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Review Article

Molecular Basis and Clinical Significance of the High-risk Phenotype of Hepatitis B Virus Genotype C

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Abstract

Hepatitis B virus (HBV) genotype C is common in East Asia and is associated with poor outcomes, particularly liver cirrhosis and hepatocellular carcinoma (HCC). Clinically, genotype C infection is generally associated with persistent viral replication, later HBeAg seroconversion, more active hepatic inflammation, and an increased risk of HCC. Current evidence suggests that these features are driven by several key molecular events, including the A1762T/G1764A double mutation in the basal core promoter, the G1896A mutation in the precore region, abnormal hepatitis B virus X protein function, and viral integration. Together, these changes may reshape viral transcription, antigen expression, host immune interactions, and oncogenic signaling, thereby contributing to disease progression and hepatocarcinogenesis. Other factors, such as epigenetic changes, dysregulated DNA damage responses, impaired tumor protein p53 function, and disrupted autophagy, may also be involved, although their exact roles remain unclear. Notably, even after effective viral suppression with potent nucleos(t)ide analogs, patients with genotype C may still have a relatively high residual risk of HCC. This review summarizes the molecular virological features, pathogenic mechanisms, immune dysregulation, and clinical significance of HBV genotype C, and discusses the potential value of genotype information in risk stratification, long-term surveillance, and clinical assessment of chronic hepatitis B.

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Introduction

Chronic hepatitis B (CHB) remains a major public health issue worldwide. Although hepatitis B vaccination has been widely implemented and antiviral therapies have significantly improved patient outcomes, hepatitis B virus (HBV)-related liver disease continues to be an important cause of morbidity and mortality, especially in the Western Pacific and African regions.[1] In patients infected with HBV before universal immunization, accurate risk assessment and long-term management remain major clinical challenges.

The clinical course of CHB varies widely. Some patients remain in an inactive phase characterized by minimal liver inflammation and near-normal liver histology, whereas others develop progressive fibrosis, cirrhosis, hepatocellular carcinoma (HCC), or hepatic decompensation.[2] This difference cannot be explained by host factors alone. Age at infection, sex, immune status, and genetic background all play important roles, but environmental exposures and viral factors also contribute.[3] Increasing evidence suggests that viral factors, especially HBV genotypes and related mutation patterns, are important determinants of disease progression and long-term prognosis.

Although HBV is a DNA virus, it replicates through reverse transcription of an RNA intermediate. Because its polymerase lacks efficient proofreading activity, HBV exhibits a relatively high mutation rate.[4] HBV is classified into at least 10 major genotypes (A–J) and multiple subgenotypes, which differ in geographic distribution, virological features, and clinical outcomes.[5] In Asia, genotypes B and C are the predominant genotypes and have been the main focus of clinical and molecular studies.

Genotype C has attracted particular attention because it is more frequently associated with adverse clinical outcomes. Compared with genotype B and some other genotypes, genotype C infection is more commonly linked to delayed hepatitis B e antigen seroconversion, persistent viral replication, more active hepatic inflammation, and a higher risk of cirrhosis and HCC.[6–8] Within genotype C, subgenotype C2 is predominantly found in East Asia.[9] Owing to its wide distribution and potential clinical significance, C2 has received considerable attention. However, much of the available high-quality evidence still concerns genotype C as a whole, whereas direct comparative studies specifically addressing C2 remain limited.

Therefore, the risk profile of C2 should be interpreted within the broader virological and clinical context of genotype C.

Current evidence suggests that the high-risk features of HBV genotype C are closely related to its molecular virological characteristics rather than being incidental. In particular, mutations in the basal core promoter (BCP) and precore (preC) region may jointly contribute to a viral phenotype characterized by high replication and low HBeAg expression.[10] In addition, abnormal hepatitis B virus X protein function, HBV integration, and the resulting activation of oncogenic signaling may also contribute to chronic inflammation, immune imbalance, and hepatocarcinogenesis.[11] Therefore, examining the clinical heterogeneity of CHB in the context of viral genotypes and their molecular mechanisms may help clarify the basis of HBV-related hepatocarcinogenesis and refine risk stratification and long-term clinical assessment.

This review focuses on the virological characteristics, pathogenic mechanisms, and clinical relevance of HBV genotype C in CHB. It summarizes the molecular basis of its high-risk features, particularly its association with hepatocarcinogenesis, and discusses the potential value of genotype-related factors in clinical risk assessment and long-term management.

Virological features of HBV genotype C

Phylogenetic classification and geographic distribution

HBV genotype C is a major genotype predominantly distributed in Asia and Oceania. It is closely associated with CHB progression, cirrhosis, and an increased risk of HCC.[12] Phylogenetic analyses based on full-length genome sequences have shown marked genetic heterogeneity within genotype C, and several subgenotypes have been identified. Among these, C1, C2, C3, and C4 are the subgenotypes most frequently discussed in clinical and epidemiological studies, whereas C5 and several rarer lineages have been reported in specific geographic regions.[13] These subgenotypes differ in geographic distribution, evolutionary history, and certain virological characteristics. C1 is prevalent in Southeast Asia, whereas C2 is common in the Chinese mainland, the Korean Peninsula, and Japan. In contrast, C3, C4, and related lineages are more frequently identified in Oceania and nearby regions.[5,9] This distribution pattern may be influenced by regional differences in historical HBV endemicity, transmission patterns, and host background. In East Asia, before hepatitis B vaccination became widespread, HBV transmission mainly occurred through mother-to-child transmission and early childhood exposure. This may have contributed to the long-term persistence and regional predominance of genotype C, particularly C2.[14]

In areas where HBV genotypes B and C co-circulate, both mixed-genotype infection and superinfection have been documented. With the introduction of more sensitive molecular methods, mixed-genotype infection may be more common than previously appreciated in such settings,[15,16] arising either from exposure to multiple viral strains during primary infection or from superinfection after chronic HBV infection has already been established.

Compared with single-genotype infection, mixed-genotype HBV infection may be associated with higher viral replication levels and more active hepatic inflammation.[17] However, these observations have not been consistent across studies, and the underlying mechanisms remain unclear. Potential explanations include interactions between coexisting viral strains, recombination between genotypes, and differential host immune responses to heterologous viral antigens. Beyond geographic distribution, major HBV genotypes also differ in HBeAg seroconversion, viral replication, mutation patterns, disease progression, and HCC risk. These risk-relevant clinical and virological differences are summarized in Table 1.[5,13,18,19–22]

HBV genome structure, regulatory regions, and key sequence features

The HBV genome is a partially double-stranded relaxed circular DNA molecule of approximately 3.2 kb.[23] Despite its limited genomic size, HBV maintains high coding efficiency through overlapping open reading frames, multiple transcripts, and compact transcriptional regulation.[24] Its major viral proteins are encoded by four highly overlapping open reading frames. The preC/core (C) region encodes HBeAg and the core protein hepatitis B core antigen. The polymerase (P) gene encodes a multifunctional enzyme with reverse transcriptase, DNA-dependent DNA polymerase, and RNase H activities. The the pre-surface/surface (preS/S) region encodes the large, medium, and small envelope proteins. The X gene encodes HBx, which is involved in viral replication and the regulation of multiple host cellular processes.[25] Because of this extensive genomic overlap, a single nucleotide change may affect more than one viral region and influence multiple viral functions (Fig. 1).

In genotype C, the key issue lies not only in the genome structure itself but also in the sequence background that may influence the emergence of important regulatory mutations. Comparative genomic studies have shown that genotype C, particularly the East Asian C2 subgenotype, carries relatively stable characteristic nucleotides in the preC region, the BCP, and other regulatory regions.[26] These sequence features may not determine the clinical phenotype by themselves. However, they may influence the likelihood of later mutations and modify their biological effects.[27]

Among the regulatory regions, the preC region and BCP are of particular importance. Both are directly involved in the regulation of HBeAg expression and are closely associated with viral replication status and disease progression.[28] One of the best-studied BCP variants is the A1762T/G1764A double mutation.[29] This mutation is more frequently detected in genotype C than in genotype B and is also commonly found in C2 strains from East Asia.[30] These observations suggest that genotype-specific sequence background may influence the development of key regulatory mutations, thereby altering HBeAg expression and viral replication.

Some genotype-specific nucleotide differences also have clearer structural and functional relevance. One representative example is nucleotide 1858 in the preC region. Genotype C usually carries 1858C, whereas genotype B more often carries 1858T.[31] The G1896A stop codon mutation requires stable base pairing within the ε stem-loop structure. Because nucleotide 1858 affects local base pairing within this structure, variation at this site can directly influence the emergence and stability of G1896A.[32] This may partly explain why the frequency and timing of G1896A differ between genotypes.

Taken together, the high-risk features associated with HBV genotype C are not simply the result of isolated mutations. They are also shaped by the intrinsic genomic background of genotype C, which may influence the selection, persistence, and functional effects of key regulatory mutations.

Key mutations and their biological effects

BCP A1762T/G1764A double mutation: The BCP, located at nucleotides 1744–1804 of the HBV genome, regulates transcription of the 3.5-kb preC mRNA and 3.5-kb pregenom-

Table 1. Risk-relevant clinical and virological features of major HBV genotypes

Feature	Genotype A	Genotype B	Genotype C	Genotype D	Key references
Geographic distribution	Europe, North America, parts of Africa	East and Southeast Asia	East Asia and Oceania; C2 common in East Asia	Mediterranean region, Middle East, India, parts of Europe	5,13,19
Asian prevalence	3.1% overall	17.8% overall; high in Vietnam, Taiwan, China	30.9% overall; high in China, Japan, Thailand, Korea	15.4% overall; high in Iran, India, Turkey	13
HBeAg seroconversion	Earlier than genotype D	Earlier than genotype C	Later than genotype B; longer HBeAg-positive/high-replication phase	Later than genotype A; often linked to HBeAg-negative CHB	19–21
Viral replication/histologic activity	Lower intrahepatic HBV DNA and histologic activity than genotype D	Lower serum HBV DNA and histologic activity than genotype C	Higher serum HBV DNA and histologic activity than genotype B	Higher intrahepatic HBV DNA and histologic activity than genotype A	19–21
Mutation pattern	Lower preC A1896 and BCP A1762T/G1764A frequency than genotype D	Higher preC A1896 but lower BCP A1762T/G1764A and pre-S deletion frequency than genotype C	Lower preC A1896 but higher BCP A1762T/G1764A and pre-S deletion frequency than genotype B	Higher preC A1896 and BCP A1762T/G1764A frequency than genotype A	19–21
Fibrosis/cirrhosis tendency	Lower than genotype D	Lower than genotype C	Higher than genotype B	Higher than genotype A	19–21
HCC risk	A vs D: no significant difference; 1.28/1,000 person-years (0.128%/year)	Lower than genotype C; 0.00/1,000 person-years (0.000%/year)	Higher than genotype B: OR = 2.05; 4.77/1,000 person-years (0.477%/year), RR vs B/D = 10.6	D vs A: no significant difference; 0.47/1,000 person-years (0.047%/year)	18,22

Directional comparisons such as higher/lower and earlier/later summarize genotype-specific trends reported in the cited reviews and comparative studies. Asian prevalence estimates are pooled prevalence values from Bello *et al*. 2023.[13] HCC incidence rates are expressed as events per 1,000 person-years, with approximate annual percentage equivalents shown in parentheses for readability; these values should not be interpreted as cumulative incidence. OR, odds ratio; RR, risk ratio; vs, versus; HBeAg, hepatitis B e antigen; CHB, chronic hepatitis B; HBV, hepatitis B virus; DNA, deoxyribonucleic acid; BCP, basal core promoter; preC, precore region; preS, pre-surface region; HCC, hepatocellular carcinoma.

ic RNA (pgRNA).[33] The preC mRNA encodes HBeAg, whereas pgRNA serves as the template for reverse transcription and also directs synthesis of the core protein HBcAg. Within this region, the A1762T/G1764A double mutation is one of the most extensively studied variants in CHB.[26,34] The two nucleotide substitutions usually occur together rather than independently, suggesting that the combined form may be selectively favored during chronic infection.

Previous studies have shown that A1762T/G1764A is more common in genotype C infection than in genotype B and becomes more frequent as disease progresses.[35] The mutation is relatively uncommon in asymptomatic carriers, but its prevalence increases in patients with active chronic hepatitis, cirrhosis, and HCC.[36] This distribution pattern suggests that the BCP double mutation may be selectively enriched during chronic infection, particularly in the setting of sustained immune pressure and ongoing hepatic inflammation.[37]

A major biological consequence of A1762T/G1764A is the combination of reduced HBeAg expression and enhanced viral replication. The double mutation suppresses preC mRNA transcription, thereby reducing HBeAg production.[38] One possible explanation is altered binding of hepatocyte transcription factors within the core promoter region.[39] At the same time, A1762T/G1764A has been reported to enhance pgRNA transcription and increase viral replication efficiency.[40] Although the precise basis for these effects remains unclear, proposed mechanisms include changes in local RNA structure, altered binding of core promoter-associated transcription factors, and increased stability of pgRNA.[41] Together, these effects produce a virological profile characterized by low HBeAg expression and relatively high replication capacity, which is thought to contribute to the development of HBeAg-negative CHB.

Because the BCP overlaps with the 3′ end of the X gene, A1762T and G1764A also produce nonsynonymous substitutions in HBx, namely K130M and V131I.[42] These amino acid changes may affect HBx conformation, stability, subcellular localization, and biological activity, and may also alter its regulatory effects on viral and host gene transcription, as well as its interactions with signaling proteins and transcriptional regulators.[39] Some studies further suggest that HBx carrying K130M/V131I may have stronger oncogenic potential, which may partly explain the association between the BCP double mutation and an increased risk of HCC.[43]

Longitudinal cohort studies and meta-analyses have shown that A1762T/G1764A has important clinical significance. Compared with wild-type virus, carriers of this double mutation have a significantly increased risk of HCC, and the association appears to be stronger in genotype C infection.[44] Even after adjustment for age, sex, cirrhosis, viral load, and alanine aminotransaminase (ALT), the BCP double mutation may still serve as an independent predictor of HCC.[45] In addition, A1762T/G1764A has been identified in a subset of non-cirrhotic HCC cases. This finding suggests that its effect

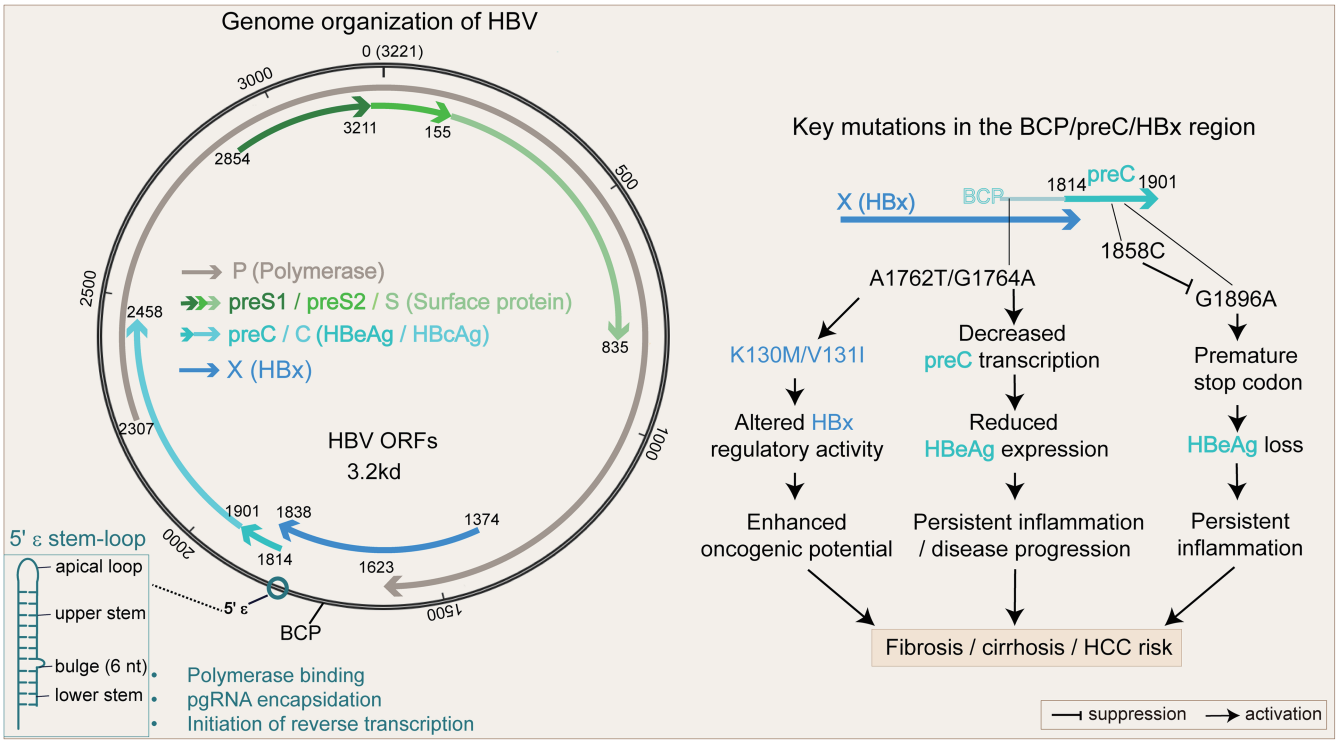

Fig. 1. Genome organization of HBV genotype C and key mutations in the BCP/preC/HBx regions associated with its high-risk phenotype. The left panel illustrates the overall genome organization of HBV, including the four major overlapping open reading frames (P, preS/S, preC/C, and X), the basal core promoter (BCP), and the ε stem-loop structure. The right panel outlines representative sequence variations in the BCP/preC/HBx regions, including the A1762T/G1764A double mutation, nucleotide 1858C, and the G1896A mutation, together with their potential effects on HBeAg expression, viral regulatory functions, persistent inflammation, and disease progression. HBV, hepatitis B virus; BCP, basal core promoter; preC, precore region; HBx, hepatitis B virus X protein; ORF, open reading frame; P, polymerase; preS/S, pre-surface/surface region; preS1/preS2/S, pre-surface 1/pre-surface 2/surface protein; preC/C, precore/core region; HBeAg, hepatitis B e antigen; HBcAg, hepatitis B core antigen; pgRNA, pregenomic RNA; nt, nucleotide; HCC, hepatocellular carcinoma; ε, epsilon.

may not be limited to indirect promotion of tumor development through inflammation and fibrosis but may also involve more direct contributions to hepatocarcinogenesis.[46] Overall, A1762T/G1764A is an important molecular marker of the high-risk phenotype associated with HBV genotype C.

G1896A stop codon mutation: The preC region encodes a 29-amino-acid signal peptide that directs the newly synthesized precore/core precursor into the endoplasmic reticulum, where it undergoes further processing to generate secreted HBeAg.[47,48] The G1896A mutation occurs at a critical codon in the preC region and converts the tryptophan codon TGG into the stop codon TAG. As a result, translation of the preC protein is prematurely terminated, leading to loss of HBeAg production without directly altering HBcAg expression from pgRNA.[49] This mutation may emerge during chronic HBV infection and is often detected around the time of spontaneous or treatment-related HBeAg seroconversion.[50] It is therefore regarded as an important molecular marker of the transition from HBeAg-positive to HBeAg-negative CHB.

However, the occurrence and persistence of G1896A are not random and are strongly constrained by the ε stem-loop structure. This structure is located in the 5′ overlapping region of pgRNA and is required for polymerase binding, pgRNA packaging, and initiation of reverse transcription.[51,52] Stable base pairing between nucleotides 1896 and 1858 is important for maintaining the integrity of the ε stem-loop.[53] In genotype C, which usually carries 1858C, acquisition of G1896A would create an unfavorable mismatch and reduce structural stability. Accordingly, G1896A is less likely to occur in genotype C. When G1896A does occur, it is often accompanied by compensatory changes at nearby sites that partially restore ε stem-loop stability and preserve replication capacity.[54] This may partly explain why G1896A is more readily observed in genotypes B and D, which more often carry 1858T. By contrast, in genotype C, it tends to occur less frequently and at a later stage of infection.

The clinical significance of G1896A is stage-dependent and is influenced by the phase of infection, the composition of the viral population, and the presence of other coexisting mutations.[55] During the immune-active HBeAg-positive phase, preC mutations may be associated with lower viral replication and relatively mild inflammatory activity.[40] After HBeAg seroconversion, however, if viral strains carrying G1896A become dominant, patients may remain HBeAg-negative despite a relatively high viral load, with recurrent ALT fluctuations, persistent hepatic inflammation, and progressive fibrosis.[56] Therefore, G1896A is not only involved in the establishment of the HBeAg-negative state but may also contribute to ongoing disease activity in HBeAg-negative CHB.[57]

Synergistic effects of BCP and preC mutations: BCP and preC mutations may co-occur during chronic HBV infection and jointly contribute to a more pathogenic viral phenotype.[58] Patients carrying both A1762T/G1764A and G1896A have been reported to show greater disease activity and a higher risk of adverse outcomes, including cirrhosis and HCC.[59,60] The association may reflect multiple mechanisms, such as altered viral replication, loss of HBeAg expression, persistent inflammation, immune escape, and increased viral population

complexity.[11,61] The coexistence of BCP and preC mutations may therefore represent a molecular pattern associated with disease progression and increased risk of liver cancer.

Quasispecies evolution and mutation enrichment: During chronic HBV infection, the virus does not exist as a single homogeneous population. Instead, it persists as a group of closely related but genetically distinct variants, referred to as a quasispecies.[62] Because HBV replicates actively and lacks efficient proofreading during reverse transcription, it shows substantial within-host genetic plasticity. This quasispecies structure allows the virus to evolve continuously under selective pressures such as sustained immune responses, changes in the host microenvironment, and antiviral therapy.[37,63] High-throughput sequencing studies have further shown that even in patients classified as wild-type by conventional Sanger sequencing, low-frequency variants with potential biological relevance are often present. Under certain selective pressures, some of these minor variants may gradually expand and become dominant.[64]

In HBV genotype C, quasispecies evolution may contribute to the occurrence and enrichment of key mutations, particularly in the BCP and preC regions.[65] As chronic infection persists, HBeAg serostatus changes and host immune pressure increases, variants with replication advantages or immune escape potential are more likely to be selected and retained. This may promote the gradual accumulation of high-risk mutations.[51] Rather than representing a static endpoint, mutation enrichment reflects ongoing viral adaptation under long-term host selection. In genotype C, this evolutionary dynamic may have particular clinical relevance.

Quasispecies evolution may influence not only viral replication and HBeAg expression but also disease activity, fibrosis progression, and HCC risk.[66] These findings suggest that quasispecies dynamics and the accumulation of key mutations may help explain the enhanced pathogenicity and clinical heterogeneity of HBV genotype C.[62]

Molecular pathogenic mechanisms: from infection to carcinogenesis

HBeAg loss, immune dysregulation, and chronic inflammation

The BCP and preC mutations discussed above not only shape the characteristic virological phenotype of HBV genotype C infection but also substantially alter the interaction between the virus and the host immune system. Among these changes, reduced or absent HBeAg expression appears to be a key link between viral mutation and immune dysregulation.

HBeAg is not only an important serological marker of HBV replication but also contributes to the establishment and maintenance of immune tolerance, especially in high-endemic regions where vertical transmission is common.[25] During mother-to-child transmission, maternal HBeAg may enter the fetal circulation and influence immune recognition of HBV antigens during a critical stage of immune system development.[67] Sustained exposure to HBeAg during the perinatal period may promote immune tolerance to HBV in newborns and thereby increase the risk of chronic infection.[68] This is one reason why chronicity is much more common after perinatal infection than after adult-acquired infection.

In HBV genotype C strains carrying BCP-related variants, reduced or absent HBeAg expression may disrupt the original balance between the virus and the host immune system.[69] Although this change may partly weaken the previous state of immune tolerance, it is usually insufficient to achieve effective viral clearance. Instead, it is more likely to result in a persistent but ineffective inflammatory response.[70] Under these conditions, inflammatory mediators remain elevated, immune cells continue to infiltrate the liver, hepatocytes undergo repeated cycles of injury, necrosis, and regeneration, and viral persistence is maintained.[71]

The resulting chronic inflammatory microenvironment promotes fibrosis progression and creates a favorable setting for hepatocarcinogenesis. Abnormal HBeAg expression is therefore not only an important virological feature of the high-risk phenotype associated with HBV genotype C but also a key link between immune dysregulation, persistent inflammation, and disease progression.

Importantly, the pathogenic significance of HBeAg deficiency does not mainly lie in a single episode of immune activation. Rather, it lies in its tendency to promote a persistent but ineffective inflammatory state.[56] In this setting, hepatocytes are repeatedly exposed to injury, necrosis, and regeneration.[72] Local oxidative stress, cytokine imbalance, and tissue remodeling also persist, thereby creating conditions for the accumulation of subsequent carcinogenic events.[73] In this sense, abnormal HBeAg expression is better understood as part of the inflammatory background of HBV-related hepatocarcinogenesis rather than as an isolated direct carcinogenic factor.

HBx/BCP variations and oncogenic mechanisms

As summarized in Table 2,[27,44,74,20,21] several BCP/preC/HBx-related variants may alter HBeAg expression, viral replication, immune escape, and oncogenic signaling. The carcinogenic potential of HBV genotype C is not solely attributable to persistent immune-mediated inflammation but may also be related to the enrichment of clinically relevant variants in the BCP/X region.[11] Because the BCP partially overlaps with the X gene coding region, these variants may affect both HBeAg regulation and HBx structure or function.[43] In genotype C infection, especially when BCP/X-related variants are present, these changes may provide a viral background that favors hepatocarcinogenesis.[75] Key viral alterations, including BCP A1762T/G1764A, preC G1896A, preS deletion, C1653T, T1753V, and HBx K130M/V131I, are summarized in Table 2.

Wingless/Int-1 (Wnt)/β-catenin and signal transducer and activator of transcription 3 (STAT3) signaling: HBx is a multifunctional regulatory protein implicated in HBV-related hepatocarcinogenesis. Among the pathways affected by HBx, Wnt/β-catenin and STAT3 signaling have been proposed as two mechanisms that may contribute to HBx-related oncogenic activity (Fig. 2).[76]

Under physiological conditions, cytoplasmic β-catenin is degraded through the destruction complex, preventing abnormal nuclear accumulation.[77] HBx has been reported to interfere with β-catenin degradation through adenomatous polyposis coli (APC)/glycogen synthase kinase 3 beta (GSK3β)-related mechanisms and to enhance Wnt signaling partly through epigenetic repression of Wnt antagonists such as SFRP1 and SFRP5.[78] These changes may promote β-catenin accumulation, nuclear translocation, and transcriptional activation of proliferative and invasive programs.[76] Some studies further suggest that BCP/X-related variants may enhance Wnt/β-catenin pathway activation.[79]

STAT3 activation is also frequently observed in HCC and may support tumor-promoting inflammation, proliferation, apoptosis resistance, and stemness-related programs.[80] HBx has been reported to disrupt mitochondrial function and increase reactive oxygen species accumulation, thereby promoting Janus kinase (JAK)/STAT3 activation.[81] HBx variants associated with BCP-related mutations, such as K130M/V131I, may further enhance HBx-related oncogenic activity.[74]

Table 2. Key HBV mutations, functional effects, and clinical relevance

Mutation/region	Main effect	Genotype relevance	Clinical relevance	Key references
BCP A1762T/ G1764A	Reduced HBeAg transcription; altered viral replication; HBx K130M/V131I due to X-gene overlap	More frequent in genotype C than B; enriched in C2/ high-risk background	Increased liver disease progression and HCC risk; OR for HCC ≈ 3.79	27,44,20
preC G1896A	Premature stop codon; loss of HBeAg production	More compatible with 1858T background; more common in B/D than C	HBeAg-negative CHB; persistent inflammatory activity in some patients	20,21
preS deletion	Impaired secretion; ER stress; immune escape	Higher frequency in genotype C than B in comparative tables	Increased HCC risk; OR ≈ 3.77	20
C1653T	Alters enhancer/X regulatory region	Often considered with BCP/ X-region high-risk variants	Increased HCC risk; OR ≈ 2.76	20
T1753V	BCP/X-region variant	Often coexists with BCP-region variants	Increased HCC risk; OR ≈ 2.35	20
HBx K130M/V131I	Amino-acid changes caused by A1762T/ G1764A overlap	BCP-related HBx variants, relevant to genotype C high-risk phenotype	May enhance oncogenic signaling and disease progression	74,20

OR values indicate the relative odds of HCC associated with specific HBV mutations or deletions. The OR values for T1753V, C1653T, A1762T/G1764A, and preS deletion are derived from Lin & Kao 2015.[20] OR, odds ratio; HBeAg, hepatitis B e antigen; CHB, chronic hepatitis B; BCP, basal core promoter; preC, precore region; preS, pre-surface region; HBx, hepatitis B virus X protein; HBV, hepatitis B virus; ER, endoplasmic reticulum; HCC, hepatocellular carcinoma.

In addition, C-terminally truncated HBx produced by viral integration may activate the STAT3/NANOG axis and promote tumor stemness and invasiveness.[83]

These findings suggest that Wnt/β-catenin and STAT3 signaling may contribute to the oncogenic background of genotype C infection, particularly when BCP/X-related variants or integration-derived truncated HBx are present. However, these pathways should not be interpreted as genotype C-exclusive mechanisms. Their relevance to genotype C is better understood in the context of enriched BCP/X-related variants and HBx alterations, and direct genotype C-specific human validation remains limited.

Additional host regulatory disturbances: In addition to Wnt/β-catenin and STAT3 signaling, HBV-related hepatocarcinogenesis may involve broader host regulatory disturbances, including epigenetic dysregulation, impaired DNA damage response, tumor protein p53 (p53) dysfunction, and autophagy abnormalities (Fig. 3). HBx has been reported to influence DNA methylation and histone-related regulation, leading to abnormal expression of tumor suppressor genes and signaling regulators.[78,83] Sustained replication stress, oxidative stress, and viral DNA integration may increase DNA damage and impair DNA damage response pathways.[84–86] HBx-related interference with p53 function may allow damaged hepatocytes to survive and expand.[88,88] HBV-associated autophagy changes may further affect viral replication, mitochondrial homeostasis, oxidative stress, and inflammatory signaling.[89–91]

These mechanisms are not specific to genotype C. Their relevance to genotype C is better interpreted within a high-risk viral background characterized by prolonged replication, BCP/X-related variants, HBx alterations, and viral integration. Therefore, they should be viewed as cooperating mechanisms that may amplify genotype C-associated carcinogenic risk rather than as independent genotype C-specific causal pathways.

Viral integration and genomic instability

HBV DNA integration into the host genome is one of the key molecular events in HBV-related hepatocarcinogenesis. Comprehensive genomic studies have shown that HBV integration is detectable in approximately 85%–90% of tumor tissues from HBV-related HCC.[92] HBV integration may occur at multiple stages of chronic infection and accumulate over time in the setting of persistent viral replication and repeated hepatocyte injury.[93] Integrated viral sequences often show fragmentation, rearrangement, and truncation. This pattern suggests that HBV integration is not a targeted viral process but is more likely a byproduct of host DNA double-strand break repair, particularly through non-homologous end joining and related pathways.[94]

Although HBV integration sites are distributed throughout the host genome, integration events are more frequently enriched in regions involved in cell-cycle regulation, telomere maintenance, and chromosomal stability.[95] Notably, integrated fragments often involve the X gene region and may generate truncated forms of HBx that continue to be expressed. These integration-derived HBx proteins may continue to be expressed even in the absence of active viral replication and may influence cell proliferation, survival, and stemness-related programs.[96]

However, HBV integration should not be interpreted as a uniform event. Comparative studies of paired tumor and non-tumorous liver tissues indicate that integration can be detected in both compartments, but their biological implications may differ.[97] In non-tumorous liver tissue, integration events are often heterogeneous, low-frequency, and broadly distributed, consistent with background infection, hepatocyte turnover, or passenger events. By contrast, tumor tissues may show clonal expansion of hepatocytes carrying selected integration events, recurrent or preferentially selected breakpoints, and integration into host genes with oncogenic relevance.[98] Large-scale analyses have further identified recurrently targeted genes, including *TERT*, *KMT2B*/*MLL4*, and *PLEKHG4B*, supporting the view that selected integration events may contribute to HCC driver mechanisms.[99]

Current sequencing approaches also have important limitations for HBV integration analysis. Short-read sequencing can

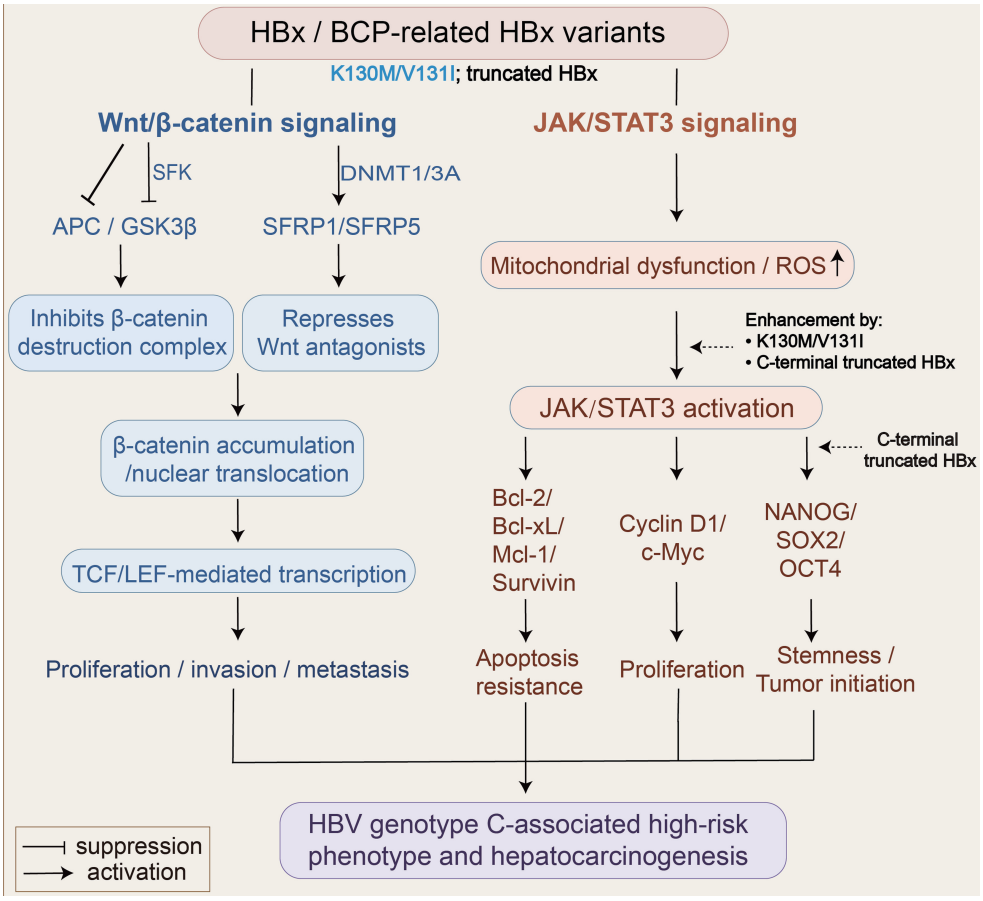

Fig. 2. HBx/BCP-related HBx variants and oncogenic signaling in HBV genotype C-associated hepatocarcinogenesis. HBx and BCP-related HBx variants, including K130M/V131I and C-terminally truncated HBx, may contribute to hepatocarcinogenesis through Wnt/β-catenin and JAK/STAT3 signaling. In the Wnt/β-catenin pathway, HBx may interfere with the β-catenin destruction complex through APC/GSK3β-related mechanisms and may repress Wnt antagonists such as SFRP1 and SFRP5 through DNMT1/3A-associated epigenetic regulation. These changes may promote β-catenin accumulation, nuclear translocation, and TCF/LEF-mediated transcription, thereby potentially supporting proliferation, invasion, and metastasis. In the JAK/STAT3 pathway, HBx-related mitochondrial dysfunction and ROS accumulation may promote JAK/STAT3 activation. K130M/V131I and C-terminally truncated HBx may further enhance this pathway and potentially support apoptosis resistance, proliferation, stemness, and tumor initiation. Together, these signaling alterations may provide a plausible mechanistic link between HBx/BCP-related variants and the high-risk phenotype of HBV genotype C, although these pathways should not be interpreted as genotype C-exclusive mechanisms, and direct genotype C-specific human validation remains limited. HBV, hepatitis B virus; HBx, hepatitis B virus X protein; BCP, basal core promoter; Wnt, Wingless/Int-1; JAK, Janus kinase; STAT3, signal transducer and activator of transcription 3; APC, adenomatous polyposis coli; GSK3β, glycogen synthase kinase 3 beta; SFK, Src family kinase; DNMT1/3A, DNA methyltransferase 1/3A; SFRP1/SFRP5, secreted frizzled-related protein 1/5; ROS, reactive oxygen species; TCF/LEF, T-cell factor/lymphoid enhancer-binding factor; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; Mcl-1, myeloid cell leukemia 1; NANOG, Nanog homeobox; SOX2, SRY-box transcription factor 2; OCT4, octamer-binding transcription factor 4; c-Myc, cellular myelocytomatosis oncogene.

detect viral-host junctions with relatively high throughput, but it may incompletely resolve long, fragmented, rearranged, or repetitive integration structures.[100] Targeted HBV-probe capture and other enrichment-based methods can improve sensitivity for rare integration events but may introduce capture bias and may not fully represent genome-wide integration patterns.[93] For these reasons, integration detection alone is insufficient to define a driver event. Integration data should be interpreted together with breakpoint recurrence, read support, clonal expansion, affected host genes, viral transcript expression, genomic instability, and clinical outcomes.

From molecular mechanisms to clinical high-risk phenotypes

Overall, the high-risk clinical phenotype of HBV genotype C reflects the long-term interaction of viral mutations, host responses, and cumulative molecular damage rather than any single molecular event (Fig. 4). BCP and preC mutations may promote a virological state characterized by high replication and low HBeAg expression, which favors persistent immune-mediated inflammation. HBx-related activation of oncogenic pathways such as Wnt/β-catenin and STAT3, together with epigenetic and stress-response abnormalities, may support hepatocyte survival, proliferation, and stemness-related programs. Viral integration and genomic instability may further promote clonal expansion and malignant transformation. Together, these mechanisms may contribute to faster fibrosis progression, later HBeAg seroconversion, earlier HCC development, and a clinically relevant residual risk even after antiviral therapy.[46]

Clinical consequences and management implications

The virological abnormalities and molecular pathogenic mechanisms described above do not act independently. Instead, they continuously interact to shape disease progres-

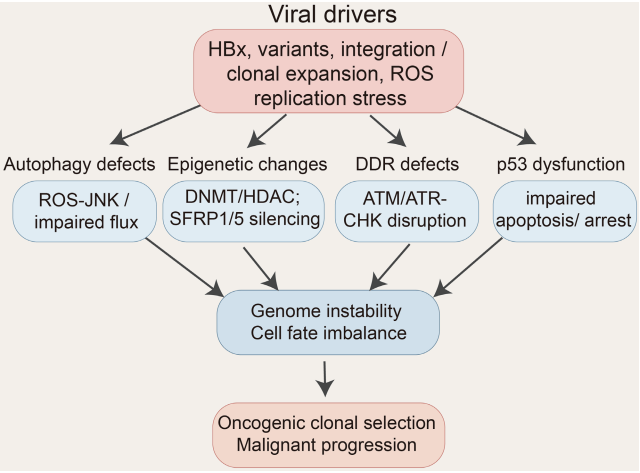

Fig. 3. HBV-related regulatory imbalance promoting malignant progression. HBx, related variants, viral integration, replication stress, and ROS may promote autophagy defects, epigenetic changes, DDR defects, and p53 dysfunction. These alterations may jointly disrupt genome stability and cell fate control, thereby favoring oncogenic clonal selection and malignant progression. HBV, hepatitis B virus; HBx, hepatitis B virus X protein; ROS, reactive oxygen species; DDR, DNA damage response; JNK, c-Jun N-terminal kinase; DNMT, DNA methyltransferase; HDAC, histone deacetylase; SFRP1/5, secreted frizzled-related protein 1/5; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related; CHK, checkpoint kinase; p53, tumor protein p53.

sion and are ultimately reflected in a more aggressive natural history, an increased risk of HCC, and a clinically relevant residual risk even after antiviral treatment.[82] The clinical significance of HBV genotype C can therefore be considered from three main perspectives: natural history, tumor risk, and long-term management.

Natural history and disease progression

The high-risk features of HBV genotype C are evident in the natural history of chronic infection. Compared with genotype B, genotype C infection is more often associated with a longer immune-active phase, more prolonged viral replication, and more active hepatic inflammation.[5] HBeAg seroconversion also tends to occur later in genotype C than that in genotype B. During this prolonged immune-active phase, patients are more likely to accumulate persistent liver injury and progressive fibrosis.[101] Multiple longitudinal studies have suggested that progression to significant fibrosis and cirrhosis occurs more rapidly in genotype C than that in genotype B.[102] This difference in disease course may lead to earlier development of cirrhosis and related complications in patients with genotype C infection, thereby contributing to an increased subsequent risk of HCC.

HCC risk: a core clinical outcome

The association between HBV genotype C and an increased risk of HCC is one of the most consistent findings in studies of chronic HBV infection. In the REVEAL-HBV prospective community-based cohort, 164 new cases of HCC were recorded during a mean follow-up of 11.4 years, highlighting the long-term cumulative nature of HBV-related hepatocarcinogenesis.[103] A subsequent genotype-based analysis of this cohort showed that, among 2,762 participants, HBV genotype C remained an independent risk factor for HCC compared with genotype B. After adjustment for age, sex, ALT, viral load, and other relevant factors, the risk of HCC was approximately 2.35-fold higher (Hazard Ratio [HR] = 2.35, 95% CI 1.68–3.30). This association remained significant in participants with baseline HBV DNA $\geq 10^4$ copies/mL (HR = 1.76, 95% CI 1.19–2.61).[75] Several subsequent cohort studies and meta-analyses have supported the same trend, showing that the risk of HCC is generally higher in patients with genotype C infection than that in those with genotype B.[18]

Antiviral therapy: efficacy and persistent residual risk

Treatment for CHB mainly relies on potent nucleos(t)ide analogs, such as entecavir and tenofovir. These agents can effectively suppress viral replication, improve fibrosis, and significantly reduce the risk of cirrhotic complications and HCC.[104,105] However, antiviral therapy does not completely eliminate genotype-related differences in risk. Available evidence suggests that even after long-term, stable virological suppression, patients with genotype C infection, especially those who have already progressed to cirrhosis, may still have a relatively high residual risk of HCC.[106,107]

The comparative effect of entecavir and tenofovir on HCC risk has been widely discussed, but the available evidence remains inconsistent. In a Korean nationwide cohort study, tenofovir treatment was associated with a lower risk of HCC than entecavir treatment in patients with CHB.[108] By contrast, another multicenter Korean cohort study reported no significant difference in HCC incidence between patients treated with entecavir and those treated with tenofovir.[109] A reconstructed individual patient data meta-analysis further suggested that there was no clinically meaningful difference in HCC risk between entecavir and tenofovir, especially when clinical cohort studies were analyzed separately.[110] In patients who had already developed HBV-related HCC, another reconstructed individual patient data meta-analysis suggested that tenofovir may be associated with improved overall survival and reduced late recurrence compared with entecavir, although this evidence applies to post-HCC prognosis rather than primary HCC prevention.[111] These apparently divergent findings should be interpreted cautiously because most comparisons between entecavir- and tenofovir-treated cohorts are observational and may be influenced by baseline differences in age, cirrhosis status, viral load, treatment era, prior antiviral exposure, follow-up duration, adherence, and residual confounding.

Therefore, in genotype C infection, the key issue is not whether one nucleos(t)ide analogue completely abolishes genotype-associated risk, but why residual HCC risk may persist despite effective viral suppression.

One possible explanation is that antiviral therapy suppresses active viral replication but does not fully reverse pre-existing oncogenic injury. Integrated HBV DNA may persist even when serum HBV DNA is undetectable, and integration-derived viral fragments, particularly those involving the X region, may continue to affect host gene regulation, genomic stability, and oncogenic signaling.[92,93] In addition, clonal expansion of hepatocytes carrying HBV integration or other premalignant alterations may have already occurred before treatment initiation, leaving an established oncogenic field that cannot be eliminated by viral suppression alone.[112]

Conventional serum HBV DNA may therefore not fully reflect residual viral activity or long-term carcinogenic risk during therapy. Complementary biomarkers, including quantitative hepatitis B surface antigen (HBsAg), hepatitis B core-related antigen (HBcrAg), and serum HBV RNA, may provide additional information on viral antigen burden, cccDNA-related activity, or residual transcriptional activity.[113,114] However, their use in genotype-informed HCC risk prediction remains insufficiently standardized. Future studies should determine whether combining genotype information, high-risk viral vari-

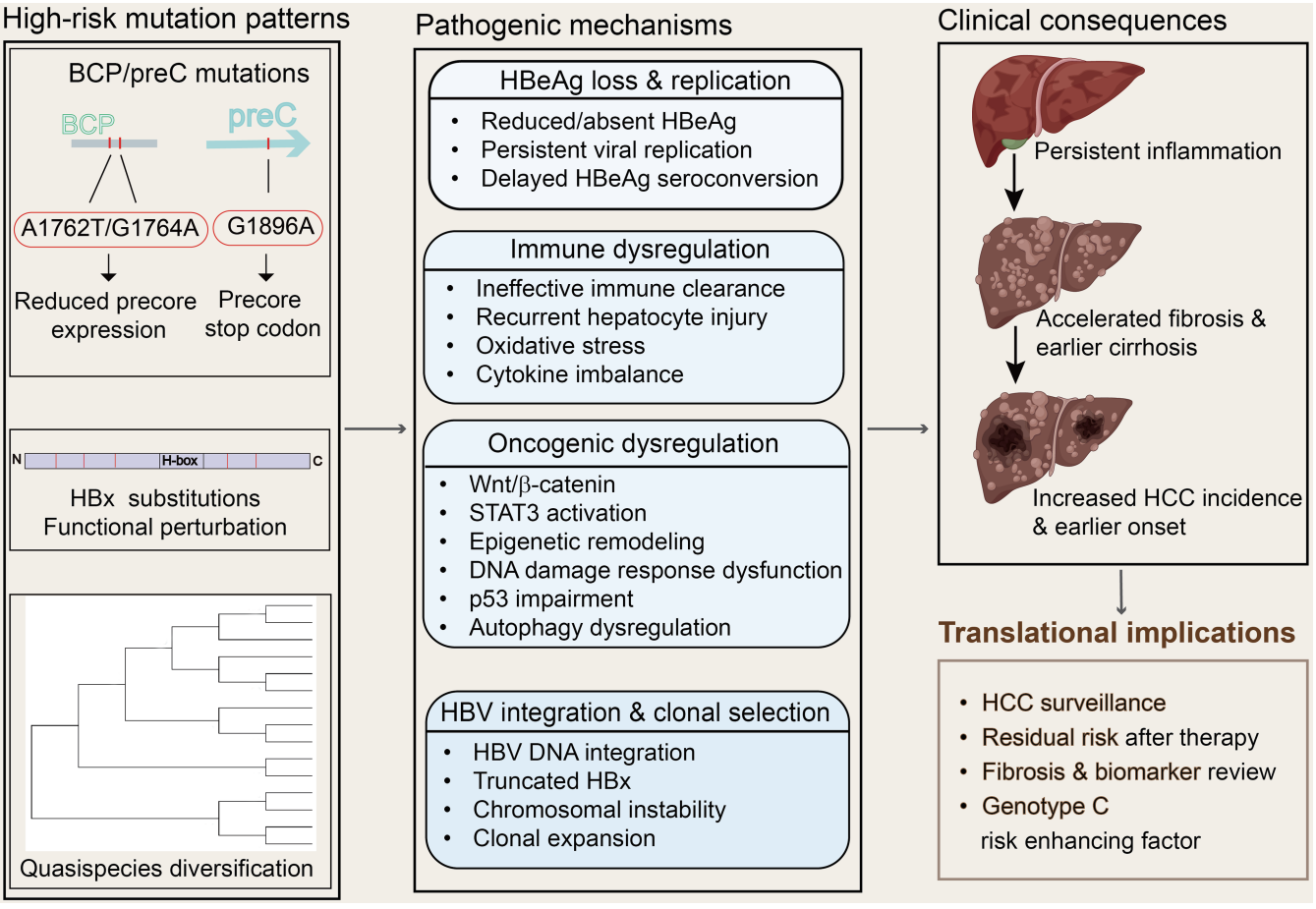

Fig. 4. Molecular basis and translational implications of the high-risk clinical phenotype of HBV genotype C. High-risk mutation patterns in HBV genotype C, including BCP/preC mutations, HBx-related alterations, and quasispecies diversification, may contribute to HBeAg loss with persistent replication, immune dysregulation, oncogenic signaling abnormalities, and HBV integration-associated instability. These processes contribute to persistent inflammation, accelerated fibrosis and cirrhosis, and increased HCC risk with earlier onset. The final module summarizes translational implications, including HCC surveillance, residual risk after antiviral therapy, fibrosis and biomarker review, and genotype C as a risk-enhancing factor. HBV, hepatitis B virus; BCP, basal core promoter; preC, precore region; HBx, hepatitis B virus X protein; HBeAg, hepatitis B e antigen; Wnt, Wingless/Int-1; STAT3, signal transducer and activator of transcription 3; DNA, deoxyribonucleic acid; HCC, hepatocellular carcinoma; p53, tumor protein p53; N, N-terminus; C, C-terminus.

ants, fibrosis stage, cirrhosis status, and emerging biomarkers can improve long-term risk stratification in patients with HBV genotype C infection.

Genotype-based risk stratification: clinical value and limitations

HBV genotypes differ in geographic distribution, natural history, mutation patterns, disease progression, HCC risk, and treatment-related outcomes.[12] Because genotype distribution is strongly region-dependent, genotype-associated risk should be interpreted within the relevant population and epidemiological context.[5,19] Among major HBV genotypes, genotype C has been most consistently associated with an unfavorable clinical profile, including delayed HBeAg seroconversion, prolonged viral replication, a longer immune-active phase, more active hepatic inflammation, and increased HCC susceptibility.[20,21] Genotype D has also been linked to delayed HBeAg seroconversion and more severe liver disease in some regions, whereas genotypes A and B generally show more favorable HBeAg seroconversion patterns in many studies.[20,21] These differences suggest that HBV genotype may reflect a viral background that shapes the duration and intensity of liver injury rather than serving merely as a phylogenetic label.

The association between genotype C and HCC risk is particularly well supported. In a meta-analysis of 43 studies including 14,545 patients, HCC was reported in 1,541/6,060 patients with genotype C and 550/4,417 patients with genotype B, corresponding to a significantly higher risk for genotype C (odds ratio [OR] = 2.05, 95% CI 1.52–2.76, $P < 0.001$). Genotype C was also associated with a higher HCC risk than genotypes A and D combined (OR = 2.34, 95% CI 1.63–3.34, $P < 0.001$), whereas genotype A and genotype D showed no significant difference in that analysis.[18] A more recent long-term cohort study from the Hepatitis B Alaska Study further supported the relevance of genotype in HCC surveillance risk stratification. In that cohort, HCC incidence differed markedly across genotypes, with genotype F and genotype C showing higher incidence rates than genotypes A, D, and B.[22] This risk difference may reflect delayed HBeAg seroconversion, prolonged immune-active disease, enrichment of BCP/X-region variants, persistent inflammation, and cumulative fibrosis- and carcinogenesis-related injury.[20,21]

However, genotype-based risk stratification should not be interpreted as genotype-only risk stratification. Age, sex,

family history of HCC, HBV DNA level, ALT, fibrosis stage, cirrhosis, metabolic factors, alcohol use, and treatment response remain central to clinical decision-making. Therefore, genotype C should be regarded as a risk modifier that complements conventional clinical variables and viral mutation profiles rather than as a stand-alone marker for determining treatment initiation, surveillance intensity, or follow-up intervals.

Translational implications for surveillance and long-term management

The clinical implication of genotype C should not be limited to describing it as a high-risk genotype. In Asian populations, where genotypes B and C commonly co-circulate, genotype C should be considered a risk-enhancing virological factor in long-term management. Long-term cohort evidence also supports the relevance of HBV genotype in determining HCC surveillance risk.[22] This does not mean that genotype C alone is sufficient to mandate antiviral treatment or a universally shortened surveillance interval. Rather, it may lower the threshold for strict surveillance adherence, repeated risk reassessment, and closer interpretation of residual HCC risk when additional adverse factors are present.

For HCC surveillance, genotype C should refine rather than replace guideline-based criteria. Ultrasound-based surveillance at 6-month intervals remains the standard approach for patients with cirrhosis and other high-risk groups.[115] In Asian patients with genotype C infection, clinicians should be particularly cautious when genotype C coexists with older age, male sex, family history of HCC, advanced fibrosis, BCP/preC mutations, metabolic dysfunction, or persistent low-grade inflammation despite viral suppression. In these settings, the practical priority is not necessarily to shorten the formal interval, but to ensure strict adherence to 6-month surveillance, avoid missed surveillance rounds, and reassess fibrosis and residual risk more actively over time.

For antiviral treatment, genotype C should not be used as a single independent indication for therapy. Treatment decisions should still follow established criteria, including HBV DNA level, ALT activity, fibrosis stage, cirrhosis status, age, and other host-related risk factors.[104,105] However, in patients near treatment thresholds, or in those with borderline biochemical activity but additional high-risk features, genotype C may support earlier reassessment, closer laboratory and fibrosis monitoring, and a lower threshold for specialist review.

For patients already receiving nucleos(t)ide analogue therapy, genotype C remains relevant because viral suppression does not necessarily eliminate HCC risk. Integrated HBV DNA may persist and continue to influence host gene regulation, genomic stability, and oncogenic signaling despite suppression of active viral replication.[3] Hepatocyte clones carrying HBV integration or premalignant alterations may also persist during antiviral treatment, partly explaining why undetectable serum HBV DNA does not fully eliminate residual HCC risk.[112] Therefore, genotype C-infected patients with cirrhosis, advanced fibrosis, or a long history of active disease should not be considered low-risk solely because HBV DNA is suppressed.

Complementary biomarkers may help identify genotype C-infected patients whose risk remains underestimated by conventional monitoring. HBcrAg has been reported to predict HCC development in patients with CHB-related cirrhosis undergoing long-term effective antiviral therapy.[112] Serum HBV RNA measured during viral suppression has been reported to predict subsequent HCC development in nucleos(t)ide analogue-treated CHB patients, supporting its potential value in post-treatment risk stratification.[116] HBV RNA and HBcrAg may reflect residual transcriptional activity and cccDNA-related activity, but their use in genotype-informed management remains insufficiently standardized.[114] These markers should not yet determine surveillance intensity on their own, but they may support closer risk reassessment when available.

Overall, a practical Asia-oriented approach is to treat genotype C as a risk-enhancing factor, not a passive descriptive label. It should not replace HBV DNA, ALT, fibrosis stage, cirrhosis status, age, sex, family history, metabolic factors, or treatment response. However, when combined with these variables, genotype C may justify stricter surveillance adherence, more frequent risk reassessment, and a lower threshold for specialist evaluation. This position recognizes genotype C as a meaningful high-risk signal without overstating it as a stand-alone determinant of treatment or surveillance decisions.

Perspectives

HBV genotype C is associated with more persistent viral replication, delayed or reduced HBeAg seroconversion, more active hepatic inflammation, increased risk of HCC, and a clinically relevant residual risk even after treatment.[101,106] Rather than being only a geographic or phylogenetic label, genotype C may represent a viral background that favors prolonged immune-active disease, enrichment of high-risk variants, HBV integration-related injury, and persistent oncogenic signaling. It should also be noted that most available evidence still treats genotype C as a single category, whereas direct comparative studies of different subgenotypes, especially subgenotype C2, remain relatively limited. Therefore, prospective studies are needed to determine whether these risk estimates apply equally across C2 and other regionally enriched subgenotypes.

First, future studies should establish and validate genotype-informed HCC risk prediction models that integrate viral factors such as genotype, BCP/preC/HBx mutation profile, HBV DNA level, quantitative HBsAg, HBcrAg, and serum HBV RNA, together with host factors including age, sex, family history, fibrosis stage, cirrhosis, metabolic dysfunction, alcohol use, and treatment response. Serum HBV RNA and HBcrAg are particularly relevant because they may provide information on residual viral transcriptional activity beyond conventional serum HBV DNA.[114] The key question is whether genotype and mutation data improve existing models in discrimination, calibration, surveillance adherence, or long-term outcomes.

Second, future work should clarify the biological basis of residual HCC risk after viral suppression. Potent nucleos(t)ide analogue therapy reduces HBV replication, but it does not necessarily remove pre-existing HBV integration, clonal hepatocyte expansion, fibrosis-related architectural distortion, or accumulated somatic and epigenetic injury. Recent evidence suggests that HBV integration and hepatocyte clonal expansion may persist despite antiviral treatment, which may partly explain residual HCC risk after serum HBV DNA suppression.[112] For genotype C infection, this issue is especially relevant because prolonged active disease may extend the time window for these events to accumulate before treatment. Longitudinal studies combining viral sequencing, integration profiling, fibrosis assessment, and circulating biomarkers are needed to identify which residual changes continue to predict HCC after virological suppression.

Third, Wnt/β-catenin and JAK/STAT3 signaling may provide mechanistic entry points for future intervention studies, but they should not be framed as genotype C-specific clinical therapies at present. Although these pathways are therapeutically relevant in HCC research, there is no direct evidence

that targeting them reduces residual HCC risk in genotype C-infected patients.[76] Therefore, the near-term priority is to determine whether activation of these pathways in genotype C-infected patients has predictive, preventive, or therapeutic value, rather than to propose routine pathway-targeted interventions.

Fourth, therapeutic vaccines, immune-modulatory approaches, and cell-based therapies remain relevant to functional cure research. These strategies may be relevant because future functional cure approaches will need to clarify whether durable viral control can be linked not only to HBsAg loss or immune restoration but also to long-term cancer prevention. However, their role in genotype C infection remains uncertain. Future studies should define which patient populations may benefit, what safety boundaries are acceptable, and whether functional cure strategies can meaningfully reduce HCC risk beyond suppression of serum HBV DNA.

Finally, real-world implementation remains a major unresolved issue. Routine HBV genotyping may be clinically informative, but its feasibility, cost-effectiveness, and added value over conventional clinical predictors need to be tested in different healthcare settings. This is especially important in regions with a high HBV burden, uneven access to molecular testing, and limited resources for long-term surveillance. Current HBV management guidelines emphasize risk-based treatment and long-term monitoring, but they do not yet provide a genotype C-specific surveillance algorithm.[104] An important next step is to test whether genotype-informed risk assessment improves surveillance adherence, timing of treatment evaluation, and patient-level outcomes. In practice, genotype information is likely to be useful only when embedded in integrated risk models rather than used as an isolated decision rule.

Conclusions

HBV genotype C represents a clinically relevant high-risk form of chronic HBV infection. It is generally associated with delayed HBeAg seroconversion, persistent viral replication, more active hepatic inflammation, faster fibrosis progression, and a higher risk of HCC. Importantly, this risk may persist even after effective antiviral suppression, especially in patients with advanced fibrosis or cirrhosis. The high-risk phenotype of genotype C appears to be related to its viral sequence background, enrichment of BCP/preC/HBx-related variants, altered HBeAg expression, immune dysregulation, HBx-related oncogenic signaling, and HBV integration-associated genomic instability. Although these mechanisms are not exclusive to genotype C, they may be more clinically relevant in genotype C infection because of the prolonged replication phase, enrichment of high-risk viral variants, and greater cumulative inflammatory and oncogenic injury. In clinical practice, genotype C should be viewed as a risk-enhancing virological factor rather than a stand-alone determinant of treatment or surveillance decisions. Combining genotype information with viral mutations, fibrosis stage, cirrhosis status, treatment response, and emerging biomarkers may help refine long-term risk assessment and surveillance planning for patients with chronic hepatitis B.

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Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Study concept and design (CH, ZL), drafting of the manuscript (CH, ZL), critical revision of the manuscript for important intellectual content (LS), administrative support (TS, JZ), and study supervision (LS, TS). All authors made significant contributions to this study and have approved the final manuscript.

References

[1] Singh SP, Madke T, Chand P. Global Epidemiology of Hepatocellular Carcinoma. J Clin Exp Hepatol 2025;15(2):102446. doi:10.1016/j.jceh.2024.102446, PMID:39659901.
[2] Mak LY, Lai JC, Liu K, Lui R, Chirapongsathorn S, Yew KC, *et al*. Chronic Hepatitis B Infection: Patient Guidance. J Gastroenterol Hepatol 2026;41(1):61–77. doi:10.1111/jgh.70177, PMID:41360731.
[3] Hui RW, Wong DK, Lyu X, Mak LY, Fung J, Seto WK, *et al*. Profiles of HBV DNA integration in humans with hepatitis B virus infection: Insights for antiviral treatment. JHEP Rep 2025;7(9):101487. doi:10.1016/j.jhepr.2025.101487, PMID:40893931.
[4] Revill PA, Tu T, Netter HJ, Yuen LKW, Locarnini SA, Littlejohn M. The evolution and clinical impact of hepatitis B virus genome diversity. Nat Rev Gastroenterol Hepatol 2020;17(10):618–634. doi:10.1038/s41575-020-0296-6, PMID:32467580.
[5] Chen J, Li L, Yin Q, Shen T. A review of epidemiology and clinical relevance of Hepatitis B virus genotypes and subgenotypes. Clin Res Hepatol Gastroenterol 2023;47(7):102180. doi:10.1016/j.clinre.2023.102180, PMID:37479136.
[6] Sukowati CHC, Jayanti S, Turyadi T, Muljono DH, Tiribelli C. Hepatitis B virus genotypes in precision medicine of hepatitis B-related hepatocellular carcinoma: Where we are now. World J Gastrointest Oncol 2024;16(4):1097–1103. doi:10.4251/wjgo.v16.i4.1097, PMID:38660644.
[7] Liu M, Tseng TC, Jun DW, Yeh ML, Trinh H, Wong GLH, *et al*. Transition rates to cirrhosis and liver cancer by age, gender, disease and treatment status in Asian chronic hepatitis B patients. Hepatol Int 2021;15(1):71–81. doi:10.1007/s12072-020-10113-2, PMID:33394321.
[8] Chan HL, Tse CH, Mo F, Koh J, Wong VW, Wong GL, *et al*. High viral load and hepatitis B virus subgenotype ce are associated with increased risk of hepatocellular carcinoma. J Clin Oncol 2008;26(2):177–182. doi:10.1200/JCO.2007.13.2043, PMID:18182659.
[9] Kim DH, Choi YM, Jang J, Kim BJ. Global prevalence and molecular characteristics of three clades within hepatitis B virus subgenotype C2: Predominance of the C2(3) clade in South Korea. Front Microbiol 2023;14:1137084. doi:10.3389/fmicb.2023.1137084, PMID:36970691.
[10] La Frazia S, Magnapera A, Piermatteo L, D'Anna S, Duca L, Svicher V, *et al*. Direct Viral Mechanisms Underlying the Onset of HBV-Related Hepatocellular Carcinoma and Implications for Therapeutic Strategies. Viruses 2026;18(2):185. doi:10.3390/v18020185, PMID:41754527.
[11] Shoraka S, Hosseinian SM, Hasibi A, Ghaemi A, Mohebbi SR. The role of hepatitis B virus genome variations in HBV-related HCC: effects on host signaling pathways. Front Microbiol 2023;14:1213145. doi:10.3389/fmicb.2023.1213145, PMID:37588887.
[12] Fernandes da Silva C, Keeshan A, Cooper C. Hepatitis B virus genotypes influence clinical outcomes: A review. Can Liver J 2023;6(3):347–352. doi:10.3138/canlivj-2023-0003, PMID:38020195.
[13] Bello KE, Mat Jusoh TNA, Irekeola AA, Abu N, Mohd Amin NAZ, Mustaffa N, *et al*. A Recent Prevalence of Hepatitis B Virus (HBV) Genotypes and Subtypes in Asia: A Systematic Review and Meta-Analysis. Healthcare (Basel) 2023;11(7):1011. doi:10.3390/healthcare11071011, PMID:37046937.
[14] Lin CL, Kao JH. The clinical implications of hepatitis B virus genotype: Recent advances. J Gastroenterol Hepatol 2011;26(Suppl 1):123–130. doi:10.1111/j.1440-1746.2010.06541.x, PMID:21199523.
[15] Yuen MF, Sablon E, Tanaka Y, Kato T, Mizokami M, Doutreloigne J, *et al*. Epidemiological study of hepatitis B virus genotypes, core promoter and precore mutations of chronic hepatitis B infection in Hong Kong. J Hepatol 2004;41(1):119–125. doi:10.1016/j.jhep.2004.03.004, PMID:15246217.
[16] Kao JH, Chen PJ, Lai MY, Chen DS. Genotypes and clinical phenotypes

of hepatitis B virus in patients with chronic hepatitis B virus infection. J Clin Microbiol 2002;40(4):1207–1209. doi:10.1128/JCM.40.4.1207-1209.2002, PMID:11923332.
[17] Jose-Abrego A, Roman S, Rebello Pinho JR, de Castro VFD, Panduro A. Hepatitis B Virus (HBV) Genotype Mixtures, Viral Load, and Liver Damage in HBV Patients Co-infected With Human Immunodeficiency Virus. Front Microbiol 2021;12:640889. doi:10.3389/fmicb.2021.640889, PMID:33746932.
[18] Wong GL, Chan HL, Yiu KK, Lai JW, Chan VK, Cheung KK, *et al*. Meta-analysis: The association of hepatitis B virus genotypes and hepatocellular carcinoma. Aliment Pharmacol Ther 2013;37(5):517–526. doi:10.1111/apt.12207, PMID:23305043.
[19] Sunbul M. Hepatitis B virus genotypes: global distribution and clinical importance. World J Gastroenterol 2014;20(18):5427–5434. doi:10.3748/wjg.v20.i18.5427, PMID:24833873.
[20] Lin CL, Kao JH. Hepatitis B virus genotypes and variants. Cold Spring Harb Perspect Med 2015;5(5):a021436. doi:10.1101/cshperspect.a021436, PMID:25934462.
[21] Liu CJ, Kao JH. Global perspective on the natural history of chronic hepatitis B: role of hepatitis B virus genotypes A to J. Semin Liver Dis 2013;33(2):97–102. doi:10.1055/s-0033-1345716, PMID:23749665.
[22] McMahon BJ, Nolen LD, Snowball M, Homan C, Negus S, Roik E, *et al*. HBV Genotype: A Significant Risk Factor in Determining Which Patients With Chronic HBV Infection Should Undergo Surveillance for HCC: The Hepatitis B Alaska Study. Hepatology 2021;74(6):2965–2973. doi:10.1002/hep.32065, PMID:34292609.
[23] Dandri M, Petersen J. cccDNA Maintenance in Chronic Hepatitis B - Targeting the Matrix of Viral Replication. Infect Drug Resist 2020;13:3873–3886. doi:10.2147/IDR.S240472, PMID:33149632.
[24] Maepa MB, Jacobs R, van den Berg F, Arbuthnot P. Recent developments with advancing gene therapy to treat chronic infection with hepatitis B virus. Curr Opin HIV AIDS 2020;15(3):200–207. doi:10.1097/COH.0000000000000623, PMID:32141890.
[25] Ghosh S, Chakraborty A, Banerjee S. Persistence of Hepatitis B Virus Infection: A Multi-Faceted Player for Hepatocarcinogenesis. Front Microbiol 2021;12:678537. doi:10.3389/fmicb.2021.678537, PMID:34526974.
[26] Kumar R. Review on hepatitis B virus precore/core promoter mutations and their correlation with genotypes and liver disease severity. World J Hepatol 2022;14(4):708–718. doi:10.4254/wjh.v14.i4.708, PMID:35646275.
[27] Liu S, Zhang H, Gu C, Yin J, He Y, Xie J, *et al*. Associations between hepatitis B virus mutations and the risk of hepatocellular carcinoma: a meta-analysis. J Natl Cancer Inst 2009;101(15):1066–1082. doi:10.1093/jnci/djp180, PMID:19574418.
[28] Kim DH, Choi YM, Jang J, Kim Z, Kim BJ. Distinct phylogeographic distributions and frequencies of precore and basal core promoter mutations between HBV subgenotype C1 rt269L and rt269I types. Sci Rep 2025;15(1):9315. doi:10.1038/s41598-025-94286-6, PMID:40102552.
[29] Yan CH, Zhao CY, Ding H, Peng YQ, Jin PY, Yan L, *et al*. Hepatitis B virus basal core promoter mutations A1762T/G1764A are associated with genotype C and a low serum HBsAg level in chronically-infected HBeAg-positive Chinese patients. Antiviral Res 2012;96(2):108–114. doi:10.1016/j.antiviral.2012.08.009, PMID:22960603.
[30] Chen Y, Yu D, Zhang W, Qiu C, Xiang G, Dai W, *et al*. HBV Subgenotype C2 Infection, A1762T/G1764A Mutations May Contribute To Hepatocellular Carcinoma with Cirrhosis in Southeast China. Iran J Public Health 2012;41(11):10–18. PMID:23304671.
[31] Chan HL, Hussain M, Lok AS. Different hepatitis B virus genotypes are associated with different mutations in the core promoter and precore regions during hepatitis B e antigen seroconversion. Hepatology 1999;29(3):976–984. doi:10.1002/hep.510290352, PMID:10051506.
[32] Nordin M, Ingman M, Lindqvist B, Kidd-Ljunggren K. Variability in the precore and core promoter region of the hepatitis B virus genome. J Med Virol 2014;86(3):437–445. doi:10.1002/jmv.23839, PMID:24249691.
[33] Mohamadkhani A, Montazeri G, Poustchi H. The importance of hepatitis B virus genome diversity in Basal core promoter region. Middle East J Dig Dis 2011;3(1):13–19. PMID:25197527.
[34] Yang D, Zou J, Guan G, Feng X, Zhang T, Li G, *et al*. The A1762T/G1764A mutations enhance HBV replication by alternating viral transcriptome. J Med Virol 2023;95(10):e29129. doi:10.1002/jmv.29129, PMID:37772469.
[35] Yin J, Zhang H, He Y, Xie J, Liu S, Chang W, *et al*. Distribution and hepatocellular carcinoma-related viral properties of hepatitis B virus genotypes in Mainland China: a community-based study. Cancer Epidemiol Biomarkers Prev 2010;19(3):777–786. doi:10.1158/1055-9965.EPI-09-1001, PMID:20160279.
[36] Wu JF, Chang KC, Ni YH, Hsu HY, Chang MH. Impacts of the Percentage of Basal Core Promoter Mutation on the Progression of Liver Fibrosis After Hepatitis B e Antigen Seroconversion. J Infect Dis 2021;223(8):1381–1389. doi:10.1093/infdis/jiaa545, PMID:32860707.
[37] Jiang ZH, Chen QY, Jia HH, Wang XY, Zhang LJ, Huang XQ, *et al*. Low host immune pressure may be associated with the development of hepatocellular carcinoma: a longitudinal analysis of complete genomes of the HBV 1762T, 1764A mutant. Front Oncol 2023;13:1214423. doi:10.3389/fonc.2023.1214423, PMID:37681020.
[38] Laras A, Koskinas J, Hadziyannis SJ. In vivo suppression of precore mRNA synthesis is associated with mutations in the hepatitis B virus core promoter. Virology 2002;295(1):86–96. doi:10.1006/viro.2001.1352, PMID:12033768.
[39] Seong MS, Hwang HJ, Jang EA, Jang JA, Aung WW, Kyaw YY, *et al*. Core promoter mutation of nucleotides A1762T and G1764A of hepatitis B virus increases core promoter transactivation by hepatocyte nuclear factor 1. J Microbiol 2022;60(10):1039–1047. doi:10.1007/s12275-022-1675-1, PMID:36167927.
[40] Lau KCK, Joshi SS, Mahoney DJ, Mason AL, van Marle G, Osiowy C, *et al*. Differences in HBV Replication, APOBEC3 Family Expression, and Inflammatory Cytokine Levels Between Wild-Type HBV and Pre-core (G1896A) or Basal Core Promoter (A1762T/G1764A) Mutants. Front Microbiol 2020;11:1653. doi:10.3389/fmicb.2020.01653, PMID:32760388.
[41] Tiwari P, Saraswat I, Gupta J. Insight into the Biology of Hepatitis B Virus and Recent Therapeutic Approaches. Curr Microbiol 2026;83(3):151. doi:10.1007/s00284-026-04725-4, PMID:41642349.
[42] Lee JH, Han KH, Lee JM, Park JH, Kim HS. Impact of hepatitis B virus (HBV) x gene mutations on hepatocellular carcinoma development in chronic HBV infection. Clin Vaccine Immunol 2011;18(6):914–921. doi:10.1128/CVI.00474-10, PMID:21490166.
[43] Pu R, Liu W, Zhou X, Chen X, Hou X, Cai S, *et al*. The Effects and Underlying Mechanisms of Hepatitis B Virus X Gene Mutants on the Development of Hepatocellular Carcinoma. Front Oncol 2022;12:836517. doi:10.3389/fonc.2022.836517, PMID:35223517.
[44] Yang Z, Zhuang L, Lu Y, Xu Q, Tang B, Chen X. Naturally occurring basal core promoter A1762T/G1764A dual mutations increase the risk of HBV-related hepatocellular carcinoma: a meta-analysis. Oncotarget 2016;7(11):12525–12536. doi:10.18632/oncotarget.7123, PMID:26848866.
[45] Du Y, Han X, Ding YB, Yin JH, Cao GW. Prediction and prophylaxis of hepatocellular carcinoma occurrence and postoperative recurrence in chronic hepatitis B virus-infected subjects. World J Gastroenterol 2016;22(29):6565–6572. doi:10.3748/wjg.v22.i29.6565, PMID:27547000.
[46] Shen C, Jiang X, Li M, Luo Y. Hepatitis Virus and Hepatocellular Carcinoma: Recent Advances. Cancers (Basel) 2023;15(2):533. doi:10.3390/cancers15020533, PMID:36672482.
[47] Hong X, Luckenbaugh L, Mendenhall M, Walsh R, Cabuang L, Soppe S, *et al*. Characterization of Hepatitis B Precore/Core-Related Antigens. J Virol 2021;95(3):e01695–20. doi:10.1128/JVI.01695-20, PMID:33148795.
[48] Hong X, Luckenbaugh L, Perlman D, Revill PA, Wieland SF, Menne S, *et al*. Characterization and Application of Precore/Core-Related Antigens in Animal Models of Hepatitis B Virus Infection. Hepatology 2021;74(1):99–115. doi:10.1002/hep.31720, PMID:33458844.
[49] Belaiba Z, Ayouni K, Gdoura M, Kammoun Rebai W, Touzi H, Sadraoui A, *et al*. Whole genome analysis of hepatitis B virus before and during long-term therapy in chronic infected patients: Molecular characterization, impact on treatment and liver disease progression. Front Microbiol 2022;13:1020147. doi:10.3389/fmicb.2022.1020147, PMID:36325017.
[50] Yang HC, Chen CL, Shen YC, Peng CY, Liu CJ, Tseng TC, *et al*. Distinct evolution and predictive value of hepatitis B virus precore and basal core promoter mutations in interferon-induced hepatitis B e antigen seroconversion. Hepatology 2013;57(3):934–943. doi:10.1002/hep.26121, PMID:23112104.
[51] Rodriguez-Frias F, Buti M, Tabernero D, Homs M. Quasispecies structure, cornerstone of hepatitis B virus infection: mass sequencing approach. World J Gastroenterol 2013;19(41):6995–7023. doi:10.3748/wjg.v19.i41.6995, PMID:24222943.
[52] González López Ledesma MM, Mojsiejczuk LN, Rodrigo B, Sevic I, Mammana L, Galdame O, *et al*. Hepatitis B virus genotype distribution and genotype-specific BCP/preCore substitutions in acute and chronic infections in Argentina. PLoS One 2015;10(3):e0121436. doi:10.1371/journal.pone.0121436, PMID:25822666.
[53] Hakami A, Ali A, Hakami A. Effects of hepatitis B virus mutations on its replication and liver disease severity. Open Virol J 2013;7:12–18. doi:10.2174/1874357901307010012, PMID:23400390.
[54] De Mitri MS, Cassini R, Morsica G, Bagaglio S, Andreone P, Loggi E, *et al*. Virological analysis, genotypes and mutational patterns of the HBV precore/core gene in HBV/HCV-related hepatocellular carcinoma. J Viral Hepat 2006;13(9):574–581. doi:10.1111/j.1365-2893.2006.00726.x, PMID:16907843.
[55] Suslov A, Meier MA, Ketterer S, Wang X, Wieland S, Heim MH. Transition to HBeAg-negative chronic hepatitis B virus infection is associated with reduced cccDNA transcriptional activity. J Hepatol 2021;74(4):794–800. doi:10.1016/j.jhep.2020.11.003, PMID:33188905.
[56] Bonino F, Colombatto P, Brunetto MR. HBeAg-Negative/Anti-HBe-Positive Chronic Hepatitis B: A 40-Year-Old History. Viruses 2022;14(8):1691. doi:10.3390/v14081691, PMID:36016312.
[57] Besharat S, Poustchi H, Mohamadkhani A, Katoonizadeh A, Moradi A, Roshandel G, *et al*. Association of Mutations in the Basal Core Promoter and Pre-core Regions of the Hepatitis B Viral Genome and Longitudinal Changes in HBV Level in HBeAg Negative Individuals: Results From a Cohort Study in Northern Iran. Hepat Mon 2015;15(2):e23875. doi:10.5812/hepatmon.23875, PMID:25788956.
[58] Park YM. Clinical utility of complex mutations in the core promoter and proximal precore regions of the hepatitis B virus genome. World J Hepatol 2015;7(1):113–120. doi:10.4254/wjh.v7.i1.113, PMID:25625002.
[59] Zhang X, Ding HG. Key role of hepatitis B virus mutation in chronic hepatitis B development to hepatocellular carcinoma. World J Hepatol 2015;7(9):1282–1286. doi:10.4254/wjh.v7.i9.1282, PMID:26019744.
[60] Akrami H, Monjezi MR, Ilbeigi S, Amiri F, Fattahi MR. The Association Between Hepatitis B Virus Mutations and the Risk of Liver Disease and Hepatocellular Carcinoma. Curr Mol Med 2022;22(6):514–523. doi:10.2174/1566524021666210816094412, PMID:34397330.
[61] Zhu C, Tang M, Fu Y, Xun Z, Lin C, Wu S, *et al*. Characterization of BCP/PreC/C region quasispecies in treatment-naive patients with different phases of HBV infection using next-generation sequencing. Int J Med Microbiol 2024;315:151619. doi:10.1016/j.ijmm.2024.151619, PMID:38564936.
[62] Hu LP, Chen QY, Huang ML, Zhang WJ, Huang XQ, Yi XF, *et al*. Full-Genome Hepatitis B Virus Genotyping: A Juxtaposition of Next-Generation

and Clone-Based Sequencing Approaches-Comparing Genotyping Methods of Hepatitis B Virus. Viruses 2026;18(1):112. doi:10.3390/v18010112, PMID:41600874.
[63] Yao ZQ, Schank MB, Zhao J, El Gazzar M, Wang L, Zhang Y, *et al*. The potential of HBV cure: an overview of CRISPR-mediated HBV gene disruption. Front Genome Ed 2024;6:1467449. doi:10.3389/fgeed.2024.1467449, PMID:39444780.
[64] Bouquet J, Speer SD, Koenig A, Livingston CM, Savarese M, Lau C, *et al*. Single nucleotide polymorphisms in the bepirovirsen binding site have limited impact on treatment response in chronic hepatitis B. J Hepatol 2026;84(5):887–897. doi:10.1016/j.jhep.2025.12.025, PMID:41544767.
[65] Elizalde MM, Tadey L, Mammana L, Quarleri JF, Campos RH, Flichman DM. Biological Characterization of Hepatitis B virus Genotypes: Their Role in Viral Replication and Antigen Expression. Front Microbiol 2021;12:758613. doi:10.3389/fmicb.2021.758613, PMID:34803982.
[66] Abu Rahma MZ, Hassan EA, Hasanain AFA, Omar MAM, Mekky MA, El-Mokhtar MA, *et al*. Detectability of hepatitis B virus DNA in peripheral blood mononuclear cells following long-term nucleos(t)ide analogue therapy-induced sustained viral suppression. Eur J Gastroenterol Hepatol 2026;38(4):503–510. doi:10.1097/MEG.0000000000003136, PMID:41604545.
[67] Lu H, Cao W, Zhang L, Yang L, Bi X, Lin Y, *et al*. Effects of hepatitis B virus infection and strategies for preventing mother-to-child transmission on maternal and fetal T-cell immunity. Front Immunol 2023;14:1122048. doi:10.3389/fimmu.2023.1122048, PMID:36875136.
[68] Zhang L, Jiang T, Yang Y, Deng W, Lu H, Wang S, *et al*. Postpartum hepatitis and host immunity in pregnant women with chronic HBV infection. Front Immunol 2022;13:1112234. doi:10.3389/fimmu.2022.1112234, PMID:36685527.
[69] Pechnikova NA, Zafeiriou-Chatziefraimidou M, Poimenidou M, Patsidou C, Iliadis I, Ostankova YV, *et al*. mRNA vaccines for HBV: Mechanisms, preclinical advances, and therapeutic clinical progress. Mol Ther Nucleic Acids 2026;37(1):102819. doi:10.1016/j.omtn.2025.102819, PMID:41583559.
[70] Lin J, Gehring AJ. Role of Immune Cells in Hepatitis B Virus and Associated Sequelae. Annu Rev Pathol 2026;21(1):399–421. doi:10.1146/annurev-pathmechdis-042524-030646, PMID:41150875.
[71] Wang Z, Cao Z, Dong Y, Hong Y, Zuo L, Wang H. Hepatocyte-hepatic stellate cell interactions in liver fibrosis: Mechanisms and therapeutic implications. Hepatol Commun 2026;10(2):e0893. doi:10.1097/HC9.0000000000000893, PMID:41564388.
[72] Rizzo GEM, Cabibbo G, Craxì A. Hepatitis B Virus-Associated Hepatocellular Carcinoma. Viruses 2022;14(5):986. doi:10.3390/v14050986, PMID:35632728.
[73] Popa GL, Popa MI. Oxidative Stress in Chronic Hepatitis B-An Update. Microorganisms 2022;10(7):1265. doi:10.3390/microorganisms10071265, PMID:35888983.
[74] Siddiqui ZI, Farooqui SR, Azam SA, Afroz M, Wajid S, Parveen S, *et al*. A comparative study of hepatitis B virus X protein mutants K130M, V131I and KV130/131MI to investigate their roles in fibrosis, cirrhosis and hepatocellular carcinoma. J Viral Hepat 2017;24(12):1121–1131. doi:10.1111/jvh.12747, PMID:28654219.
[75] Yang HI, Yeh SH, Chen PJ, Iloeje UH, Jen CL, Su J, *et al*. Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma. J Natl Cancer Inst 2008;100(16):1134–1143. doi:10.1093/jnci/djn243, PMID:18695135.
[76] Zheng J, Wang S, Xia L, Sun Z, Chan KM, Bernards R, *et al*. Hepatocellular carcinoma: signaling pathways and therapeutic advances. Signal Transduct Target Ther 2025;10(1):35. doi:10.1038/s41392-024-02075-w, PMID:39915447.
[77] Hsieh A, Kim HS, Lim SO, Yu DY, Jung G. Hepatitis B viral X protein interacts with tumor suppressor adenomatous polyposis coli to activate Wnt/β-catenin signaling. Cancer Lett 2011;300(2):162–172. doi:10.1016/j.canlet.2010.09.018, PMID:20971552.
[78] Xie Q, Chen L, Shan X, Shan X, Tang J, Zhou F, *et al*. Epigenetic silencing of SFRP1 and SFRP5 by hepatitis B virus X protein enhances hepatoma cell tumorigenicity through Wnt signaling pathway. Int J Cancer 2014;135(3):635–646. doi:10.1002/ijc.28697, PMID:24374650.
[79] Chen Z, Tang J, Cai X, Huang Y, Gao Q, Liang L, *et al*. HBx mutations promote hepatoma cell migration through the Wnt/β-catenin signaling pathway. Cancer Sci 2016;107(10):1380–1389. doi:10.1111/cas.13014, PMID:27420729.
[80] Lee C, Cheung ST. STAT3: An Emerging Therapeutic Target for Hepatocellular Carcinoma. Cancers (Basel) 2019;11(11):1646. doi:10.3390/cancers11111646, PMID:31731457.
[81] Zou LY, Zheng BY, Fang XF, Li D, Huang YH, Chen ZX, *et al*. HBx co-localizes with COXIII in HL-7702 cells to upregulate mitochondrial function and ROS generation. Oncol Rep 2015;33(5):2461–2467. doi:10.3892/or.2015.3852, PMID:25778742.
[82] Ching RHH, Sze KMF, Lau EYT, Chiu YT, Lee JMF, Ng IOL, *et al*. C-terminal truncated hepatitis B virus X protein regulates tumorigenicity, self-renewal and drug resistance via STAT3/Nanog signaling pathway. Oncotarget 2017;8(14):23507–23516. doi:10.18632/oncotarget.15183, PMID:28186991.
[83] Zheng DL, Zhang L, Cheng N, Xu X, Deng Q, Teng XM, *et al*. Epigenetic modification induced by hepatitis B virus X protein via interaction with de novo DNA methyltransferase DNMT3A. J Hepatol 2009;50(2):377–387. doi:10.1016/j.jhep.2008.10.019, PMID:19070387.
[84] Kim S, Lee HS, Ji JH, Cho MY, Yoo YS, Park YY, *et al*. Hepatitis B virus X protein activates the ATM-Chk2 pathway and delays cell cycle progression. J Gen Virol 2015;96(8):2242–2251. doi:10.1099/vir.0.000150, PMID:25872745.
[85] Luo J, Luckenbaugh L, Hu H, Yan Z, Gao L, Hu J. Involvement of Host ATR-CHK1 Pathway in Hepatitis B Virus Covalently Closed Circular DNA Formation. mBio 2020;11(1):e03423–19. doi:10.1128/mBio.03423-19, PMID:32071277.
[86] Chauhan R, Michalak TI. Kinetics of DNA damage repair response accompanying initial hepadnavirus-host genomic integration in woodchuck hepatitis virus infection of hepatocyte. Cancer Genet 2020;244:1–10. doi:10.1016/j.cancergen.2020.02.001, PMID:32062411.
[87] Wang XW, Gibson MK, Vermeulen W, Yeh H, Forrester K, Stürzbecher HW, *et al*. Abrogation of p53-induced apoptosis by the hepatitis B virus X gene. Cancer Res 1995;55(24):6012–6016. PMID:8521383.
[88] Chan C, Wang Y, Chow PK, Chung AY, Ooi LL, Lee CG. Altered binding site selection of p53 transcription cassettes by hepatitis B virus X protein. Mol Cell Biol 2013;33(3):485–497. doi:10.1128/MCB.01189-12, PMID:23149944.
[89] Zhong L, Shu W, Dai W, Gao B, Xiong S. Reactive Oxygen Species-Mediated c-Jun NH(2)-Terminal Kinase Activation Contributes to Hepatitis B Virus X Protein-Induced Autophagy via Regulation of the Beclin-1/Bcl-2 Interaction. J Virol 2017;91(15):e00001–17. doi:10.1128/JVI.00001-17, PMID:28515304.
[90] Tang H, Da L, Mao Y, Li Y, Li D, Xu Z, *et al*. Hepatitis B virus X protein sensitizes cells to starvation-induced autophagy via up-regulation of beclin 1 expression. Hepatology 2009;49(1):60–71. doi:10.1002/hep.22581, PMID:19065679.
[91] Kim SJ, Khan M, Quan J, Till A, Subramani S, Siddiqui A. Hepatitis B virus disrupts mitochondrial dynamics: induces fission and mitophagy to attenuate apoptosis. PLoS Pathog 2013;9(12):e1003722. doi:10.1371/journal.ppat.1003722, PMID:24339771.
[92] Zhang M, Chen H, Liu H, Tang H. The impact of integrated hepatitis B virus DNA on oncogenesis and antiviral therapy. Biomark Res 2024;12(1):84. doi:10.1186/s40364-024-00611-y, PMID:39148134.
[93] Zoulim F, Chen PJ, Dandri M, Kennedy PT, Seeger C. Hepatitis B virus DNA integration: Implications for diagnostics, therapy, and outcome. J Hepatol 2024;81(6):1087–1099. doi:10.1016/j.jhep.2024.06.037, PMID:38971531.
[94] Qian Z, Liang J, Huang R, Song W, Ying J, Bi X, *et al*. HBV integrations reshaping genomic structures promote hepatocellular carcinoma. Gut 2024;73(7):1169–1182. doi:10.1136/gutjnl-2023-330414, PMID:38395437.
[95] Zhao LH, Liu X, Yan HX, Li WY, Zeng X, Yang Y, *et al*. Genomic and oncogenic preference of HBV integration in hepatocellular carcinoma. Nat Commun 2016;7:12992. doi:10.1038/ncomms12992, PMID:27703150.
[96] Ma L, Chen S, Wang H, Chen L. Hepatitis B virus integration and hepatocarcinogenesis. Liver Res 2025;9(3):189–198. doi:10.1016/j.livres.2025.09.002, PMID:41112515.
[97] Jiang Z, Jhunjhunwala S, Liu J, Haverty PM, Kennemer MI, Guan Y, *et al*. The effects of hepatitis B virus integration into the genomes of hepatocellular carcinoma patients. Genome Res 2012;22(4):593–601. doi:10.1101/gr.133926.111, PMID:22267523.
[98] Li X, Zhang J, Yang Z, Kang J, Jiang S, Zhang T, *et al*. The function of targeted host genes determines the oncogenicity of HBV integration in hepatocellular carcinoma. J Hepatol 2014;60(5):975–984. doi:10.1016/j.jhep.2013.12.014, PMID:24362074.
[99] Lin SY, Zhang A, Lian J, Wang J, Chang TT, Lin YJ, *et al*. Recurrent HBV Integration Targets as Potential Drivers in Hepatocellular Carcinoma. Cells 2021;10(6):1294. doi:10.3390/cells10061294, PMID:34071075.
[100] Zhuo Z, Rong W, Li H, Li Y, Luo X, Liu Y, *et al*. Long-read sequencing reveals the structural complexity of genomic integration of HBV DNA in hepatocellular carcinoma. NPJ Genom Med 2021;6(1):84. doi:10.1038/s41525-021-00245-1, PMID:34642322.
[101] Ratnaparkhi MM, Vyawahare CR, Gandham NR. Hepatitis B virus genotype distribution and mutation patterns: Insights and clinical implications for hepatitis B virus positive patients. World J Exp Med 2025;15(2):102395. doi:10.5493/wjem.v15.i2.102395, PMID:40546674.
[102] Cheng JY, Shan GY, Wan H, Liu YY, Zhang YX, Shi WN, *et al*. Hepatitis B virus-induced cirrhosis: Mechanisms, global variations, and treatment advances. World J Hepatol 2024;16(12):1515–1523. doi:10.4254/wjh.v16.i12.1515, PMID:39744198.
[103] Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, *et al*. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295(1):65–73. doi:10.1001/jama.295.1.65, PMID:16391218.
[104] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2025;83(2):502–583. doi:10.1016/j.jhep.2025.03.018, PMID:40348683.
[105] Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva: World Health Organization; 2024.
[106] Abdelhamed W, El-Kassas M. Hepatitis B virus as a risk factor for hepatocellular carcinoma: There is still much work to do. Liver Res 2024;8(2):83–90. doi:10.1016/j.livres.2024.05.004, PMID:39959873.
[107] Lin CL, Kao JH. Development of hepatocellular carcinoma in treated and untreated patients with chronic hepatitis B virus infection. Clin Mol Hepatol 2023;29(3):605–622. doi:10.3350/cmh.2022.0342, PMID:36788759.
[108] Choi J, Kim HJ, Lee J, Cho S, Ko MJ, Lim YS. Risk of Hepatocellular Carcinoma in Patients Treated With Entecavir vs Tenofovir for Chronic Hepatitis B: A Korean Nationwide Cohort Study. JAMA Oncol 2019;5(1):30–36. doi:10.1001/jamaoncol.2018.4070, PMID:30267080.
[109] Oh H, Yoon EL, Jun DW, Ahn SB, Lee HY, Jeong JY, *et al*. No Difference in Incidence of Hepatocellular Carcinoma in Patients With Chronic Hepatitis B Virus Infection Treated With Entecavir vs Tenofovir. Clin Gastroenterol Hepatol 2020;18(12):2793–2802.e6. doi:10.1016/j.cgh.2020.02.046, PMID:32135246.
[110] Tan DJH, Ng CH, Tay PWL, Syn N, Muthiah MD, Lim WH, *et al*. Risk of Hepatocellular Carcinoma With Tenofovir vs Entecavir Treatment for Chron-

ic Hepatitis B Virus: A Reconstructed Individual Patient Data Meta-analysis. JAMA Netw Open 2022;5(6):e2219407. doi:10.1001/jamanetworkopen.2022.19407, PMID:35767258.
[111] Peng JX, Wang LZ, Wang QT, Li HL, Lin LJ, He JM. Tenofovir versus entecavir on the prognosis of hepatitis B virus-related hepatocellular carcinoma: a reconstructed individual patient data meta-analysis. Front Pharmacol 2024;15:1393861. doi:10.3389/fphar.2024.1393861, PMID:39239648.
[112] Chow N, Wong D, Lai CL, Mak LY, Fung J, Ma HT, *et al*. Effect of Antiviral Treatment on Hepatitis B Virus Integration and Hepatocyte Clonal Expansion. Clin Infect Dis 2023;76(3):e801–e809. doi:10.1093/cid/ciac383, PMID:35594553.
[113] Chang KC, Lin MT, Wang JH, Hung CH, Chen CH, Chiu SY, *et al*. HBcrAg Predicts Hepatocellular Carcinoma Development in Chronic B Hepatitis Related Liver Cirrhosis Patients Undergoing Long-Term Effective Anti-Viral. Viruses 2022;14(12):2671. doi:10.3390/v14122671, PMID:36560675.
[114] Tian Y, Yu H, Chen J. Emerging Serum Biomarkers for Chronic Hepatitis B: Focus on Serum HBV RNA and HBcrAg. J Clin Transl Hepatol 2025;13(9):766–775. doi:10.14218/JCTH.2025.00064, PMID:40951536.
[115] Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, *et al*. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology 2023;78(6):1922–1965. doi:10.1097/HEP.0000000000000466, PMID:37199193.
[116] Kumada T, Toyoda H, Yasuda S, Koshiyama Y, Ito T, Akita T, *et al*. Hepatitis B Virus RNA Predicts Hepatocellular Carcinoma Despite Viral Suppression. Aliment Pharmacol Ther 2026;63(8):1089–1098. doi:10.1111/apt.70483, PMID:41328676.