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TOPIC HIGHLIGHT

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Hepatitis B virus mutations related to liver disease progression of Korean patients

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Abstract

Hepatitis B virus (HBV) infection is a global health problem and more than 350 million people worldwide are chronic carriers of the virus. Despite the recent dramatic decline in HBV chronic patients through successful programs of hepatitis B surface antigen vaccination, South Korea is still recognized as an endemic area of HBV infection. HBV infections in South Korea exhibit several distinct features in epidemiologic and clinical aspects. In this review paper, we summarize the distinct HBV mutation patterns related to clinical severity and the molecular epidemiologic traits in Korean chronic patients based on previous reports. Generally, several lines of evidence, including our previous results, have led to the conclusion that a combination of the exclusive predominance of genotype C2, which is prone to mutations, the high prevalence of basal core promoter double mutations, and the presence of distinct immune responses against HBV proteins in the Korean population may generate the distinct HBV variants rarely or not encountered in other areas, which results in distinct clinical manifestations in Korean chronic patients. This may provide a novel insight into the relationships between clinical severity, HBV genotype distribution, and HBV naturally occurring variants.

Key words: Hepatitis B virus; Mutation; South Korea; Hepatocellular carcinoma; Genotype C2

Core tip: In this review paper, we summarize the distinct hepatitis B virus (HBV) mutation patterns related to clinical severity and the molecular epidemiologic traits in Korean chronic patients based on previous reports. Generally, several lines of evidence have led to the conclusion that a combination of the exclusive predominance of genotype C2, which is prone to mutations, the high prevalence of basal core promoter double mutations, and the presence of distinct immune responses against HBV proteins in the Korean population may generate the distinct HBV variants rarely or not encountered in other areas, which results in distinct clinical manifestations in Korean chronic patients.

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INTRODUCTION

Hepatitis B virus (HBV) infection is a global health problem, and more than 350 million people worldwide are chronic carriers of the virus[1]. The infection is associated with a large spectrum of clinical manifestations ranging from acute or fulminant hepatitis to various forms

of chronic infection, including asymptomatic carriers, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC)[2]. HBV vaccination was first introduced into the Korean population in 1983[3], and it dramatically reduced the prevalence of hepatitis B surface antigen (HBsAg) positive chronic carriers from more than 10% to 3.7% in 2007 during a period of approximately 30 years[4].

Despite the recent dramatic decline in HBV chronic patients through the successful program of HBsAg vaccination, South Korea is still recognized as an endemic area of HBV infection. HBV infections in South Korea have exhibited some distinct features from both epidemiologic and clinical aspects. First, among the Organisation for Economic Co-operation and Development nations, South Korean infections have exhibited the highest incidence of HCC that is primarily induced by HBV infection[5]. Second, relatively lower antiviral responses against alpha interferon and/or lamivudine were found in Korean patients compared with patients in other countries[6]. Third, of particular note, it was reported that only genotype C2 infections, which are known to be more prone to mutations and are related to greater severity in liver diseases compared with genotype B[7], were found in an exclusive manner in this area[8], which contribute to the distribution of characteristic HBV mutation patterns related to the progression of liver diseases. These features lead to the hypothesis that there may be a distinct naturally occurring HBV mutation related to clinical severity and lower antiviral responses in chronic patients in South Korea. In order to prove this hypothesis, we have attempted to determine the HBV variants related to the progression of liver diseases, particularly HCC, and to analyze the mutation frequency in HBV encoding antigens from Korean patients[9-22].

In this review paper, we summarize the distinct HBV mutation patterns related to the clinical severity and molecular epidemiologic traits in Korean chronic patients, primarily focusing on the mutation patterns of 4 regions, preS[9,15,16], surface (S)[12,13,20], precore/core (preC/C)[11,17], and X[14,18,22].

DISTRIBUTION OF HBV GENOTYPES IN KOREAN CHRONIC PATIENTS

HBV has been divided into eight genotypes, types A-H, based on one of the following criteria: an intergroup divergence of 8% or greater in terms of its complete genome nucleotide sequence or a 4.1% divergence or greater for the surface antigen gene[23-25]. These genotypes reflect the geographical distribution of HBV. It has also been suggested that the area-specific localization of HBV genotypes is associated with anthropologic history[26]. In addition, remarkable differences have been reported in the clinical and virological characteristics of patients infected with different genotypes[27]. For example, in Asia, genotype C has been found to have a greater ability to induce disease than genotype B[7]. Our previous molecular epidemiologic study based on the direct sequencing protocol targeting the partial *S* gene (541 bp) found that all HBV strains from 209 Korean chronic patients belonged to genotype C2 (100%)[8]. Other studies based on serology[28] and polymerase chain reaction (PCR) restriction fragment length polymorphism analysis, or genotypic-specific PCR[29], also support these results. The exclusive predominance of genotype C infection without coexistence with other genotypes is the most distinct epidemiologic trait shown in Korean chronic patients[8], and this may affect the clinical manifestations of Korean chronic patients as well as the virological traits such as mutation frequency.

MUTATION FREQUENCY AND PATTERNS IN THE PRES REGION IN KOREAN CHRONIC PATIENTS

The envelope of HBV is composed of three forms of HBsAg sharing 226 amino acids at the C-terminus: the large (coded using the *preS1/S2/S* gene), middle (the preS2/S gene), and small (the *S* gene) envelope proteins. During the viral life cycle, at least two essential functions have been attributed to the preS domain: attachment to the hepatocyte membrane and budding of the virus at the endoplasmic reticulum (ER)[30,31]. Thus far, several lines of evidence that mutants occurring naturally in the preS region correlate with more progressive forms of liver disease have been documented[32-34]. The mutations, particularly deletions, in the preS region may affect the ratio between the small and large envelope proteins, which results in the ER stress associated with the aggravation of liver disease. Furthermore, integration of the truncated large or middle envelope protein into the host chromosome enhances the potential development of HCC by increasing the transactivating capacity[35].

Our report regarding the prevalence of preS deletions in Korean chronic patients demonstrated that a relatively high level of preS deletions was found in Korean chronic patients (30.8%, 37/120 patients)[16]. The comparisons of the clinical information between chronic patients with and without preS deletions indicated that patients with deletions were older (54.3 ± 12.7 *vs* 45.1 ± 18.2, P = 0.006), had more severe liver disease (liver cirrhosis and HCC; 73% *vs* 41%, P = 0.001), and had a higher HBV DNA level (378.4 *vs* 70, P = 0.009) than those without the deletion. These results suggest that the acquisition of preS deletions may contribute to the progression into severe types of disease such as HCC and liver cirrhosis, at least in genotype C-infected Korean chronic patients[16].

Although preS deletion in Korean chronic patients was significantly associated with severe forms of liver diseases, a difference between the preS1 and preS2 deletions in relation to HCC and liver cirrhosis was found. For example, preS1 deletions were observed more frequently in HCC patients than in patients with liver cirrhosis [32.5% (13/40 patients) *vs* 19.9% (4/21 patients)], and the opposite was observed in preS2 deletion variants [15.0% (6/40

Table 1 Mutations in 4 hepatitis B virus regions related to the progression of liver diseases in Korean chronic patients

Region		Mutations related to severe liver diseases	*P* value	Ref.
PreC/C	PreC	W28* [HCC 12/35 (34.3%) *vs* LC+ CH + C 5/35 (14.3%)]	0.093	Kim *et al*[11]
	C	P5H/L/T [HCC 5/35 (14.3%) *vs* LC + CH + C 0/35 (0%)]	0.020	Kim *et al*[11]
		E83D [HCC 4/35 (11.4%) *vs* LC + CH + C 0/35 (0%)]	0.039	Kim *et al*[11]
		I97F/L [HCC 13/35 (37.1%) *vs* LC + CH + C 4/35 (11.4%)]	0.024	Kim *et al*[11]
		L100I [HCC 6/35 (17.1%) *vs* LC + CH + C 1/35 (2.9%)]	0.046	Kim *et al*[11]
		Q182K/* [HCC 4/35 (11.4%) *vs* LC + CH + C 0/35 (0%)]	0.039	Kim *et al*[11]
PreS	preS1	W4P/R [HCC 13/96 (13.5%) *vs* CH 0/32 (13.2%)]	0.028	Lee *et al*[9]
		PreS1 start deletion [HCC 9/40 (22.5%) *vs* C 1/38 (2.6%)]	0.048	Mun *et al*[16]
	preS2	F141L [HCC 26/99 (26.3%) *vs* LC 2/52 (3.8%)]	0.001	Mun *et al*[15]
		PreS2 deletion [HCC 35/99 (35.4%) *vs* CH 6/45 (13.3%)]	0.020	Mun *et al*[15]
S	S	W182* [HCC + LC 56/176 (31.8%) *vs* CH + C 17/99 (17.2%)]	0.010	Lee *et al*[12]
X	X	V5M/L [HCC 30/60 (50.0%) *vs* LC 11/42 (26.2%)]	0.024	Kim *et al*[22]
		P38S [HCC 13/60 (21.7%) *vs* C 2/41 (4.9%)]	0.023	Kim *et al*[22]
		H94Y [HCC 24/60 (40.0%) *vs* C 2/41 (4.9%)]	< 0.001	Kim *et al*[22]
		I127T/N [HCC 22/60 (36.7%) *vs* CH 6/41 (14.6%)]	0.023	Kim *et al*[22]
		KV130MI [HCC 52/60 (86.7%) *vs* CH 25/41 (61.0%)]	0.004	Kim *et al*[22]

HCC: Hepatocellular carcinoma; LC: Liver cirrhosis; CH: Chronic hepatitis; C: Carrier.

patients) *vs* 38.1% (8/21 patients)], which suggests that the preS1 and preS2 deletions cause different patterns of disease progression, at least in Korean chronic patients[16]. Furthermore, a discrepancy between the two deletion groups according to hepatitis B e antigen (HBeAg) serostatus was also observed. While the preS1 deletion was not related to the HBeAg serostatus (HBeAg negative *vs* HBeAg positive; 21.3% *vs* 18.6%), the frequency of preS2 deletions was positively related to the HBeAg negative serostatus (HBeAg negative *vs* HBeAg positive; 23% *vs* 6.8%, $P = 0.02$), which implies that preS2 may be more sensitive to the host immune response than preS1[16].

A total of four types of specific mutations in the preS region, *i.e.*, two types in the preS1 region (preS1 start codon deletion[16] and W4P/R mutation[9]) and two types in the preS2 region (preS2 deletion[16] and F141L mutation[15]), were related to disease progression in Korean chronic patients (Table 1). The deletion type of the preS1 start codon, which leads to the deletion of 11 amino acids at the N-terminus of the large surface protein characteristic of genotype D, exhibited a very high prevalence in HCC patients [22.5% (9/40) HCC *vs* 5.3% (1/38) asymptomatic carriers, $P = 0.048$][16]. It has been reported that some genotype D strains lead to intracellular retention of surface proteins in mixed infections with genotype A, which could induce hepatic carcinogenesis through activating the ER stress pathway[36]. Although the exact mechanism remains to be elucidated, the possible cause of HCC in the deletions of the preS1 start codon might be similar to the genotype D case described above. This deletion type was also found in two of three Korean HCC patients in a previous report[21], but it has rarely been found in chronic patients from other countries. Therefore, the possibility that the deletion of the preS1 start codon might be prevalent among Korean patients cannot be excluded. Our recent report[10] that the preS1 start deletion was found with a high frequency in Korean patients related to HBV occult infection also strongly supports this hypothesis.

Furthermore, our recent molecular epidemiologic study based on real time PCR introduced novel preS1 substitutions (W4P/R) that were significantly related to severe liver diseases in Korean chronic patients infected with genotype C [HCC and liver cirrhosis (12.4%, 19/153 patients) *vs* chronic hepatitis and carrier (1.1%, 1/94 patients), $P < 0.001$], which changes the tryptophan to proline or arginine at the 4th codon from the preS1 start. Surprisingly, all W4P/R mutants (20 patients) were found in male patients only, which implies that the W4P/R mutation may occur predominantly in males[9]. Therefore, our study led to the conclusion that W4P/R may make an important contribution to the disease severity in male chronic patients infected with genotype C. It may also provide a partial explanation as to the relatively high ratio of male to female incidence of HCC generation in Korean chronic patients. To our knowledge, W4P/R is the first mutation of the virus gene associated with gender disparity[9].

Our previous molecular epidemiologic study based on the Mbo Ⅱ PCR restriction fragment length polymorphism analysis method proved that two types of preS2 mutations, *i.e.*, the preS2 deletion and F141L mutation, were significantly related to severe forms of liver diseases in Korean chronic patients[15]. Of these two mutations, several lines of evidence have already suggested that the preS2 deletion correlates with more progressive forms of liver disease through affecting the ratio between the small and large envelop proteins, which results in the ER stress associated with the aggravation of liver disease[37]. The relationship of the F141L mutation to disease progression was first introduced by our study. Our data demonstrated that F141L mutations, but not preS2 deletion, are significantly prevalent in HCC patients compared with patients with any other stage of liver disease and even LC patients, which suggests that F141L and preS2 deletion affect different stages in the progression of liver disease[15]. While pre-S2 deletions may have a function in the transition from chronic hepatitis to liver cirrhosis, the F141L mutation have

a pivotal function in the progress from liver cirrhosis to HCC. Using a functional study based on the stable cell lines, we proved that large surface proteins with the F141L mutation could contribute to the pathogenesis of HCC through the induction of cell proliferation and transformation[15].

It should also be noted that two types of preS deletion related to disease progression in Korean chronic patients, i.e., the deletion in preS1 start codon and preS2 deletion, were also significantly prevalent in HBV occult subjects compared with chronic patients at the carrier stage[10], which indicates that they may induce a mechanism such as the defect in the secretion of virions or HBsAg leading to ER stress, which can explain both occult infection and disease progression.

MUTATION FREQUENCY AND PATTERNS IN THE S REGION IN KOREAN CHRONIC PATIENTS

The *S* gene of HBV contains a dominant neutralizing epitope, termed the "a" determinant, in the major hydrophilic region (MHR) of the *S* gene, which spans amino acid positions 100-160. The "a" determinant is widely regarded to be located between amino acids 124 and 147 of HBsAg[38]. Mutations in MHR, particularly the "a" determinant, are known to be associated with the generation of vaccine escape variants or persistent infection by reducing the binding affinity between the HBsAg and antibody to the HBsAg[39]. It is important that the prevalence and types of variants of the *S* gene found in endemic populations should be monitored, because this will affect policy decisions relating to vaccine and diagnostic reagents design[40,41]. When compared with previous results obtained in Japanese patients with genotype C by Ogura *et al*[42], our previous report demonstrated that there were several distinct epidemiologic traits in the prevalence of S variants in Korean chronic patients. First, an unexpectedly higher prevalence of naturally occurring MHR variants (46.5%, 47/101) was observed in the Korean patients compared with 24% prevalence in Japanese patients. Second, a relatively higher mutation frequency (37.3%, 22/59) and unique mutation patterns were observed in positions outside the "a" determinant region, while most mutations in Japanese patients were concentrated inside the "a" determinant region[20]. These traits observed in Korean patients may result from the exclusive predominance of the genotype C prone to mutations, which could influence the virological aspects of the HBV populations in the region[43]. Furthermore, the possibility of the presence of distinct immune pressures against HBV antigens in Korean patients cannot be excluded, and these could induce the distinct HBV mutation patterns that are not encountered in other areas. Our recent report regarding HBV occult infections demonstrating the presence of several novel HBsAg variants related to occult infections in Korean patients strongly supports this hypothesis[10].

Recently, we introduced a novel mutation type in the outside MHC regions of *S* gene (*sW182**) that resulted in a premature stop at codon 182 in the *S* gene of genotype C[12]. Our molecular epidemiologic study based on a multi-probe real time PCR proved that the prevalence of sW182* was significantly higher in patients with progressive forms of the disease (HCC and liver cirrhosis) than in patients with less severe forms of the disease (chronic hepatitis and carrier) [31.8% (56/176 patients) *vs* 17.2% (17/99 patients), $P = 0.010$][12] (Table 1). Furthermore, an *in vitro* study based on the stable cell lines stable expressing the S protein with sW182* also strongly supported its relationship with HCC[12]. Interestingly, sW182* has been reported to be the most frequently encountered mutation among occult infections related to HBsAg mutations in Korean patients, which suggests the possibility of its horizontal transfer among the Korean population[10]. Comparison of the clinical data between patients with and without the *sW182** mutation demonstrated that the HBV DNA levels of patients with variants were significantly lower than those with wild types, which indicates that there may be mechanisms that lower the DNA level itself. One potential mechanism is that the truncated S protein could interrupt the formation of normal virions, leading to a loss of infectivity and, in turn, DNA levels. The study using the full HBV genomic DNA harboring the *sW182** mutation proved that it failed to form normal HBV virions, which also provided a likely explanation as to its prevalence in subjects with HBV occult infections as well as patients with severe types of liver diseases[12].

MUTATION FREQUENCY AND PATTERNS IN THE PREC/C REGION IN KOREAN CHRONIC PATIENTS

The HBV C protein (HBcAg), which is the protein shell of the virus core, is 183 residues long, of which 149 residues of the N-terminal are the assembly domain[44]. HBcAg is the principal target for the host immune response, particularly cytotoxic T lymphocyte attacks, in which non-synonymous mutations may lead to the production of immune escape variants, resulting in the persistence of HBV[45,46]. Moreover, since the mutation of HBcAg can lead to simultaneous mutations in HBeAg, which is a key HBV immune-regulatory protein, and can profoundly affect the natural course of HBV chronic infection[47].

Our previous report regarding the mutations in the precore/core (preC/C) region from 70 Korean chronic patients led to several significant results. First, a positive relationship between the preC/C mutation frequency and old age [wild type (36.9) *vs* mutation (51.9), $P = 0.001$] was found[11], which indicates that the accumulation of preC/C mutations during the natural course of chronic hepatitis B contributes to the persistent infection of HBV in areas where vertical infection is predominant. Second, the preC/C mutations were found more frequently in immuno-active regions than in immuno-inactive regions

(2.2% *vs* 1.7%, $P = 0.016$)[11], which implies that the host immune pressure at the T cell level is the significant driving force of the preC/C mutations[48,49]. Notably, a significant higher level of mutation rates in the major histocompatibility complex (MHC) class Ⅱ restricted region (2.3% *vs* 1.7%, $P = 0.009$), but not in the MHC class I restricted region, was found when compared with the immuno-inactive region, which indicates that former, *i.e.*, the target of the CD4 T helper cell, is more prone to mutations induced by the host immune response than the latter, *i.e.*, the target of the CD8 cytotoxic T cell[11]. Third, five mutations in the C region (C-P5H/L/T, C-E83D, CI97F/L, C-L100I, and C-Q182K/*) and one in the preC (preC-W28*), which is known to be a HCC-related preC mutation at nucleotide 1896 (G→A)[17,50], were found to be related to HCC patients compared with patients in other stages of the disease[11] (Table 1). It should be noted that four of the five HCC-related C mutations, *i.e.*, C-P5H/L/T, C-E83D, C-I97F/L, and C-L100I, were located in the MHC class Ⅱ restricted regions (one at aa 1-20 and three at aa 81-105), which implies that evasion of the CD4 T cell-mediated immune response, primarily through mutations in the "hot spot" region of aa residue 81-105, has a function in the hepatocarcinogenesis of chronic patients infected with genotype C[11]. Of the five HCC-related mutations in the C region, two types (C-L100I and C-Q182K/*) were introduced for the first time in that study[11]. Collectively, our data indicates that the HBV variants in the C region, particularly in the MHC class Ⅱ restricted regions, may contribute to the HCC progress in chronic patients infected with genotype C via immune evasion of the CD4 T cell-mediated immune response. It also implies the presence of a distinct immune pressure at the CD4 T cell level against HBcAg in the Korean population, which results in contributing to the HBV persistent infections via the generation of immune evading HBcAg variants[11].

MUTATION FREQUENCY AND PATTERNS IN THE X REGION IN KOREAN CHRONIC PATIENTS

HBV X protein (HBx) has been the focus of significant attention in recent years because it is strongly implicated in hepatocarcinogenesis. It is a 154-amino acid protein with an N-terminal negative regulatory domain and a C-terminal transactivation domain. The HBx protein is multifunctional and affects gene transcription, signaling pathways, genotoxic stress responses, cell-cycle control, and apoptosis; it also has an essential function in viral replication[51,52]. Several reports have demonstrated that specific point mutations in the HBx gene are related to severe forms of liver disease, such as cirrhosis of the liver and/or HCC[22,53]. In addition, deletions, especially COOH terminal truncations or insertions, have also been frequently detected in tissues and sera samples in HCC patients[14].

Our previous report using a cohort of 267 Korean patients demonstrated that the prevalence of deletions or insertions in the X region was significantly higher in patients with severe liver disease, HCC, or cirrhosis of the liver (7.2%, 10/132) compared with patients who were carriers or had chronic hepatitis (1.5%, 2/135) ($P = 0.017$)[14], which implies that the deletions or insertions in the X region may contribute to disease progression in Korean patients with genotype C infection.

Our other report regarding mutations in the X regions from a cohort of 184 Korean patients demonstrated that a total of five mutation types (V5M/L, P38S, H94Y, I127T/N, and K130M and V131I) affecting the six codons were related to clinical severity[22] (Table 1). Several noteworthy findings regarding these mutations are as follows. First, the V5M/L mutation first discovered during the present study was always significantly more frequent in HCC patients than in other patients, even patients with liver cirrhosis (Table 1) [HCC (50%) *vs* liver cirrhosis (26.2%), $P = 0.024$][22], which implies that it has a pivotal function in the progression from liver cirrhosis to HCC. Second, three mutations (H94Y, I127V/I, and K130 and V131) were also related to mutational "hot spots" of the overlapped enhancer II (H94Y: C→T of nt 1653) or BCP (I127T/N:T→V of nt 1753, K130M and V131I: A →T of nt 1762 and G→A of nt 1764). In particular, the double mutations of K130 and V131 overlapped in the BCP mutations were observed with the highest frequency (66.1%, 123/184 patients), which strongly supports the previous result of the very high prevalence of BCP in Korean chronic patients[22]. The recent study using a large cohort of Taiwanese showed that the prevalence of the BCP double mutation was significantly higher in patients infected with HBV genotype C than in those infected with HBV genotype B (43.0% *vs* 21.4%; $P < 0.001$)[54]. But, even the prevalence of BCP double mutation in genotype C infected Taiwanese (43.0%) is lower than that in genotype C infected Korean (66.1%).

Third, two types of mutation, *i.e.*, V5M/L [HBeAg negative (40%) *vs* HBeAg positive (19.1%), $P = 0.004$] and H94Y [HBeAg negative (30.4%) *vs* HBeAg positive (22.6%), $P = 0.087$], were related significantly and nearly significantly to HBeAg negative serostatus, respectively[22]. Fourth, three mutation types, *i.e.*, V5M/L [K130M and V131I (36.6%) *vs* no mutation (8.2%), $P < 0.001$], H94Y [K130M and V131I (35%) *vs* no mutation (6.6%), $P < 0.001$], and I127T/N [K130M and V131I (31.7%) vs no mutation (11.5%), $P = 0.003$], were strongly related to the BCP mutations[22]. This implies that the subsequent substitutions in specific codons of the X region following BCP double mutations may have a pivotal function in the progression of liver disease, at least in Korean chronic patients. Our previous report that the deletions of long lengths and amino acid substitutions followed by BCP double mutations[19] might contribute to the diversity of HBV quasispecies strongly supports this hypothesis.

In summary, our data suggest that an accumulation of mutations in the X region, in particular the subsequent

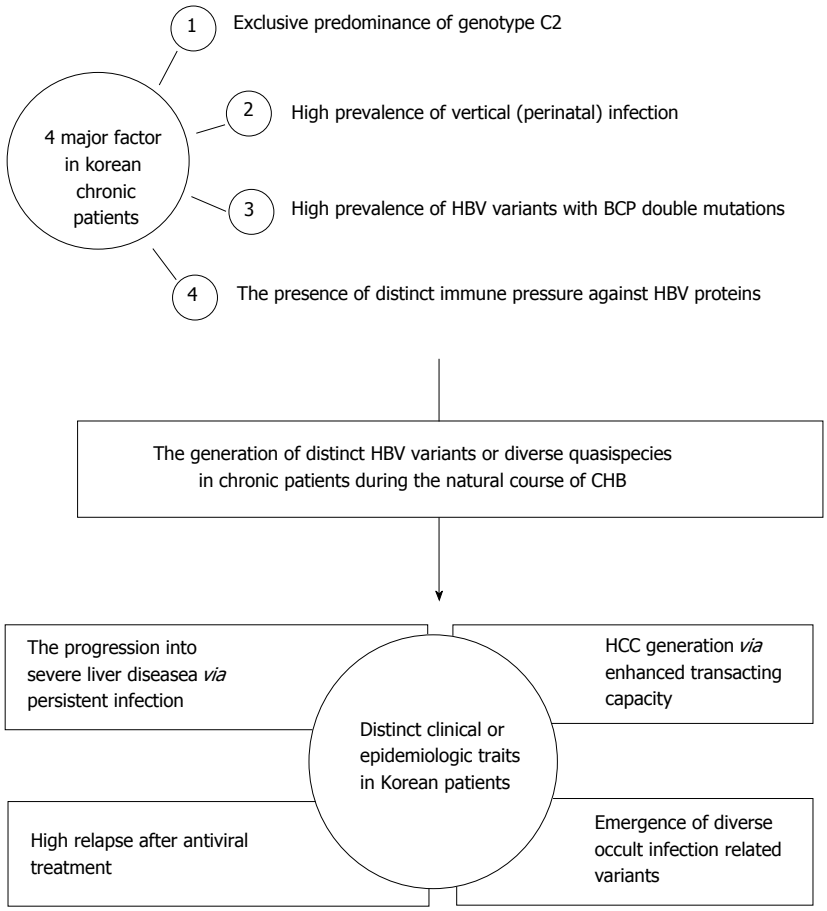

Figure 1 The 4 major factors in Korean chronic patients leading to distinct clinical or epidemiologic traits for hepatitis B virus. Combinatorial effect of 4 major factors (1) exclusive predominance of genotype C2; (2) high prevalence of perinatal infection; (3) high prevalence of basic core promoter mutations; and (4) the presence of distinct immune pressure) could generate distinct hepatitis B virus (HBV) variants or diverse quasispecies during the natural course of chronic hepatitis B, resultantly leading to distinct clinical or epidemiological traits in Korean chronic patients. HCC: Hepatocellular carcinoma; CHB: Chronic hepatitis B.

mutations in specific codons following the BCP double mutations, contributes to disease progression in Korean patients with chronic genotype C infections (Figure 1).

CONCLUSION

Several reports regarding HBV mutations from Korean chronic patients have led to the conclusion that the combination of four main factors, *i.e.*, the exclusive predominance of only genotype C2 prone to mutations[8], the predominance of a perinatal infection route providing sufficient time for the generation of variants[55], the high prevalence of BCP double mutations leading to subsequent mutations with high frequency[19,22,50], and the presence of distinct immune responses against HBV in Korean population[11], may lead to the generation of the distinct HBV variants rarely or not encountered in other areas in the course of CHB (Figure 1). The production of HBV variants may contribute to clinical or epidemiologic manifestations that are distinct in Korean chronic patients. First, it could contribute to the progression into severe types of liver disease through persistent infection by evading host immune responses[9-22]. Second, several types of mutation such as sW182* in the *S* gene[12] and F141L in the preS1[15] could contribute to the HCC generation via enhanced transacting capacity. This provides a potential explanation for the high relapse after antiviral treatments being observed in Korean chronic patients compared with other countries[6]. Finally, it may be responsible for the generation of highly diverse HBV variants related to occult infections that have been observed in Korean patients[10] (Figure 1).

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