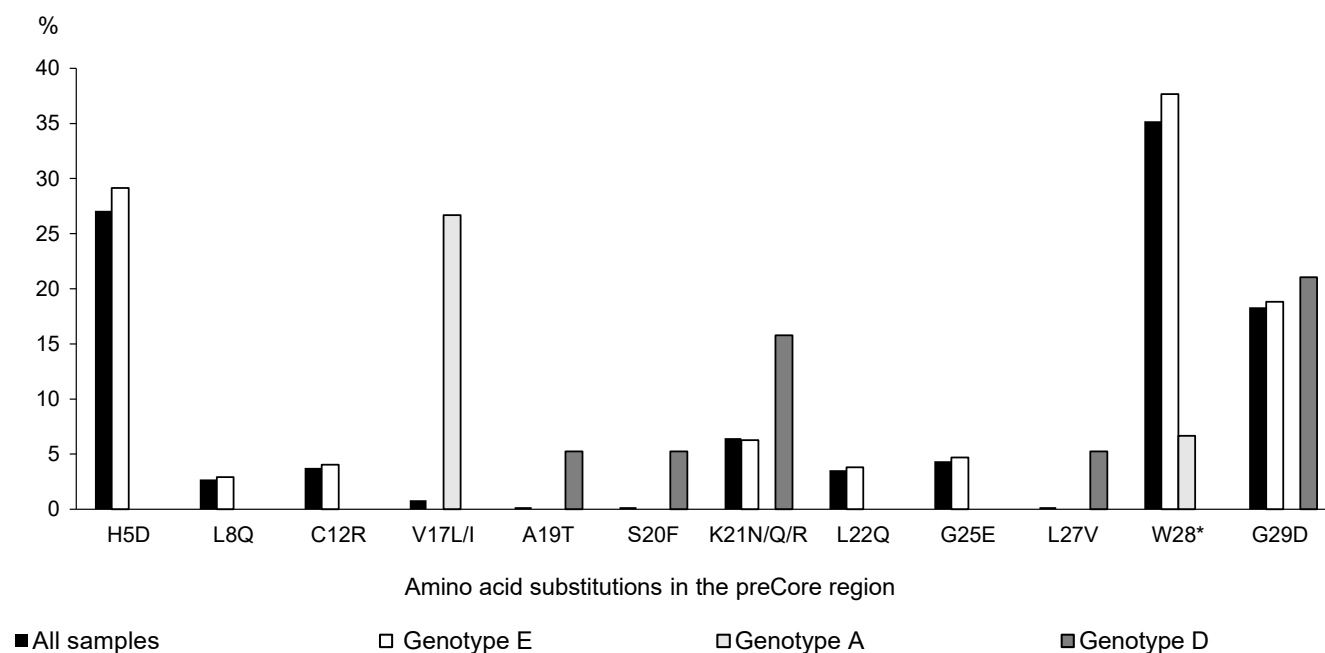
The distribution of Core region mutations among HBV genotypes E, A and D is also significantly different ( $p < 0.0001$ ). For genotype E, substitutions *S21H*,

**Table 1.** Hepatitis B virus genotypes circulating among pregnant women in the survey group

Genotype	Quantity	Share, %	95% CI
A1	8	1,67	0,72–3,26
A3	7	1,46	0,59–2,98
D1	3	0,63	0,13–1,82
D2	5	1,04	0,34–2,41
D3	11	2,29	1,15–4,06
E	446	92,9	90,24–95,05

<sup>4</sup> URL: <https://hbv.geno2pheno.org/>

<sup>5</sup> URL: <https://www.genomedetective.com/app/typingtool/hbv/>



**Fig. 1.** Frequency of amino acid substitutions occurrence in the preCore region of the hepatitis B virus genome in the examined group and according to genotypes.

\* — stop codon. Amino acid substitutions are presented relative to the consensus sequence of the Mart-B47 virus (HE974377.1, genotype D) with additional analysis relative to genotype-specific reference sequences AY128092.1 (genotype A), NC\_003977.2 (genotype D) and AB032431.1 (genotype E).

*V27I, R28K, Y38F, R39G, E46D, P79Q, M93V/I, G94A, F103L, I105T, T114P/V, F122C, W125T, R133T, S141P, L143T, T146N, V149I, R152G, R166P, R181P, Q184R/K/H*, were identified, though not represented among HBV genotype A and D samples. Only mutations *A11S, A34S, G63V, E77D/Q, L95I, T142I/S, D153G, R159G, S183P* were detected among HBV genotype A, and mutations *I3L, D4Y, F9I, V13G, L15F, S17L, L19F, D29G, Q57R, L162N, S178T* were found among HBV genotype D samples. Evaluation of the distribution of polymorphic variants identified in at least 2 genotypic groups demonstrated significant ( $p < 0.0001$ ) differences with higher frequency of occurrence and diversity of substitutions among HBV genotype E. Comparative inter-genotype analysis of the most common Core region amino acid substitutions occurrence in the examined group also showed differences ( $p < 0.0001$ ).

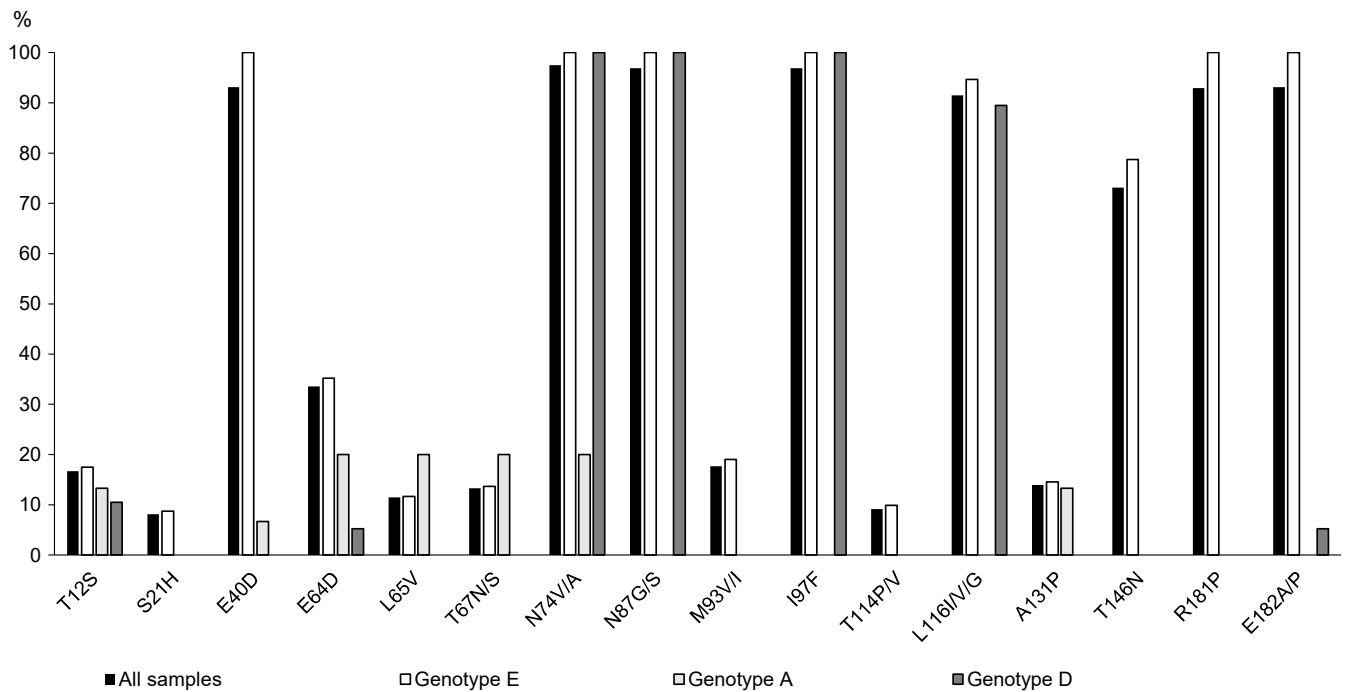
The *A1762T/G1764A* double mutation was detected in the BCP of 74 HBV genotype E samples, accounting for 15.42% (95% CI 12.3–18.96%) of the total group and 16.59% (95% CI 13.26–20.38%) of patients with HBV genotype E. Information about the most frequent clinically significant BCP and preCore/Core region mutations in the group is presented in **Table 2**.

### Discussion

The C gene and the Pre-C region of 555 nt and 87 nt, respectively, encode two proteins: HBcAg of 185 amino acids and HBeAg of 150 amino acids, which are the product of alternative translation initiation from

two AUG codons and post-translational modification. From the inner AUG codon, the structural polypeptide of the viral capsid Core protein of 21 kDa in size is synthesized. A 24 kDa preCore protein is encoded from the upstream AUG codon. The Core protein plays a key role in the HBV life cycle, and changes in its sequence can serve as potential markers of disease progression [12]. HBcAg serves as a key target for the host immune response, especially attack by CD4 and CD8 cytotoxic T-lymphocytes, whereby nonsynonymous mutations that alter immune epitopes can lead to the formation of escape variants from the immune response, resulting in HBV persistence. Moreover, as substitutions in Core region can lead to simultaneous substitutions in HBeAg, a key immunity regulation protein of the virus, they can have a significant impact on the natural course of chronic HBV [28]. BCP also plays a crucial role in viral replication, contributing to the formation of preCore and pregenomic RNA [29], which means that mutations in this region may also contribute to disease development. Mutations in different regions of the viral genome leading to such changes may be a consequence of both natural evolution of the virus and external influence, since both endogenous and exogenous selective effects lead to modification of the pathogen genome structure due to its high variability, especially during the long-term course of the disease [24].

In the study group, 15 people had HBV genotype A, including 8 cases of genotype A1, which is endemic to Africa and has a long evolutionary history on the



**Fig. 2.** Frequency of the most common amino acid substitutions occurrence in the Core region of the hepatitis B virus genome in the examined group and according to genotypes.

Amino acid substitutions are presented relative to the consensus sequence of the Mart-B47 virus (HE974377.1, genotype D) with additional analysis relative to genotype-specific reference sequences — AY128092.1 (genotype A), NC\_003977.2 (genotype D) and AB032431.1 (genotype E).

continent. It has been previously shown that Africans infected with subgenotype A1 have a 4.5-fold higher risk of developing liver cancer than those infected with other genotypes, with cancer developing at an earlier age [30].

The majority of the cohort studied in the present study consisted of patients with HBV genotype E. This genotype is one of the most common variants in sub-Saharan Africa, including the Republic of Guinea and its neighboring countries. Despite its widespread occurrence, this variant of the virus has a relatively low genome variability compared to others, which may indicate its shorter evolutionary history [31]. At the same time, some researchers have raised concerns about the efficacy of HBV vaccine in genotype E, as breakthrough infections have often been observed in this genotype. Presumably, this may be due to the double mutation *A1762T/G1764A* in BCP, associated not only with the progression of liver disease, but also with a reduced level of secreted HBeAg, eluding the immune response [32]. Thus, the high incidence of HCC known for HBV genotype E may be related to both the prevalence of genome alterations leading to disease progression and the previously mentioned late detection of infection, with one factor complementing the other [31]. A high occurrence of the *A1762T/G1764A* double mutation (15.42%) was shown in our study group. Furthermore, a significant number of mutations in the preCore/Core region of HBV were detected, including a high frequen-

cy of the preCore *G1896A* mutation (35.21%), leading to the appearance of a stop codon (W28\*), premature termination of the HBeAg precursor, responsible for more than 90% of cases of defective HBeAg secretion and, consequently, cancellation of antigen expression, which is characteristic of patients infected with HBV genotype E [33]. Note that a similarly high prevalence of the *G1896A* mutation (47.11%) was previously shown in residents of the Republic of Guinea with HBV genotype E [22]. The preCore region amino acid substitution H5D of HBV genotype E in HBsAg-negative genotype E identified in the present study is associated with severe liver disease. This mutation may also partially explain the high prevalence of HCC in Africa. Two more mutations, *K21N/Q/R* and *G29D* in the preCore region, significant for the development of HCC and associated with severe disease in HBsAg-negative individuals, were identified among isolates of genotypes E and D [26]. A significant number of mutations in the Core region at positions 113–143, known to affect antigenicity and particle stability and resulting in immune eluding mutants leading to chronic persistence of the virus, were found in the examined group.

For most of the amino acid substitutions identified in the Core-region, there is no reliable information on their clinical significance; however, HBeAg immune recognition sites are known, including target epitopes for human CD4<sup>+</sup> T cells (amino acid positions 1–20, 50–69, 81–105, 117–131, 141–165), cytotoxic T lym-



**Table 2.** The most prevalent clinically significant mutations identified in the BCP and preCore/Core region in examined group

HBV genome region	Mutation	Frequency of occurrence in the group (n = 480)			Genotype	Clinical significance of the mutation
		n	%	95% CI		
BCP	A1762T/G1764A	74	15,42	12,30–18,96	E	Disease progression, liver cirrhosis and HCC [24, 25]
PreCore	H5D	130	27,08	23,16–31,30	E	Associated with severe liver disease in HBsAg-negative HBV genotype E. This mutation could partially explain the high prevalence of HCC in Africa [26]
PreCore	K21N/Q/R	31	6,46	4,43–9,04	E, D	Presumably associated with disease progression, especially in HBsAg-negative patients [26]
PreCore	W28* (G1896A)	169	35,21	30,93–39,67	E, A	Disease progression, liver cirrhosis and HCC [24, 25]
PreCore	G29D (G1899A)	88	18,33	14,97–22,09	E, D	
Core	E64D	161	33,54	29,33–37,96	E, A, D	Disease progression, liver cirrhosis and HCC, immune escape [24, 25]
Core	E113Q	19	3,96	2,40–6,11	E, A	Immune escape, selection of specific antibodies, chronic persistence of the virus, disease progression, liver cirrhosis and HCC [24, 25]
Core	T114P/V	44	9,17	6,74–12,11	E	
Core	L116I/V/G	439	91,46	88,59–93,8	E, D	
Core	F122C	11	2,29	1,15–4,06	E	
Core	W125T	13	2,71	1,45–4,59	E	
Core	P130T	29	6,04	4,08–8,56	E, D	
Core	A131P	67	13,96	10,98–17,38	E, A	
Core	R133T	11	2,29	1,15–4,06	E	
Core	S141P	12	2,5	1,30–4,33	E	
Core	L143T	14	2,92	1,60–4,85	E	
Core	T146N	351	73,13	68,92–77,04	E	Enhance the formation of HBV cccDNA during intracellular amplification, but impair cccDNA formation during infection [27]. Immune escape, selection of specific antibodies, chronic persistence of the virus, disease progression, liver cirrhosis and HCC [24, 25]

phocytes/CD8<sup>+</sup> T cells (amino acid positions 18–27, 88–96, 130–140, 141–151), and B-cell epitopes (amino acid positions 74–89, 107–118, 127–138). Mutations in such immunogenic regions of HBcAg are vital for virus persistence, host immune response, and disease progression [25]. Thus, among the detected amino acid substitutions, a number of mutations are of potential clinical significance, contributing to the development of chronic HBV, for example, localized at T cell epitope sites (*T12S*, *E64D*, *L65V*, *M66I*, *T67N/S*, *A69S*, *N87G/S*, *T91N/S*, *M93V/I*, *G94A*, *I97F*, *F103L*, *I105T*, *F122C*, *W125T*, *P130T*, *A131P*, *S141P*, *L143T*, *T146N*, *V149I*, *R151Q*, *R152G*, *S157T*) and B cells (*N74V/A*, *P79Q*, *A80T*, *N87G/S*, *L108I*, *E113Q*, *T114P/V*, *L116I/V/G*, *P130T*, *A131P*, *R133T*). Amino acid substitutions in key immune epitopes have the potential to evade the immune response, which in turn may be one of the causes of HBsAg-negative HBV, lead to persistent infection and high variability in all regions of the viral genome [34]. It should be noted that among the listed mutations there are those that are significantly associated with the development of liver cirrhosis and HCC, including those located in B-cell epitopes *E77D/Q*, *A80T*

and *L116I/V/G*, as well as in T-cell epitopes *E64D* and *T91N/S*. Given the high occurrence of such substitutions, their significant role in the increased prevalence of severe liver diseases in African countries, especially in cases of HBV genotype E, cannot be excluded. The amino acid substitutions of particular interest are those detected in absolutely every genotype E individual examined — *E40D*, *N74V/A*, *N87G/S*, *I97F*, *R181P*, *E182A/P*, which, given their 100% representation, may be characteristic of genotype E in general or associated with the peculiarities of this genetic variant of the virus in the Republic of Guinea, but, on the other hand, are associated with the progression of liver disease.

The study showed greater variability in the pre-Core/Core region of genotype E compared to A and D, while it is known that HBV genotype E in general is characterized by relative heterogeneity compared to other genotypes. It is apparent that the results of this study contradicting this fact are related to the fact that isolates of genotype E prevailed in the group, while genotypes A and D are represented by single cases.

The occurrence of mutations among HBV genotype E isolates has increased significantly over the past

15 years. In 2009, P. Garmiri et al. demonstrated that in the Republic of Guinea, 26.0% of HBV genotype E cases had 1 or more mutations at positions 1762, 1764 and/or 1896, a premature stop codon associated with the *G1896A* mutation was observed in 20.8% of sequences, and 5.2% had a triple mutation [35]. In this current study, *G1896A* presented 1.5 times more frequently (35.21%), and triple mutation was shown in 47 individuals – 9.79% (95% CI 7.28–12.81%) of the total group and 10.54% (95% CI 7.85–13.77%) of those with genotype E. These mutations most likely represent a consequence of natural polymorphism of the virus. However, mutations in positions 1762, 1764, 1896 are among the most common. In Pakistan, *A1762T/G1764A* was observed in 30% of cases, *G1896A* — in 38% of cases [36]. In Ethiopia, the occurrence of *A1762T/G1764A* was 25.9% of cases and *G1896A* was 25.2% of cases [37]. In Brazil, the occurrence of *A1762T/G1764A* was 59.3% of cases and *G1896A* was 84.1% of cases [38]. Furthermore, the occurrence of these mutations is often associated with the virus genotype. For example, the occurrence of *A1762T/G1764A* in Vietnam was 93.3% for genotype C and 50% for genotype B, and *G1896A* was 74.2% for genotype B and 2.2% for genotype C [39]. The analysis of 6479 HBV sequences of different genotypes from the international database allowed us to determine the overall frequency of *A1762T/G1764A* — 28.9%, the representation of this double mutation in relation to genotypes was as follows: A — 26.9%; B — 15.5%; C — 46.1%; D — 21.5%; E — 11%; F — 22.5%; G — 97.5%; H — 3.8%, but it should be noted that the sample volume of genotypes E-H was significantly smaller than the other genotypes [40]. This seems to be the reason for the relatively low occurrence of *A1762T/G1764A* in genotype E, whereas, for example, in Nigeria, where the study population was predominantly genotype E, *A1762T/G1764A* was detected in 43% of cases and *G1896A* in 57% of cases [41].

It should be noted that in our cohort HBsAg-negative and low viral load samples showed more variability throughout the preCore/Core region, which may be

related to the inhibition of HBV replication due to mutations in preCore/Core region. Numerous studies have described an association between the frequency of mutations in the preCore/Core region and the progression of liver disease in HBV-infected patients, but the association between amino acid substitutions and clinical severity of disease varies considerably both between different populations and between studies conducted in the same populations. This apparent discrepancy can be explained by various factors, including virus genotype, patient ethnicity, host immune competence, and coinfection with other viruses. Nevertheless, a number of mutations that have been shown to be significantly associated with liver cirrhosis and HCC, as well as affecting HBeAg serological status, may serve as diagnostic and prognostic markers for early detection of liver disease progression in HBV-infected individuals.

### Conclusion

The prevalence of clinically significant amino acid substitutions in HBV preCore/Core region in treatment-naïve pregnant women in the Republic of Guinea reflects their occurrence in the population and indirectly explains the reasons for the extremely high incidence of HCC in African countries. A number of such amino acid substitutions, associated with disease progression as shown for genotypes A and D, are characteristic of genotype E. Identification of genotypes and mutations in the virus genome can be used to predict disease progression. The identified variability indicates the need to study the peculiarities of the pathogen and host immune response, including in HBsAg-negative HBV infections. The results of this study demonstrate the necessity to raise awareness of the growing epidemic crisis of HBV in sub-Saharan Africa. This region is at the bottom of the list in terms of access to a range of health care services, including screening, diagnosis and treatment of people infected with the virus. The results of the study can serve as baseline data for estimating national HBV incidence and planning mass HBV immunization in the Republic of Guinea.



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