Host nucleotide polymorphism in hepatitis B virus-associated hepatocellular carcinoma

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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 (rs22275959 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 660,000 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, 18], IL-6[14], 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\textsuperscript{26}. COX-2-765G/C is related to the risk of skin, esophageal, colorectal, breast and gastric cancers\textsuperscript{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\textsuperscript{30-32}, but other studies reported that no such correlation exists\textsuperscript{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\textsuperscript{25,35}, but is not associated with HCC\textsuperscript{37}. A recent meta-analysis by Chen et al\textsuperscript{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 + 8477T/C.

**IL-1alpha and 1beta**

IL-1\(\alpha\) is a potent pro-inflammatory cytokine and has many different biological functions, including cell survival, proliferation, and anti-apoptosis\textsuperscript{38,39}. IL-1\(\beta\) is also reported to inhibit interferon-induced antiviral activity\textsuperscript{40} and is assumed to be closely associated with the pathogenesis of chronic hepatitis C. Several polymorphisms of the IL-1\(\alpha\) gene that are thought to affect IL-1\(\beta\) production have been reported\textsuperscript{41}. -31T SNPs of IL-1\(\beta\) have been shown to enhance IL-1\(\beta\) transcriptional activity\textsuperscript{42} and several studies reported that -511C/-31T is a risk factor for the development of cancer and liver diseases\textsuperscript{43-45}. Wang et al\textsuperscript{41} showed that IL-1\(\beta\)-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\textsuperscript{46-52}. 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\textsuperscript{53}. Several studies demonstrated that CDH1-347 SNPs are significantly associated with HCC risk\textsuperscript{52,54-57}. However, the correlation between CDH1-160 SNPs showed conflicting results. Some studies\textsuperscript{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\textsuperscript{60}.

**Peroxisome proliferator-activated receptor gamma**

Peroxisome proliferator-activated receptor gamma (PPAR\(\gamma\)) is a hormone receptor, present in adipose tissue and plays a critical role in the regulation of fatty acid storage and glucose metabolism\textsuperscript{61}. PPAR\(\gamma\) has been shown to be associated with type 2 diabetes mellitus (T2DM)\textsuperscript{62}. PPAR\(\gamma\) contains two isoforms, PPAR\(\gamma\)1 and PPAR\(\gamma\)2 and several variants in the PPAR\(\gamma\) gene have been identified\textsuperscript{63}. The A allele of PPAR\(\gamma\)2 is associated with a significant decrease in the development of T2DM\textsuperscript{64}. The relationship between PPAR and HCC is not clear. Although experimental studies have shown that PPAR may have a role in HCC\textsuperscript{65,66}, the implications of these findings are unclear. Koytak et al\textsuperscript{66} investigated the effect of the PPAR\(\alpha\) L162V polymorphism on clinical outcome in a patient with HCC caused by hepatitis viruses. They concluded that there was a relationship between the PPAR\(\alpha\) L162V polymorphism and HBV-induced HCC and was associated with advanced HCC. This polymorphism was shown to enhance PPAR\(\alpha\) transcriptional activity and is associated with lipid abnormalities and an increased body mass index\textsuperscript{67-70}.

**TNF\(\alpha\)-inducible protein 3**

TNF\(\alpha\)-inducible protein 3 (TNF\(\alpha\)IP3), a cytoplasmic zinc finger protein with ubiquitin-modifying activity, has been shown to inhibit NF-\(\kappa\)B activity and TNF\(\alpha\)-mediated apoptosis\textsuperscript{71-74}. TNF\(\alpha\)IP3 polymorphisms have been linked to inflammatory, autoimmune and malignant diseases. A recent study reported that there was no association between TNF\(\alpha\)IP3 rs2230926 polymorphism and susceptibility to chronic HBV infection or the progression of HBV-related diseases\textsuperscript{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\textsuperscript{76}. CTLA-4 polymorphisms are associated with several autoimmune diseases, including thyroid and liver diseases\textsuperscript{77,78}. It has been shown that SNPs in CTLA-4 may be associated with HBV progression and viral persistence\textsuperscript{79}. CTLA-4 SNPs can be used as a marker for predicting treatment outcome in chronic HCV-infected patients\textsuperscript{80-82}.

**TNF\(\alpha\)**

TNF\(\alpha\) 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\textsuperscript{83,84}. It has been suggested that genetic polymorphisms of TNF\(\alpha\) may contribute to the pathogenesis of liver diseases, infectious diseases and inflammatory disorders\textsuperscript{45,85}. For example, TNF\(\alpha\) SNPs affect TNF\(\alpha\) 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 TNF\(\alpha\) promoter is associated with the outcome of HBV infection and disease progression\textsuperscript{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.

**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. 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 (102-103). GSTs polymorphisms have been shown to be associated with colorectal cancer,

**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 (104,105). Upon ligand binding, the two EGFR domains undergo activation of a diverse signaling network that includes the RAS/phosphatidylinositol 3-kinase pathway and the Janus homology 2 domain containing proteins.

**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 (106,107). P53 is also referred to as the guardian of the genome because it can activate DNA repair pathways, arrest cell cycle at the G1/S regulation checkpoint or initiate apoptosis if the damage cannot be repaired.

**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 (108). The 280 aa mature TIM3 is selectively expressed on CD4+ Th1 and CD8+ Tc1 cells, but not on CD4+ Th2 cells (109). It interacts with its ligand galectin-9 and drives death Th1 T cells (110). Blocking TIM3-mediated signaling restores dysfunctional CD4 and CD8+ T cell-specific adaptive immune responses (111). TIM3 is upregulated on CD4 and CD8+ T cells in chronic HBV infected individuals (112).

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 (113). TIM3-1516 G/T (rs10053538) polymorphism has been shown to predispose individuals to cirrhosis and/or HCC (114,115). One study reported that TIM3 SNPs do not have a functional effect (116), whereas others have reported a significant effect of these TIM3 polymorphic variants. 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, 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 included chronic hepatitis B patients who 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, ferrodoxin 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 ferrodoxin 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[158,199]. 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
SNPs and HCC\cite{206,207,208,209}. There are contrasting reports with some studies reporting a positive association between -509C > T (rs1800469) and HCC risk\cite{207}, whereas another study reported a weak or no association\cite{209}. In addition, the Arg25Pro change at +915G/C (rs1800471) was not correlated with HCC risk\cite{206}. The mutation in codon 10 (Leu > Pro) was very strongly correlated with HCC according to one study\cite{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 liver cancer, thus it is important to identify these key mutations involved in the development of HCC.

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

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

| Polymorphism | Genotype | Significance | Ref. |
|--------------|----------|--------------|------|
| COX-2        | -1195G > A | P < 0.001\cite{26} | He et al\cite{26} |
|              | 765G > C   | P < 0.05 and 0.41\cite{26} | Chen et al\cite{26} |
|              | +8473T > C | P = 0.83\cite{26} | Wang et al\cite{26} |
| IL-1α, β     | -509C > T  | P = 0.02\cite{26} | Li et al\cite{26}, Chen et al\cite{26} |
|              | -1516G > T | P = 0.01\cite{26} | Koytak et al\cite{26} |
|              | -1031T/C   | P = 0.01\cite{26} | Zhang et al\cite{26} |
|              | +61A > G   | P = 0.006\cite{26} | Wei et al\cite{26} |
| CDH1         | -147G > A  | P = 0.17\cite{26} and < 0.05\cite{26} | Liu et al\cite{26}, Chen et al\cite{26} |
| PPARγ        | L162V     | P = 0.01\cite{26} | Liu et al\cite{26} |
| TNFAIP3      | F127C     | P = 0.15\cite{26} | Jiang et al\cite{26} |
| TNFα         | -1031T/C   | P = 0.06\cite{26} | Ezzikouri et al\cite{26} |
|              | -863C/A    | P = 0.09\cite{26} | Li et al\cite{26} |
|              | -857C/T    | P = 0.04\cite{26} | Long et al\cite{26} |
|              | -208G/A    | P = 0.03\cite{26} | Al-Qahtani et al\cite{26} |
| GST          | GSTM1 + GSTT1 | P = 0.01\cite{26} | Liu et al\cite{26} |
| EGFR         | +61A > G   | P < 0.01\cite{26} | Jiang et al\cite{26} |
| MDM2         | +309G > T  | P = 0.001\cite{26} | Li et al\cite{26} |
| TIM3         | -1516G > T | P = 0.001\cite{26} | Long et al\cite{26} |
| XPC          | K599Q     | P = 0.01\cite{26} and 0.318\cite{26} | Qi et al\cite{26} |
| 1p36.22, 11q22.3, 6p21, 8p12 22q11.21 | Include genes HLA-DQB2, HLA-DQA1, TCF19, HLA-C, UBE2L3, LTL, FDX1, MICA, UBE4A8 and PG |  |  |
| TGFβ1        | -509C > T  | P < 0.01\cite{26} and 0.318\cite{26} | Qi et al\cite{26} |
|              | -1195G/A   | P = 0.02\cite{26} | Hosseini Razavi et al\cite{26} |
|              | -765G/C    | P = 0.02\cite{26} | Kim et al\cite{26} |
|              | +8473T/C   | P = 0.02\cite{26} | Kim et al\cite{26} |

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.
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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