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REVIEW

Host nucleotide polymorphism in hepatitis B virus-associated hepatocellular carcinoma

Shilu Mathew, Hany Abdel-Hafiz, Abbas Raza, Kaneez Fatima, Ishtiaq Qadri

Shilu Mathew, Center of Excellence in Genomic Medicine Research, King Abdul Aziz University, Jeddah 21589, Saudi Arabia

Hany Abdel-Hafiz, University of Colorado Denver AMC, Aurora, CO 80045, United States

Abbas Raza, Department of Immunobiology, University of Vermont, Burlington, VT 05405, United States

Kaneez Fatima, IQ-Institute of Infection and Immunity, Lahore 54000, Pakistan

Ishtiaq Qadri, King Fahd Medical Research Center, King Abdul Aziz University, Jeddah 21589, Saudi Arabia

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Correspondence to: Ishtiaq Qadri, PhD, Professor, King Fahd Medical Research Center, King Abdul Aziz University, PO Box 80216 Jeddah 21589,
Saudi Arabia. ishtiaq80262@yahoo.com
Telephone: +966-12-6400000
Fax: +966-12-6952067

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Abstract

Hepatocellular carcinoma (HCC) is etiologically linked with hepatitis B virus (HBV) and is the leading cause of death amongst 80% of HBV patients. Among HBV affected patients, genetic factors are also involved in modifying the risk factors of HCC. However, the genetic factors that regulate progression to HCC still remain to be determined. In this review, we discuss several single nucleotide polymorphisms (SNPs) which were reportedly associated with increased or reduced risk of HCC occurrence in patients with chronic HBV infection such as cyclooxygenase (COX)-2 expression specifically at COX-2 -1195G/A in Chinese, Turkish and Egyptian populations, tumor necrosis factor α and the three most commonly studied SNPs: PAT-/+, Lys939Gln (A33512C, rs2228001) and Ala499Val (C21151T, rs2228000). In genome-wide association studies, strong associations have also been found at loci 1p36.22, 11q22.3, 6p21 (rs1419881, rs3997872, rs7453920 and rs7768538), 8p12 (rs2275959 and rs37821974) and 22q11.21. The genes implicated in these studies include *HLA-DQB2*, *HLA-DQA1*, *TCF19*, *HLA-C*, *UBE2L3*, *LTL*, *FDX1*, *MICA*, *UBE4B* and *PG*. The SNPs found to be associated with the above-mentioned genes still require validation in association studies in order to be considered good prognostic candidates for HCC. Screening of these polymorphisms is very beneficial in clinical experiments to stratify the higher or lower risk for HCC and may help in designing effective and efficient HCC surveillance programs for chronic HBV-infected patients if further genetic vulnerabilities are detected.

Key words: Hepatitis B virus; Hepatocellular carcinoma; Subtypes; Genetic polymorphism; Liver cirrhosis

Core tip: In this review, we discuss various common associations between hepatitis B virus (HBV) and host polymorphisms. These single nucleotide polymorphisms which have been found to be associated with various genes still require validation in association studies in order to be considered good prognostic candidates for hepatocellular carcinoma (HCC). Screening of these polymorphisms is very beneficial in clinical experiments to stratify the higher or lower risk for HCC and may help in designing effective and efficient HCC surveillance programs for chronic HBV-infected patients if further genetic vulnerabilities are detected.

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HEPATITIS B VIRUS

Hepatitis B virus (HBV) infection is the third most common cause of cancer-related deaths in relation to hepatocellular carcinoma (HCC) with a high incidence in Asian countries. HCC is responsible for approximately 660000 deaths worldwide each year and 85%-90% of these deaths are due to primary liver cancers[1]. It is recognized that these cancers are mainly due to HBV infection with 60% of HCC cases seropositive for this virus[2]. Many risk factors including viral factors (*e.g.*, genomic mutations, genotypes, HBV-DNA levels), host factors and unhealthy lifestyles all contribute to the development of liver diseases[3].

Both epigenetic and genetic factors play a role in the malignant transformation of liver cells[4]. Multiple cellular signaling genes are enhanced by the incorporation of HBV into the host's genome which promotes transactivation of HBx protein[5]. This process activates/inactivates suppressor genes (*e.g.*, *p53*), oncogenic genes (*e.g.*, *c-fos* and *c-myc*), induces loss of heterozygosity and activates transcriptional factors [*e.g.*, nuclear factor kappa-B (NF-κB) and AP-1][6].

However, underlying disease and the duration of severity vary significantly between each phase. Moreover, clinical progression varies between patients. Liver injuries in patients with HBV infection are thought to be the outcome of the host's immune responses against HBV. For example, cytotoxic T lymphocyte-mediated, an HLA-class Ⅰ antigen-restricted, response to the HBV antigen expressed on hepatocytes results in necrosis and apoptosis[7].

Several genome wide association studies have identified candidate single nucleotide polymorphisms (SNPs) by comparing the SNPs present in HCC patients and those present in asymptomatic HBV carriers[8]. Therefore, to specifically evaluate genetic factors, it is vital that the controls and patients are well matched regarding these factors to identify the correct SNP. The results of many studies suggest that several SNPs are associated with HBV clearance and persistent infection. Functional analyses are necessary to confirm these results[6,7]. In this review, we discuss several SNPs which are reportedly associated with increased or reduced risk of HCC occurrence in patients with chronic HBV infection[9].

INFLAMMATORY GENETIC POLYMORPHISM

It has been reported previously that SNPs can affect disease progression after HBV infection. Cytokines, such as tumor necrosis factor-α (TNFα) and interleukin (IL)-10, have a significant role in regulating viral infection. Genetic variation of these cytokines is linked with the outcome of HBV infection[10-16].

Several studies have shown that genetic polymorphisms in multiple genes such as *TP53*[17], *IL-6*[18], and DNA repair genes[19], are associated with the development of chronic HBC infection, progression of the infection and increased risk of HCC. These may serve as biomarkers in identifying HCC risk[20]. However, these studies were predominantly performed in HBV-positive populations or populations with a high infection rate.

Genetic variation in tumor suppressor genes or oncogenes is capable of altering gene function and, consequently, may contribute to the development of cancer. Significant research has been conducted to investigate the association between polymorphisms in tumor suppressor genes and oncogenes and the risk of HCC; however, the results are controversial.

ASSOCIATIONS BETWEEN HBV AND THE HOST POLYMORPHISM

Cyclooxygenase-2

Cyclooxygenase-2 (COX-2) is involved in many cellular functions, including inflammation, inhibition of apoptosis, carcinogenesis, angiogenesis, invasion and metastasis[21,22]. COX-2 is overexpressed in many cancers including HCC, indicating that there is an association between COX-2 expression and the development of cancer[23,24]. Selective COX-2 inhibitors have been shown to suppress the growth of HCC cells *in vitro* and *in vivo*[25]. A polymorphism in the promoter region of the *COX-2* gene could functionally upregulate the transcriptional activity of COX-2, indicating a possible mechanism by which COX-2 may contribute to genetic susceptibility to HCC[21]. Several studies have reported that COX-2 point mutations including -1195G/A, -765G/C and +8473T/C were correlated with liver diseases and

HBV-related HCC[26]. COX-2-765G/C is related to the risk of skin, esophageal, colorectal, breast and gastric cancers[27-29]. With regard to HCC, contradictory and inconclusive results were found. Some studies have reported a correlation between COX-2-765G/C and HBV-related HCC risk[30-32], but other studies reported that no such correlation exists[26,33,34]. It has been reported that these inconsistent results were possibly due to limited sample sizes and ethnic variation in those studies. COX-2 + 8473T/C is associated with oral and breast cancers[35,36], but is not associated with HCC[37]. A recent meta-analysis by Chen *et al*[26] on Chinese, Turkish and Egyptian populations, concluded that COX-2-1195G/A may be associated with HCC risk, but not COX-2-765G/C or COX-2 + 847T/C.

IL-1alpha and 1beta

IL-1α is a potent pro-inflammatory cytokine and has many different biological functions, including cell survival, proliferation, and anti-apoptosis[38,39]. IL-1β is also reported to inhibit interferon-induced antiviral activity[40] and is assumed to be closely associated with the pathogenesis of chronic hepatitis C. Several polymorphisms of the *IL-1* gene that are thought to affect IL-1β production have been reported[41]. -31T SNPs of IL-1β have been shown to enhance IL-1β transcriptional activity[42] and several studies reported that -511C/-31T is a risk factor for the development of cancer and liver diseases[43-45]. Wang *et al*[41] showed that IL-1β-31 polymorphism was associated with HCC, after controlling for other confounding clinical parameters.

E-cadherin (CDH1)

E-cadherin is a transmembrane protein that mediates cell-cell adhesion and is expressed in most normal epithelial cells. Downregulation of E-cadherin may lead to a loss of E-cadherin-mediated adhesion, resulting in increased susceptibility to tumor development and is associated with poor prognosis in various carcinomas including HCC[45-52]. In addition, HBV and HCV reduce E-cadherin expression and promote tumor recurrence in HCC patients. One of the mechanisms that have been proposed for reduced E-cadherin expression is SNPs in the promoter region of the *CDH1* gene. CDH1-160 C/A and -347G/GA polymorphisms result in the downregulation of E-cadherin protein and is associated with cancer susceptibility[53]. Several studies demonstrated that CDH1-347 SNPs are significantly associated with HCC risk[52,54-57]. However, the correlation between CDH1-160 SNPs showed conflicting results. Some studies[58,59] have shown that CDH1-160 SNP carriers have an increased risk of prostate and bladder cancer, while others showed that it was not associated with the development of prostate, HCC, colorectal or gastric cancer[60].

Peroxisome proliferator-activated receptor gamma

Peroxisome proliferator-activated receptor gamma (PPARγ) is a hormone receptor, present in adipose tissue and plays a critical role in the regulation of fatty acid storage and glucose metabolism[61]. PPARγ has been shown to be associated with type 2 diabetes mellitus (T2DM)[62]. PPARγ contains two isoforms, PPARγ1 and PPARγ2 and several variants in the *PPARγ* gene have been identified[63]. The A allele of PPARγ2 is associated with a significant decrease in the development of T2DM[64]. The relationship between PPAR and HCC is not clear. Although experimental studies have shown that PPAR may have a role in HCC[65,66], the implications of these findings are unclear. Koytak *et al*[66] investigated the effect of the PPARα L162V polymorphism on clinical outcome in a patient with HCC caused by hepatitis viruses. They concluded that there was a relationship between the PPARα L162V polymorphism and HBV-induced HCC and was associated with advanced HCC. This polymorphism was shown to enhance PPARα transcriptional activity and is associated with lipid abnormalities and an increased body mass index[67-70].

TNFα-inducible protein 3

TNFα-inducible protein 3 (TNFαIP3), a cytoplasmic zinc finger protein with ubiquitin-modifying activity, has been shown to inhibit NF-κB activity and TNF-mediated apoptosis[71-74]. TNFαIP3 polymorphisms have been linked to inflammatory, autoimmune and malignant diseases. A recent study reported that there was no association between TNFαIP3 rs2230926 polymorphism and susceptibility to chronic HBV infection or the progression of HBV-related diseases[75].

Cytotoxic T lymphocyte-associated factor 4

Cytotoxic T lymphocyte-associated factor 4 (CTLA-4) is a protein receptor expressed in T cells and it functions as a negative regulator of the immune system. Several *CTLA-4* gene polymorphisms have been identified including -318C>T, A49G and CT60[76]. CTLA-4 polymorphisms are associated with several autoimmune diseases, including thyroid and liver diseases[77,78]. It has been shown that SNPs in CTLA-4 may be associated with HBV progression and viral persistence[79]. CTLA-4 SNPs can be used as a marker for predicting treatment outcome in chronic HCV-infected patients[80-82].

TNFα

TNFα is a multifunctional cytokine that regulates the inflammatory reaction and has an important role in the development and progression of a number of diseases, including liver disease[83,84]. It has been suggested that genetic polymorphisms of TNFα may contribute to the pathogenesis of liver diseases, infectious diseases and inflammatory disorders[43,85]. For example, TNFα SNPs affect TNFα production leading to a greater risk of HCC. The polymorphism at site -1031T/C, -863C/A, -857C/T, -376, -308G/A and -238G/A of the TNFα promoter is associated with the outcome of HBV infection and disease progression[86-89].

IL-10

IL-10 is an important anti-inflammatory cytokine produced in macrophages. Three SNPs in the *IL-10* gene promoter, at -1082, -819 and -592, are associated with IL-10 production and secretion by peripheral blood monocytes. It has been shown that IL-10-592 A/C polymorphism was associated with susceptibility to HBV infection[90].

Glutathione S-transferases

The glutathione S-transferases (GSTs) enzymes play an important role in maintaining the cellular defense mechanism against the effects of reactive oxygen species and various exogenous toxins, and have been shown to be overexpressed in several cancers[91,92]. Deletion polymorphism of *GST* genes results in diminished enzyme activity leading to the insufficient defense of cells from metabolites and free radicals, elevated concentration of endogenous mutagens and a high risk of various tumors, including HCC[93-96]. GSTs polymorphisms have been shown to be associated with colorectal cancer, lung cancer, squamous cell carcinoma of the head and neck, HBV-related HCC, and various urogenital and gastrointestinal disorders[97-99]. For example, meta-analyses have shown that GSTM1, GSTP1 and GSTT1 are associated with an increased risk of HCC[100,101].

Epidermal growth factor

Epidermal growth factor (EGF) and its respective receptor (EGFR) signaling are important regulators of proliferation and the pathogenesis of many human carcinomas[102,103]. Upon ligand binding, the two EGFR domains undergo trans-autophosphorylation at specific tyrosine residues[104]. These phosphotyrosines are recognized by Src homology 2 domain containing proteins[105] and activate a diverse signaling network that includes the RAS/extracellular signal-regulated kinase pathway[106], the phosphatidylinositol 3-kinase pathway[107] and the Janus kinase/Signal transducer and activator of transcription pathway[108].

Activation of EGF has also been shown to be required for hepatocyte growth during liver regeneration[109]. In addition, many viruses such as Epstein Barr virus and HBV can tweak EGF receptor expression in their favor[110-112]. The role of EGF polymorphism has been explored in numerous meta-analyses[113-116] and was shown to be highly associated with susceptibility to HCC[117]. Prominent among these is the EGF + 61A > G transversion (rs4444903) which was shown to regulate expression of the *EGF* gene[118,119]. This SNP is found in the 5′ untranslated regions of the *EGF* gene and was shown in cell lines to enhance the stability of EGF mRNA[119]. The G/G allele is associated with higher serum levels of EGF compared with the A/A allele[119,120]. Numerous follow-up studies have validated the positive association between this G/G and G/A genotype with HCC in diverse genetic populations[117,121-123] and thus can be considered a good prognostic marker for the genetically susceptible population.

Murine double minute 2

Murine double minute 2 (MDM2) is a ubiquitin ligase that controls the turnover rate of an important tumor suppressor, p53, which is deleted or mutated in 50% of all human tumors[124]. P53 is also referred to as the guardian of the genome because it can activate DNA repair pathways[125], arrest cell cycle at the G1/S regulation checkpoint[126] or initiate apoptosis if the damage cannot be repaired[127]. All these important networks converge in the active form of p53, which is kept in check by MDM2. The addition of ubiquitin subunits to critical lysine residues transfers the active p53 to 26S proteasome for degradation along with MDM2[128,129]. In addition, the binding of MDM2 can block p53-mediated transactivation functions[130]. The activity of MDM2 protein is equally important in regulating this DNA repair-cell cycle-apoptosis nexus and variation in the expression levels of this protein was shown to have serious consequences in cells or organisms[131]. Bond *et al*[132] showed that the SNP 309T > G (rs 2279744) located in the promoter region of MDM2 can enhance the transcriptional levels of this protein and subsequent perturbation of p53 functions in the cell. This T > G mutation is thought to generate a binding site on the MDM2 promoter for Sp1 transcription factor[133] and thus enhances the levels of MDM2 protein in the cell.

The positive association between this SNP 309T > G (rs 2279744) in the *MDM2* gene and HCC was shown by numerous ethnic-based studies[134-136] and meta-analyses[137,138]. This epidemiological finding together with functional assays of MDM2 levels point to the relevance of MDM2 SNP 309T > G polymorphism as an important player in susceptibility to HCC development.

T cell immunoglobulin mucin-3

T cell immunoglobulin mucin-3 (TIM3) negatively regulates the autoimmune and allergic responses and has been linked to T cell dysfunction associated with HBV-related HCC[139]. The 280 aa mature TIM3 is selectively expressed on $CD4^+$ Th1 and $CD8^+$ Tc1 cells, but not on $CD4^+$ Th2 cells[140]. It interacts with its ligand galectin-9 and drives death Th1 T cells[141,142]. Blocking TIM3-mediated signaling restores dysfunctional CD4 and $CD8^+$ T cell-specific adaptive immune responses[143]. TIM3 is upregulated on CD4 and $CD8^+$ T cells in chronic HBV infected individuals[144].

Numerous potential SNPs (-1541C/T, -1516G/T, -882C/T, -574G/T and +4259T/G) in TIM3 have been tested for their association with chronic HBV and HCC[145]. TIM3-1516 G/T (rs10053538) polymorphism has been shown to predispose individuals to cirrhosis and/or HCC[146,147]. One study reported that TIM3 SNPs do not have a functional effect[148], whereas others have reported a significant effect of these TIM3 polymorphic variants[149]. Further studies are needed to determine the functional relevance of this polymorphism.

Xeroderma pigmentosum complementation group C

Xeroderma pigmentosum complementation group C (XPC) protein along with seven other core members (ERCC1, XPA, XPB, XPC, XPD, XPE, XPF and XPG) constitutes the nucleotide excision repair pathway (NER). This pathway is required for the repair of DNA damage including pyrimidine dimers, photo products, chemical adducts and cross-links[150,151]. XPC requires an association with HR23B in order to recognize damaged DNA[152]. The protein HR23B is a human homolog of *Saccharomyces cerevisiae* RAD23 and binding of XPC-HR23B to a DNA lesion unwinds the helix[153]. The XPA protein can then bind and the whole repair machinery of the NER can be recruited onto the damaged base.

Many studies have investigated the association between XPC sequence variants and cancer risk[154-158]. The three most commonly studied SNPs in the literature are: PAT-/+[159], Lys939Gln (A33512C, rs2228001)[155] and Ala499Val (C21151T, rs2228000)[160]. The poly (AT) insertion/deletion polymorphism (PAT) is located on intron 9 and has been shown to be linked to head and neck cancer risk[161] and to lung cancer[162], but no studies have found an association with HCC risk. The XPC codon Lys939Gln alleles, on the other hand, significantly increased HCC risk[163,164]. The Ala499Val variant homozygous genotype is a risk factor for bladder cancer[158], but has not been studied for HCC.

IL-16

IL-16 is a pro-inflammatory cytokine and was initially called lymphocyte chemoattractant factor[165]. It can activate a diverse set of immune cells such as $CD4^+$ T cells, monocytes, macrophages, eosinophils and dendritic cells[166-169]. In addition to inducing activation and chemotaxis of immune cells, IL-16 can upregulate the IL-2 receptor[170] and HLA-DR4 expression[171]. Upon CD4 receptor binding, IL-16 signaling increases intracellular calcium and inositol triphosphate, and translocation of protein kinase C from the cytosol to the plasma membrane[172,173]. Moreover, IL-16 can stimulate the production of further pro-inflammatory mediators including LI-1β, IL-6, IL-15 and TNFα, *e.g.*, by monocytes[174] thereby initiating and/or sustaining the inflammatory response.

Genetic polymorphisms in IL-16 have recently been reported and shown to affect susceptibility to a range of cancers including colorectal, gastric and prostate cancer and nasopharyngeal carcinoma[175-178]. Data regarding HCC and IL-16 polymorphisms are scarce in the literature and only two studies were found to have assessed three SNPs (rs11556218T > G, rs4778889T > C, and rs4072111C > T)[179]. In the study by Li *et al*[180], no association with HCC was found for all three SNPs (rs11556218T/G $P = 0.511$, rs4072111C/T $P = 0.308$ and rs4778889T/C $P = 0.070$). The other study by Thomas *et al*[178] did not include HCC patients. However, this study did include chronic hepatitis B patients who showed a positive association between rs11556218T > G, a negative association between rs4778889T > C and a positive association between rs4072111C > T polymorphisms and patient susceptibility to chronic hepatitis B infection[179].

Genome-wide association studies

Numerous genome-wide association studies (GWAS) have been carried out with chronic HBV and HCC patients to identify novel susceptible loci contributing to disease[6,181-186]. Of these, strong associations were found at 1p36.22, 11q22.3, 6p21 (rs1419881, rs3997872, rs7453920 and rs7768538), 8p12 (rs2275959 and rs37821974) and 22q11.21. The genes implicated in these studies include HLA-DQB2, HLA-DQA1, transcription factor 19 (TCF19), HLA-C, ubiquitin-conjugating enzyme E2 (UBE2L3), LTL, ferredoxin 1 (FDX1), MICA, UBE4B and PG.

HLA-DQ is an MHC class Ⅱ cell surface receptor found on antigen presenting cells, whereas HLA-C is an MHC class Ⅰ receptor expressed by all cells. TCF19, as the name suggests, is an important transcription factor during cell cycle G1/S transition[187]. UBE2L3 is a typical E2 ligase that accepts ubiquitin from the E1 complex and transfers it to targeted proteins[188]. Leukocyte telomere length (LTL) has been associated with the risk of developing many malignancies[189] and LTL-related SNPs are potential targets for such GWAS studies. FDX1 is a gene that codes for a small iron-sulfur protein that transfers electrons from NADPH through ferredoxin reductase to mitochondrial cytochrome P450[190]. In addition, it is involved in steroid, vitamin D, and bile acid metabolism[191].

These SNPs found to be associated with the above-mentioned genes still require validation in association studies in order to be considered good prognostic candidates for HCC.

Tumor growth factor beta

Tumor growth factor beta (TGFβ) is a tumor suppressor gene located on chromosome 19q13.1-13.39. The protein TGFβ is involved in pleiotropic biological processes such as cell growth[192], differentiation[193], extracellular matrix synthesis[194], hematopoiesis[195], angiogenesis[196], and cellular apoptosis[197]. TGFβ1 is one of TGFβ isoforms and is upregulated in HCC tissues correlating with the carcinogenesis and prognosis of HCC[198,199]. TGFβ1 also suppresses HBV replication by reducing hepatocyte nuclear factor-4-alpha[200]. Thus, the relevance of this cytokine and its single nucleotide polymorphism in HBV-associated HCC is of paramount importance.

Seven TGFβ1 polymorphisms have been described in the literature, of which three lie in the upstream region of the gene at positions -988C > A, -800G > A, and -509C > T, one insertion in a nontranslated region at position +72C, two in exon 1 (Leu10Pro and Arg25Pro); and 1 in exon 5 (Thr263Ile)[201]. Numerous studies have investigated the association between these

Table 1 List of polymorphic genes and their contribution to hepatocellular carcinoma

Polymorphism	Genotype	Significance	Ref.
COX-2	-1195G > A	$P < 0.00$[26]	He *et al*[31]
	-765G > C	$P < 0.05$[31] and 0.41[26]	Chen *et al*[26]
	+8473T > C	$P = 0.83$[26]	
IL-1α, β	511C > T	$P = 0.02$[41]	Wang *et al*[41]
	-31C > T	$P = 0.02$[41]	
CDH1	-347G > A	$P = 0.171$[209] and < 0.05[60]	Li *et al*[209], Chien *et al*[60]
PPARγ	L162V	$P = 0.071$[66]	Koytak *et al*[66]
TNFAIP3	F127C	$P = 0.15$[75]	Zhang *et al*[75]
TNFα	-1031T/C	$P = 0.85$[86]	Wei *et al*[86]
	-863C/A	$P = 0.006$[86]	
	-857C/T	$P = 0.09$[86]	
	-308G/A	$P = 0.046$[86]	
	-238G/A	$P = 0.003$[86]	
GST	GSTM1 + GSTT1	$P = 0.001$[210]	Liu *et al*[210]
EGF	+61A > G	$P < 0.001$[117]	Jiang *et al*[117]
MDM2	309G > T	$P = 0.001$[133]	Ezzikouri *et al*[133]
TIM3	-1516G > T	$P = 0.001$[146]	Li *et al*[146]
XPC	K939Q	$P = 0.001$[163]	Long *et al*[163]
1p36.22, 11q22.3, 6p21, 8p12 22q11.21	Include genes *HLA-DQB2*, *HLA-DQA1*, *TCF19*, *HLA-C*, *UBE2L3*, *LTL*, *FDX1*, *MICA*, *UBE4B* and *PG*	$P = 1.7 \times 10^{-18}$	Al-Qahtani *et al*[181]
		$P = 4.3 \times 10^{-8}$	
		$P = 0.0266$	
		$P = 0.0067$	
		$P = 1.71 \times 10^{-12}$	
TGFβ1	-509C > T	$P = 0.01$[206] and 0.318[207]	Qi *et al*[206]
	R25P	$P = 0.472$[207]	Hosseini Razavi *et al*[207]
	L10P	$P < 0.02$[208]	Kim *et al*[208]

COX-2: Cyclooxygenase-2; IL-1α, β: Interleukin-1α, β; CDH1: Cadherin 1; PPARγ: Peroxisome proliferator-activated receptor γ; TNFAIP3: Tumor necrosis factor alpha-induced protein 3; TNFα: Tumor necrosis factor α; GST: Glutathione S transferase; EGF: Epidermal growth factor; MDM2: Mouse double minute 2 homolog; TIM3: T-cell immunoglobulin 3; XPC: Xeroderma pigmentosum; TGFβ1: Transforming growth factor beta 1.

SNPs and HCC[202-205]. There are contrasting reports with some studies reporting a positive association between -509C > T (rs1800469) and HCC risk[206], whereas another study reported a weak or no association[204]. In addition, the Arg25Pro change at +915G/C (rs1800471) was not correlated with HCC risk[207]. The mutation in codon 10 (Leu > Pro) was very strongly correlated with HCC according to one study[208]. There is still limited information regarding other polymorphisms of TGFβ1 and further studies are required to draw firm conclusions on their association with HCC. Table 1 lists the polymorphic genes and their contribution to HCC.

DISCUSSION

In this article, we discuss the association between the HBV genotype and its mutations in the development of liver cancer and the possibility that individuals with inherited genetic mutations have a hereditary predisposition for HBV-related HCC. Such individuals can inherit a germ-line mutation in one allele of the gene; somatic mutation of the second allele facilitates tumor progression. Although the inherited germ-line mutation may not be adequate to affect tumor development, it is likely that HBV proteins also induce many alterations in the genome. Analysis of the whole transcriptome in these individuals with genetic predisposition would be a useful indicator. It is now well understood that host genetic differences significantly influence susceptibility and resistance to HBV infection and the development of liver cancer, thus it is important to identify these genotype-phenotype associations for better treatment of the disease (Figure 1). Genome-wide sequencing studies have identified numerous germline mutations associated with liver cancer predisposition and large numbers of somatic alterations. It is difficult to assess the difference between background and HBV-related mutations as HBV infection plays an important role in the development of host genetic mutations, due to impairment in the DNA repair process. To elucidate the role of HBV-related genetic variations, researchers have used traditional biological methods to identify genetic mutations. More recently, advanced techniques such as next generation sequencing technology have been used to identify key mutations involved in the development of HCC. Important HCC-associated mutations have been found in key regulatory genes including COX-2, IL-1α and 1β, E-cadherin (CDH1), PPARγ, TNFαIP3, CTLA-4, TNFα, IL-10, GSTM1/GSTT1 Deletion Oxidative stress, EGF, MDM2, TIM3), XPC, IL-16, TGFβ, 1p36.22, 11q22.3, 6p21, 8p12 and 22q11.21 candidate SNPs in GWAS. The association between each locus and the outcome of liver disease is discussed in detail in this article.

Based on these findings, we predict that advanced sequence analysis of host genome will provide us with a better understanding of the viral and host genetic factors involved in the development of HCC. Further studies are needed to evaluate and understand the role

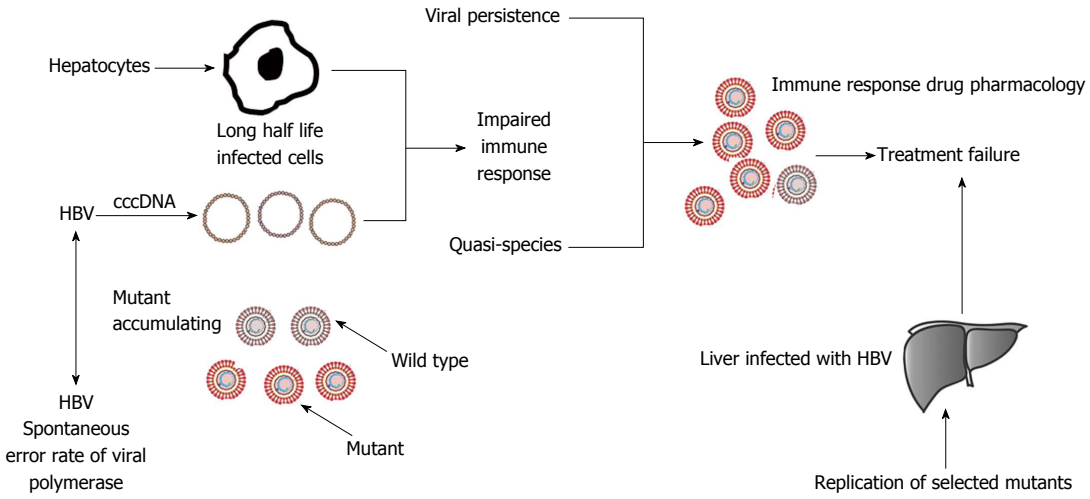

Figure 1 Mechanisms of selection and emergence of hepatitis B virus drug-resistant mutants. HBV: Hepatitis B virus; cccDNA: Covalently closed circular DNA.

of host-HBV interactions in HBV-related HCC to generate effective diagnostic and therapeutic treatments.

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