Research Square

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Genotypic variability and the mutational landscape of the hepatitis B virus among HIV-infected patients living in the regions of Western Siberia (Russia)

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Abstract

Background. Hepatitis B is a major public health problem due to its prevalence, complications, and genetic variability, which requires detailed molecular characterization for effective treatment. HIV-HBV co-infection exacerbates the course of hepatitis B, increases the risk of liver damage and death, and also reduces the effectiveness of antiviral therapy. The genetic diversity of the hepatitis B virus in HIV-positive individuals has not been sufficiently studied, so such research is extremely important for developing more effective control and treatment strategies.

Materials and methods. The study analyzed 708 blood serum samples were collected from patients with confirmed HIV infection. For primary screening for HBV DNA, a commercial "AmpliSens HBV-FL" kit was used. For the selected positive samples, next-generation sequencing on the Illumina MiSeq platform was used to obtain full-genomic HBV nucleotide sequences, which were serotyped, genotyped, and analyzed for the presence of clinically significant mutations

Objective. To identify and characterize the variants of hepatitis B in HIV-infected patients from three geographically close regions of Western Siberia (Novosibirsk Region, Tomsk Region, and the Altai Republic).

Results. The incidence of HBV genetic material in the study group was 8.5% (95% CI = 6.6–10.8). The work analyzed 60 full-genomic sequences of the identified HBV variants. All studied HBV variants were assigned to genotype D, and the distribution of HBV subgenotypes in the regions was different and consistent with previously obtained data. The overall detection rate of mutations in the hepatitis B virus surface antigen (S gene) was 55.0%, BCP mutations – 28.3%, PreCore mutations – 66.7%, mutations in the Core and X genes were detected in each of the 60 analyzed genome-wide sequences of HBV variants.

Conclusion. The results highlight the importance of continuous molecular monitoring for the development of diagnostic strategies, improving the effectiveness of vaccination, and clinical management of HBV patients, especially among people living with HIV.

Background

Infection caused by the hepatitis B virus (HBV infection) is considered a socially significant disease, which is due to the widespread prevalence of HBV infection in the population, especially in high-risk groups, and the wide variability of clinical outcomes, with a high frequency of complications such as liver cirrhosis and hepatocellular carcinoma [1, 2, 3].

The hepatitis B virus is a DNA-containing virus with a compact genome featuring overlapping reading frames. Despite its small genome size (approximately 3,200 bp), HBV exhibits significant variability: 10 genotypes have been described (with a nucleotide sequence difference of at least 8% between different genotypes and up to 4% between different subgenotypes) and 9 serotypes [4, 5]. Furthermore, due to the

specific features of the HBV life cycle (replication via a viral polymerase that lacks proofreading functions), HBV is characterized by a high frequency of mutations, some of which can confer an advantage to mutant variants under evolutionary pressure (the widespread implementation of hepatitis B vaccination and the use of nucleoside analog antiviral therapy) [5, 6].

Knowledge about the nature and prevalence of HBV mutations among different population groups is important for making decisions about adjusting strategies to combat HBV infection; genetic characterization of the HBV variant in a specific patient is the basis for personalized therapy. Studying the prevalence of HBV genotypes and serotypes is also important for a more comprehensive understanding of the epidemiological situation in regions, as it allows one to determine the presence of epidemiological links [1, 6, 7, 8, 9].

Infection caused by the human immunodeficiency virus (HIV) also belongs to the group of socially significant diseases [1, 10]. Due to the commonality of transmission routes, HBV coinfection is often observed in HIV-infected patients (up to 10% of HIV-infected individuals worldwide are also infected with HBV) [3, 8], and the prevalence of HBV-HIV co-infection among HIV-infected individuals varies depending on the endemicity of each infection in different regions (from 5 to 20%) [3, 11].

According to literature data, the effect of HBV on the course of HIV infection is minimal [3], while HIV has a significant effect on the progression of HBV infection: compared with HBV-monoinfected patients, patients with HBV-HIV coinfection have a higher incidence of chronicity after acute HBV infection [10, 11], higher mortality rates [3, 10, 12], a higher incidence of cirrhosis and hepatocellular carcinoma and more pronounced biochemical indicators of liver damage [2, 3, 12], while the effectiveness of antiviral therapy for HBV infection in the context of immunosuppression in HIV-infected patients is significantly reduced [3, 8, 11]. Furthermore, there is growing evidence that people with co-infection of HIV and hepatitis B are more likely to have certain mutations in the hepatitis B viral genome, which contribute to the rapid progression of liver damage in such patients [6, 13].

Despite the fairly widespread occurrence of HBV-HIV co-infection and the relevance of the problem, studies devoted to the molecular-genetic diversity of HBV (especially mutant variants) remain relatively scarce [6, 12].

Objective

To identify and characterize the variants of hepatitis B in HIV-infected patients from three geographically close regions of Western Siberia (Novosibirsk Region, Tomsk Region, and the Altai Republic).

Materials and methods

The study was conducted on 708 serum samples from 708 HIV-infected patients (133 patients from the Novosibirsk Region, 326 from the Tomsk Region, and 249 from the Altai Republic). The patients had not

previously received antiviral therapy for HIV and HBV. The groups of patients from the studied regions were practically comparable by gender (the proportion of men was 54.9 ± 8.5%, 52.2 ± 5.4% and 57.4 ± 6.1%, respectively, $p > 0.05$) and by age (the average age in the groups was 34.9 ± 2.8, 32.2 ± 1.6%, and 35.2 ± 1.8 years, respectively, $p > 0.05$). HIV and HBV coinfection was defined as documented HIV infection and the presence of HBV DNA in the patient's blood serum.

The study complies with the provisions of the Helsinki Declaration and was approved by the Ethics Committee of the State Research Center of Virology and Biotechnology «Vector» of Rosportebnadzor (Protocol No. 5). Each of the patients included in this study signed an informed voluntary consent to participate in the study.

Nucleic acids were extracted from clinical samples using the commercial kit – «RIBO-prep» («AmpliSense®», Russia). The presence of HBV DNA was determined by real-time PCR using the "AmpliSens HBV-FL" kit (analytical sensitivity — 50 IU/ml, «AmpliSense®», Russia). The identified positive samples were selected for further development of the complete HBV genome using nested PCR using internal overlapping primers jointly flanking the complete HBV genome (S, P, C, X genes) according to the previously described method [14]. The PCR quality was visually determined in a 2% agarose gel (100V, 45 min; 1×TBE) stained with ethidium bromide. High-throughput sequencing on the Illumina MiSeq platform was used to determine the HBV nucleotide sequence. All stages of the study were conducted in accordance with the protocols of the manufacturing companies.

The phylogenetic analysis of the obtained nucleotide sequences of the identified HBV variants was carried out in Mega XII using a three-parameter T92 evolution model. For phylogenetic analysis, prototypes of hepatitis B virus sequences from the international GenBank database were used, as well as 275 hepatitis B virus sequences from the GenBank database obtained from people living in both close and remote regions, relative to those studied in this study. Since most of the sequences included in the phylogenetic analysis are the nucleotide sequence of the S-gene of HBV, the maximum likelihood method was chosen for phylogenetic analysis, since this method is applicable to aligned sequences of different lengths and allows for more accurate genotyping results. To assess the reliability of the constructed trees, a bootstrap was performed for 500 repetitions.

HBV genotyping was performed using constructing a phylogenetic tree with prototype HBV sequences from the international GenBank database. HBV serotypes were determined based on the amino acid sequence of HBsAg (translation of the S gene) according to the previously described method [15]. Clinically significant changes in the genome of the identified variants, which may affect the course of the disease, prognosis, and treatment effectiveness, were determined based on the obtained nucleotide and amino acid sequences (translation of the S gene, P gene, X gene, Core and PreCore region of the HBV genome) of various regions of the genome according to previous studies [9, 16, 17, 18].

Statistical data processing was performed using the Statistica 12.6 software package (StatSoft, USA). To assess the differences in the data obtained by pairwise comparing the proportions of HBV variants in the studied groups, the χ^2 test (Pearson’s chi-square test) was used. Differences were considered

statistically significant at $p < 0,05$. The average values were estimated taking into account 95% CI using the Clopper–Pearson method and the standard deviation.

Results

According to the results, the incidence of HBV-HIV coinfection in the studied groups was 8.5% (60/708, 95% CI = 6.6–10.8), for the group of patients from the Tomsk region this indicator was 7.1% (23/326, 95% CI = 4.7–10.4), for the group from the Novosibirsk region – 8.3% (11/133, 95% CI = 4.7–14.2), for patients in the Altai Republic – 10.4% (26/249, 95% CI = 7.2–14.9).

The results of the phylogenetic analysis of the identified HBV variants are shown in Fig. 1. The HBV reference sequences were the full-genomic HBV sequences (GeneBank database) recommended by ICTV for genotyping, as well as a number of other HBV variants for which the HBV subgenotype was known. The detailed distribution of HBV subgenotypes in the studied groups is shown in Fig. 2.

The percentage of differences in the nucleotide sequence of the identified HBV variants was 3.06 ± 1.21%, while the divergence within the subgenotype was 2.83 ± 0.56, 1.19 ± 0.61 and 3.3 ± 0.87% for D1, D2 and D3, respectively.

A large-scale comparative phylogenetic analysis was also conducted to identify geographical clusters of HBV circulation and potential distribution routes. The results are shown in Fig. 3.

All variants with D1 and D3 genotypes belong to the ayw2 subtype, while D2 shows great variability: most variants (24/30) encode ayw3, 2 isolated cases of adw3 and ayr were also identified, and serotype could not be determined in four variants due to point mutations at position C/A533G (P/T127A).

The overall detection rate of clinically significant mutations in the HBV surface antigen (S) gene, including in the "a" determinant region (amino acids 124–147) was 55.0% (33/60, 95% CI = 42.5–66.9), BCP mutations (basal core promoter) – 28.3% (17/60, 95% CI = 18.5–40.8), PreCore mutations – 66.7% (40/60, 95% CI = 54.1–77.3), mutations in the Core and X genes were detected in each of the 60 analyzed genome-wide sequences of HBV variants (100%, 60/60, 95% CI = 94.0-100.0). It was noted that mutations of the S gene were statistically significantly more common in HBV variants of genotype D2 compared with other genotypes (100%, 30/30, 95% CI = 88.6–100.0, $p_{D1<D2}<0.001$, $p_{D3<D2}<0.001$), while PreCore mutations were statistically significantly more common in HBV variants of genotypes D1 and D3 (92.9%, 13/14, 95% CI = 68.5–98.7% and 100%, 16/16, 95% CI = 80.6–100.0%, respectively, p D1, D3 > D2 < 0.001). There were no statistically significant differences in the occurrence of mutations in other regions between variants of different HBV genotypes.

A detailed description of the frequencies of clinically significant mutations identified in the studied HBV variants is shown in Fig. 4.

Discussion

The frequency of HIV-HBV co-infection in the studied groups are consistent with those reported in similar studies (6.6% [11] and 5.08% [1] for HBV-HIV co-infection among patients with chronic hepatitis B; 6.73% [2], 7.2% [6], and 15.2% [8] for HBV-HIV co-infection among HIV-positive patients). Differences in prevalence rates may be due to differences in study designs, criteria for inclusion in the study groups, and the endemicity of these infections in the studied regions.

All identified HBV variants were assigned to genotype D (Fig. 1.). The data obtained are consistent with those obtained earlier (the proportion of HBV genotype D among the identified HBV variants in HIV-infected patients was 100% [8, 12], 83.3% [2] and 84.2% [6]). Despite the fact that two other genotypes also circulate in the Russian Federation [5], the overall prevalence of genotype D in the studied sample may be explained by the dominance of genotype D in the structure of circulating genotypes in the Russian Federation [2, 8], and may also indicate the predominant spread of this genotype among HIV-infected individuals, which may be associated with the mode of infection, as previously shown [12]. The clinical features of HBV genotype D include a lower frequency of spontaneous HBeAg seroconversion, longer immunoactive phases, and an increased likelihood of progressive liver disease compared to genotype A. In addition, genotype D has more nucleotide variations in the surface gene, which may affect HBsAg expression, its ability to evade the immune system, and its sensitivity to laboratory tests [6, 19].

The distribution of HBV subgenotypes in the studied group of HIV-infected patients from the Novosibirsk region (D2 — 90.9%, D3 — 9.1%) is similar to the distribution of HBV subgenotypes in a similar group in a previous study (D2 — 96.4%, D3 — 3.6%) [8]. The distribution of subgenotypes in the studied group of HBV-infected HIV patients in the Altai Republic (D2 — 90.9%, D3 — 9.1%) is most similar to the distribution of HBV subgenotypes in the group of HIV-infected patients in the Arkhangelsk Region, Russia (D1 — 39.3%, D2 — 32.1%, and D3 — 28.6%) [12]. Due to the small number of similar studies, it was not possible to determine the similarity of the distribution of HBV subgenotypes in the group of HIV-infected patients in the Tomsk Region with other studies.

Phylogenetic analysis of the identified HBV variants in HIV-infected individuals in the study group shows that they cluster well with previously detected variants circulating in various regions of Russia (primarily Western Siberia) among the population, including those without HIV infection (Fig. 3). It is also worth noting that the genotypes assigned to the previously studied HBV sequences have been confirmed.

The percentage of differences in the nucleotide sequence of the identified HBV variants is higher than previously reported results, which may indicate increased genetic heterogeneity of the circulating variants HBV, due to selective pressure (including as a result of vaccination and antiviral therapy), the spread of imported/recombinant forms, or the specific characteristics of the studied groups [12, 20]. The lower genetic variability of D2 HBV variants compared to D1 and D3 may indicate a later introduction of D2 into the population and/or a close geographical origin of the studied variants [20].

The results of serotyping are consistent with the data obtained by other researchers and confirm the previously identified close relationship between serotype and genotype [3, 20, 21]..

Among the identified clinical significant mutations of the S gene, the A128V mutation was the most common. The mutation is located within the a-determinant of HBsAg, which is the main target for neutralizing antibodies produced both during natural infection and after vaccination against hepatitis B. It can lead to the production of HBsAg that differs from the usual form [22, 23], which in turn results in reduced binding to antibodies, evasion of the virus from vaccine-induced immunity, and false-negative results of diagnostic tests [6, 16]. The remaining identified mutations of the S gene (Y100C, Q101H, T118A, Q129R/H, S143L, D144A, G145A, S167L) also belong to the so-called escape-mutations and can lead to the same clinically significant consequences [16, 17, 24, 25, 26]. Special attention should be paid to the mutation identified in one variant HBV at position 145 (G145A). Although the most well-known mutation at this position is G145R (the replacement of glycine with arginine), the role of which in the virus's evasion of the immune response and diagnostics has been proven in numerous studies, a similar effect is observed when glycine is replaced with alanine at this position (G145A), although there are significantly fewer such studies [16, 27].

In each of the identified HBV variants, at least 1 mutation was detected that had previously been described as a mutation potentially associated with accelerated disease progression. Among them, it is worth noting BCP mutations (A1762T/G1764A), which are considered "classic" BCP mutations, the PreCore G1896A (W28*) mutation, which leads to partial or complete blocking of HBeAg synthesis, as well as amino acid substitutions in the Core region (F24Y, E64D, E77Q, A80T/V/I, E113Q, T114V, L116I/V, A131P) and gene X (V5L, K130M, V131I, H94Y) [9, 18, 28]. It is worth noting that the most common mutation in the studied group is the L116I/V mutation (98.3%, 59/60, 95% CI = 91.1–99.7); this mutation has also been detected in many HBV variants in other studies (94.73% [3] and 91.46% [18]). However, despite the fact that the detected mutations have already been proven to play a role in evading the immune response and/or in the development of liver diseases, these relationships should be treated with caution. They indicate potential "hot spots" of mutations that require further study using larger longitudinal cohorts and functional analyses [6]. None of the identified variants showed mutations associated with primary or secondary drug resistance (mutations in the P gene). Since the study group included only patients who had not previously received antiviral therapy with nucleoside analogues, the absence of evolutionary pressure in the form of antiviral therapy may explain the lack of mutations in this region [29]. Nevertheless, the high frequency of clinically significant mutations detected in other regions of the HBV genome underscores the importance of continuous molecular monitoring of HBV in the group of HIV-infected patients to accurately track the evolution of the virus and ensure the effectiveness of preventive and diagnostic measures.

Conclusions

The study updates the data on the prevalence of HIV-HBV co-infection and the molecular-genetic characteristics of the HBV virus in HIV-infected patients in three regions of the Russian Federation: the Tomsk and Novosibirsk regions, as well as in the Altai Republic. The prevalence of HBV in the study group was 8.47%, which is consistent with the data from similar studies. All identified HBV variants were assigned to genotype D. The genetic diversity of HBV variants in the study group of HIV-infected

individuals is similar to the diversity observed in the general population. The high frequency of clinically significant mutations (including escape-mutations) underscores the need for continuous molecular monitoring of HBV in HIV-infected patients, which will make it possible to promptly identify HBV variants with altered antigenic properties, prevent false-negative diagnostic results, and predict the course of the disease and the risk of progressive liver damage. Limitations of this study include the small sample size, so the data on the distribution of genotypes, serotype frequencies, and the prevalence of clinically significant mutations may not be fully representative of the entire study population, especially for patients from other regions.

Abbreviations

HBV
Hepatitis B virus
HBsAg
Hepatitis B surface antigen
HBeAg
Hepatitis B e-antigen
HIV
Human immunodeficiency virus
HDV
Hepatitis D virus
DNA
Deoxyribonucleic acid
PCR
Polymerase chain reaction
bp
Base pairs
BCP
Basal core promoter
PreCore
Precore region
S gene
Surface gene
P gene
Polymerase gene
C gene
Core gene
X gene
X gene
IU/ml

International units per milliliter
CI
Confidence interval
ICTV
International Committee on Taxonomy of Viruses
GenBank
Genetic sequence database (NCBI)
NCBI
National Center for Biotechnology Information
TBE
Tris-Borate-EDTA (buffer)
MEGA
Molecular Evolutionary Genetics Analysis (software)

Declarations

Ethics approval and consent to participate. The study was carried out in compliance with the principles of voluntariness and confidentiality in accordance with the «Fundamentals of the legislation of the Russian Federation on the protection of the health of citizens» (as amended by Decree of the President of the Russian Federation dated December 24, 1993 No. 2288, Federal laws dated March 2, 1998 No. 30-FZ, dated December 20, 1999 No. 214-FZ). The study was conducted with voluntary informed consent of the patients. The study protocol was approved by the decision of the ethical committee of the State Scientific Center of Virology and Biotechnology «Vector» of Rospotrebnadzor (protocol №5 of July 21, 2022).

Consent for publication. Not applicable.

Availability of data and material. The sequences presented in the study have been deposited in the GenBank, accession numbers PP393566-PP393591, MT 579898-MT579903, PZ879506-PZ879510, PX116478- PX116500. Further inquiries can be directed to the corresponding author.

Competing interests. The authors declare that they have no competing interests.

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Authors' contributions. Conceptualization: A. Zh., M. K.; collection and processing of material, compilation of a database: A. Zh., M. K.; methodology: M. K., K. S., A. Zh.; writing original draft preparation: A. Zh; review and editing: M. K.; supervision: M. K.; funding acquisition: M. K. All authors read and approved the final manuscript.

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Figures

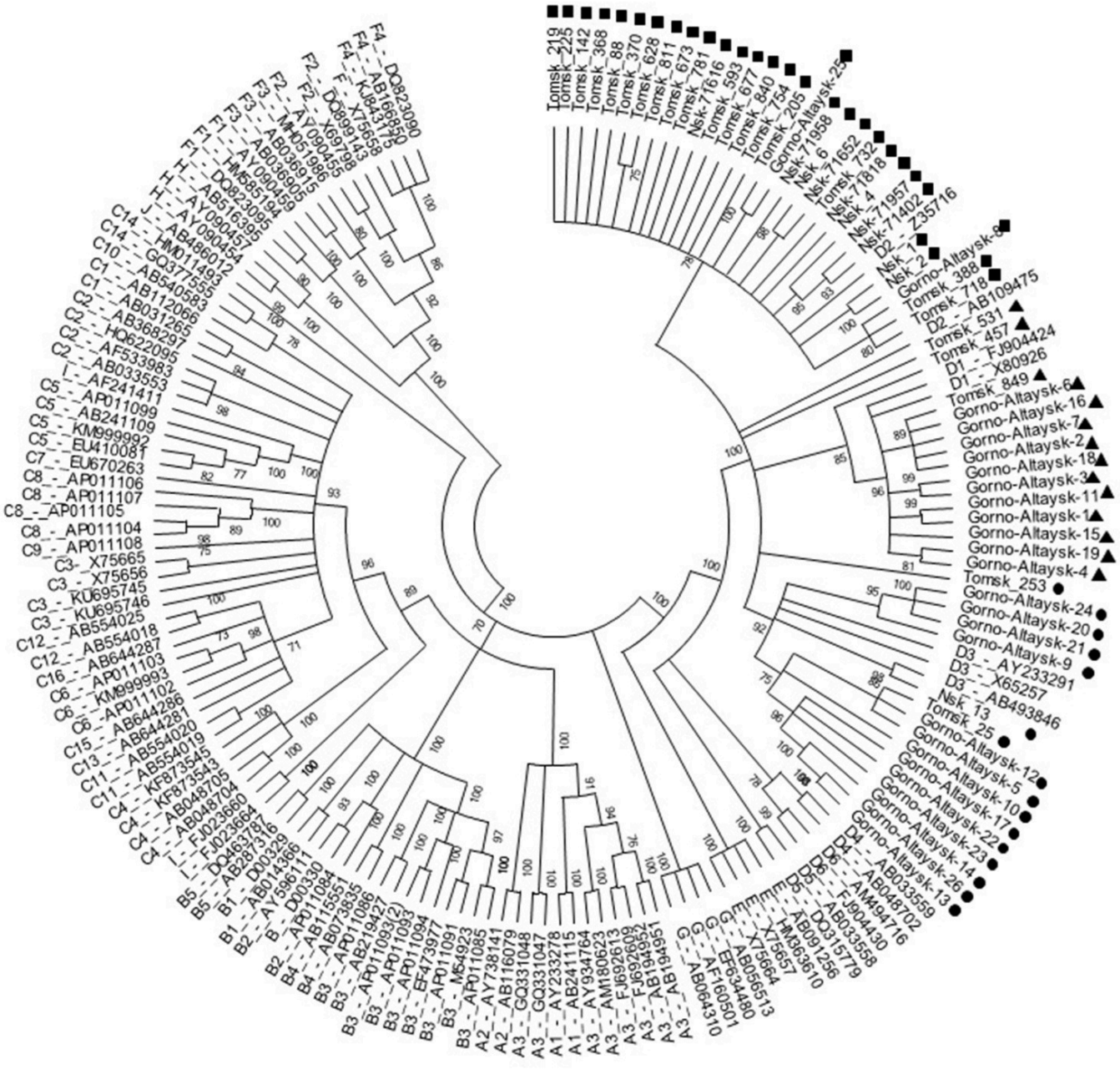


Figure 1

Genotyping of identified HBV variants. Reference sequences are indicated by GenBank codes with genotype information. Black triangles denote the whole-genome HBV sequences examined in this study that were assigned to genotype D1; black squares denote D2; black dots denote D3. Numbers indicate bootstrap values ≥70.

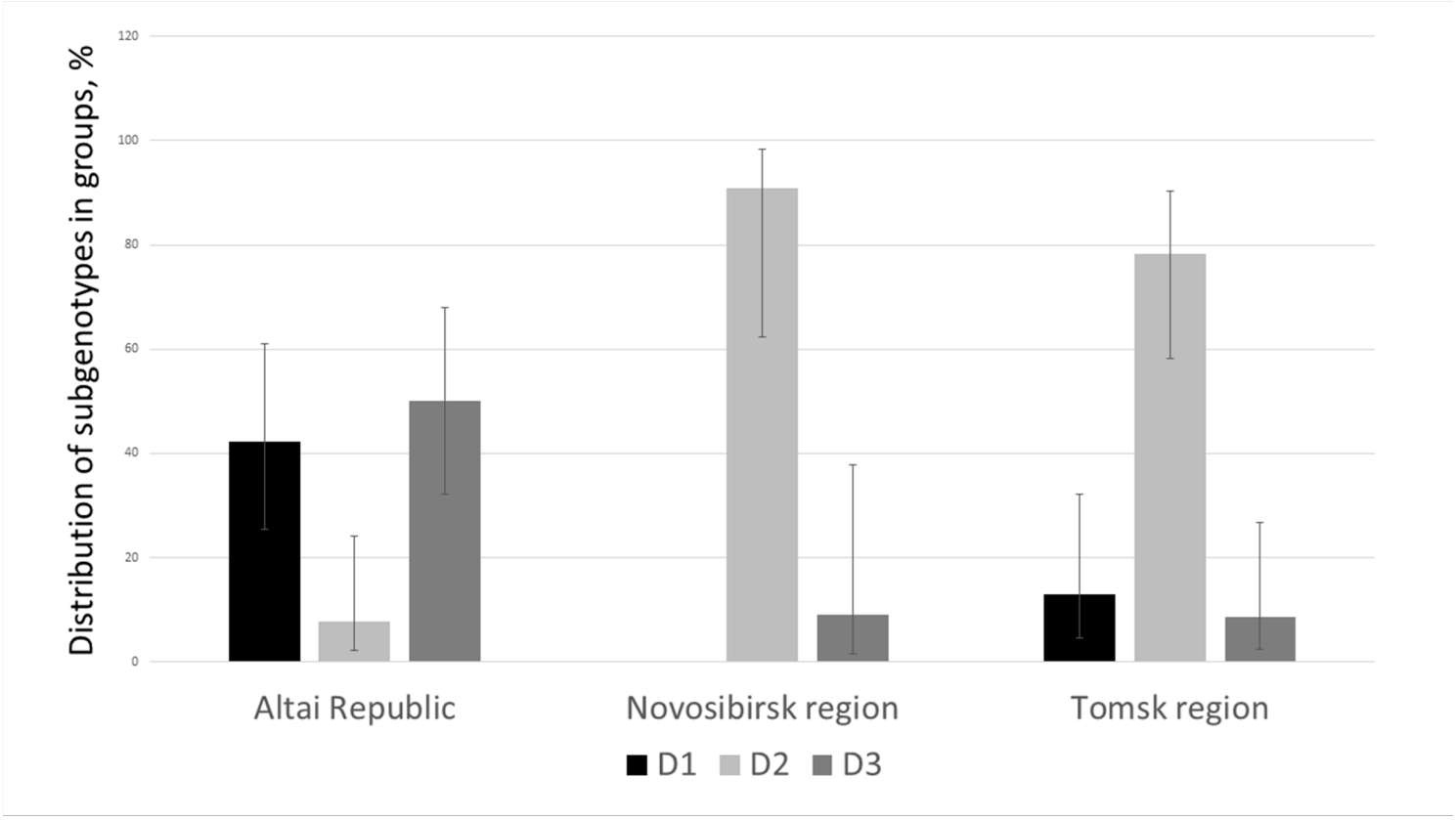


Figure 2

Distribution of HBV subgenotypes in the studied groups.

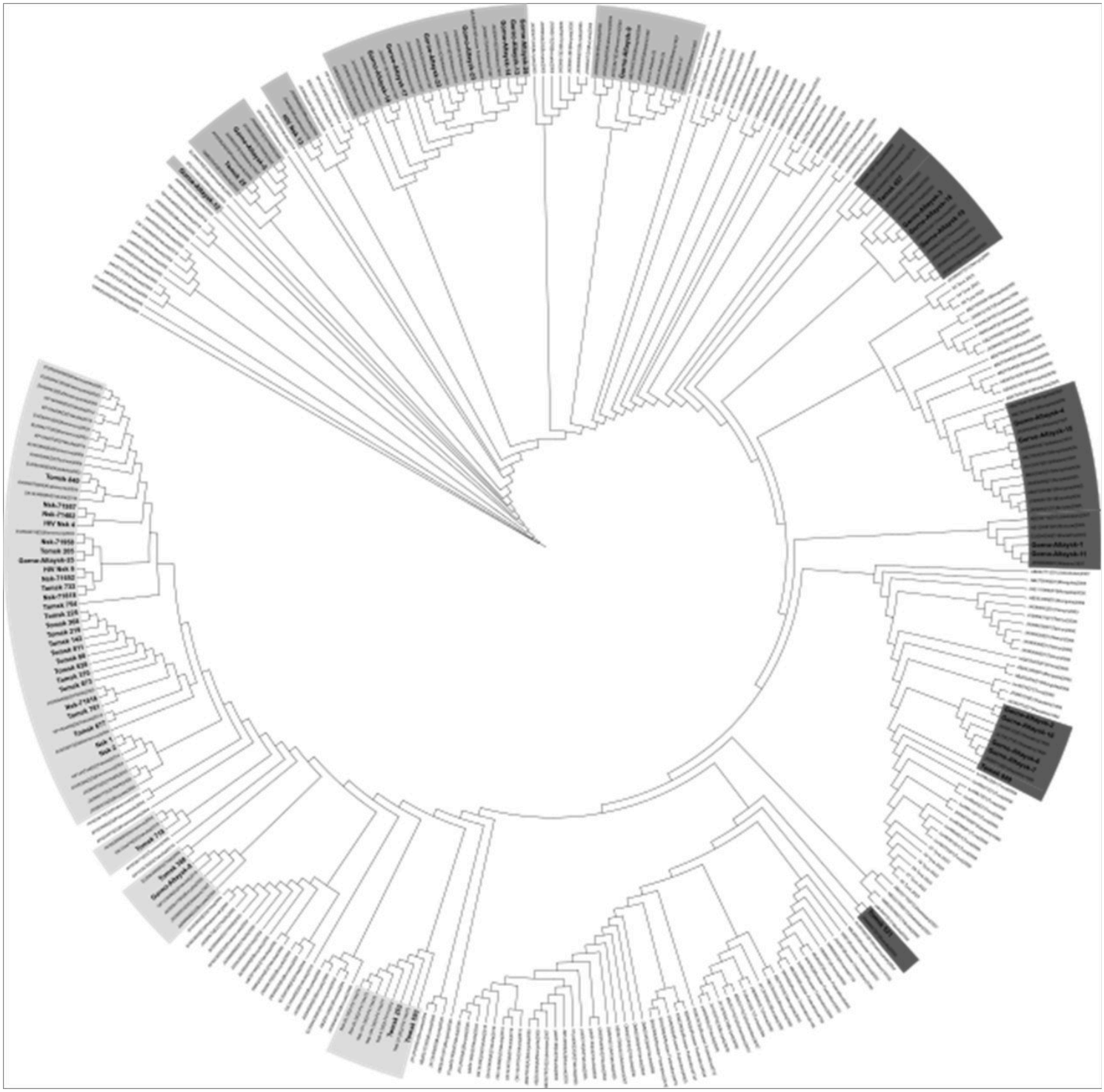


Figure 3

Phylogenetic tree of the studied HBV variants isolated from HIV-infected patients, in comparison with HBV sequences presented in the GenBank international database (various regions of the Russian Federation + nearby neighboring countries (Uzbekistan, China, Mongolia, Kazakhstan). The clusters of genotype D2 are indicated by light gray zones, the clusters of genotype D1 by gray zones, and the clusters of genotype D3 by dark gray zones. The HBV sequences obtained in this work are marked in bold.

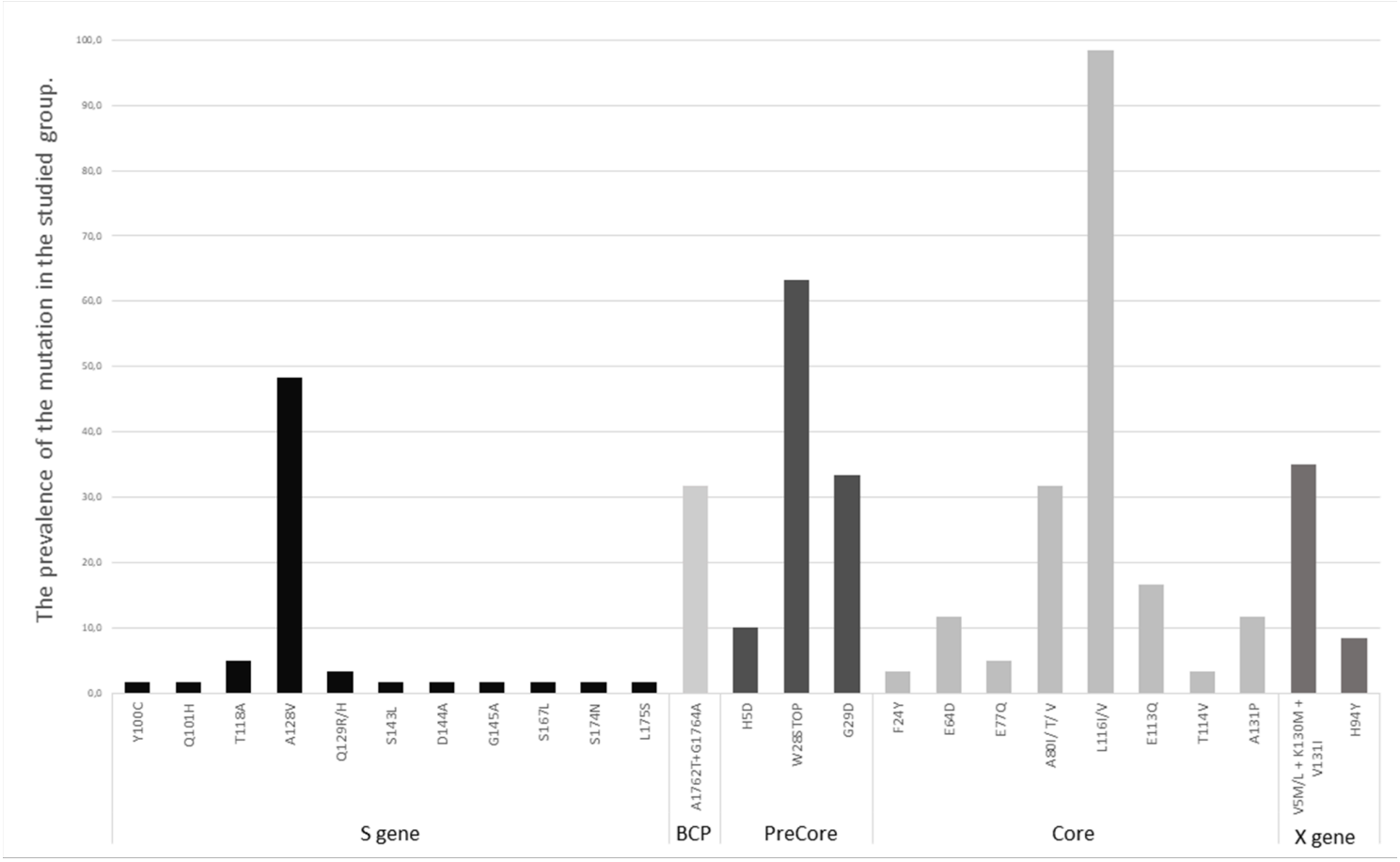


Figure 4

Characteristics of the frequencies of identified clinically significant mutations in the studied HBV variants