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**Host nucleotide polymorphism in hepatitis B virus-associated hepatocellular carcinoma**

Mathew S *et al*. Host nucleotide polymorphism in hepatitis B virus-associated HCC

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**Abstract**

Hepatocellular carcinoma (HCC) is etiologically linked with hepatitis B virus (HBV) and is the leading source of death amongst 80% of HBV patients. Among the HBV affected patients, genetic factors also are involved in modifying the risk factors of HCC. Though, genetic factors that regulate advancement towards HCC remain still to be explored. In this review, we discuss that 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 on Chinese, Turkish and Egyptian population, tumor necrosis factor (TNF) α as well as the three most common studied SNPs such as PAT–/+, Lys939Gln (A33512C, rs2228001) and Ala499Val (C21151T, rs2228000). Among the genome-wide association studies, strong association has been also 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. These SNPs found to be associated with the above-mentioned genes still require validation from 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 as well as might pay a way to design effective and efficient HCC surveillance programs for chronic HBV-infected patients if further genetic vulnerabilities are detected.

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

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**Core tip:** In this review, we discuss various common associations of hepatitis B virus (HBV) with host polymorphism. These single nucleotide polymorphisms found to be associated with the above-mentioned genes still require validation from 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 as well as might pay a way to design effective and efficient HCC surveillance programs for chronic HBV-infected patients if further genetic vulnerabilities are detected.

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**HEPATITIS B VIRUS**

Third most common cause of cancer-related deaths with higher incidence in Asian countries is caused by hepatocellular carcinoma (HCC). HCC accounts is responsible for approximately 660000 deaths worldwide each year and 85-90% of these are primary liver cancers[[1](#_ENREF_1)]. These are recognized mainly to hepatitis B virus (HBV) infections with 60% of HCC cases seropositive for this virus[[2](#_ENREF_2)]. Many risk factors including viral factors (*e.g.*, genomic mutations, genotypes, HBV-DNA levels), host factors and unhealthy lifestyles all add to the development of liver diseases[[3](#_ENREF_3)].

Both epigenetic and genetic factors play in to reach malignant transformation of liver cells[[4](#_ENREF_4)]. Multiple cellular signaling genes are enhanced by incorporation of HBV into the host’s genome and promotes transactivation of HBx protein[[5](#_ENREF_5)]. This process activates inactivates suppressor genes (*e.g.*, *p53*), oncogenic genes (*e.g.*, *c-fos* and *c-myc*), induces the loss of heterozygosity and activates transcriptional factors [*e.g.*, nuclear factor kappa-B (NF-κB) and AP-1][[6](#_ENREF_6)].

However, underlying disease and the duration severity vary significantly between each phase. Moreover, the clinical progression varies between patients. The liver injuries in patients with HBV infection are deliberated 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](#_ENREF_7)].

Several genome wide association studies have recognized candidate single nucleotide polymorphisms (SNPs) by comparing HCC patients and the SNPs present in asymptomatic HBV carriers[[8](#_ENREF_8)]. Therefore, to specifically evaluate genetic factors, it is vital that the controls and patients are well accorded for 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](#_ENREF_6),[7](#_ENREF_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](#_ENREF_9)].

**INFLAMMATORY GENETIC POLYMORPHISM**

It has been reported previously that SNPs can affect disease progression after HBV infection. Cytokines, such as tumor necrosis factors-α and interleukin (IL)-10, perform a significant role in regulating viral infection. Genetic variation of such cytokines is linked with the upshot of HBV infection[[10-16](#_ENREF_10)].

Several studies have shown that genetic polymorphisms in multiple genes such as TP53[[17](#_ENREF_17)], IL-6[[18](#_ENREF_18)], and DNA repair genes[[19](#_ENREF_19)], are associated with the development of chronic HBC infection, the progression of the infection and increased risk of HCC. These may serve as biomarkers in identifying HCC risk[[20](#_ENREF_21)]. 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 researches have been conducted to investigate the association between polymorphisms in tumor suppressor genes and oncogenes and the risk of HCC; however, the results remain controversial.

**ASSOCIATIONS OF HBV WITH THE HOST POLYMORPHISM**

***Cyclooxygenase-2***

The cyclooxygenase-2 (COX-2) is involved in many cellular functions, including inflammation, inhibition of apoptosis, carcinogenesis, angiogenesis, invasion and metastasis[[21](#_ENREF_22),[22](#_ENREF_23)]. 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](#_ENREF_24), [24](#_ENREF_25)]. The selective COX-2 inhibitors have been shown to suppress the growth of HCC cells *in vitro* and *in vivo*[[25](#_ENREF_26)]. 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](#_ENREF_22)]. 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](#_ENREF_27)]. The COX2-765G/C is related to the risk of skin, esophageal, colorectal, breast and gastric cancers[[27-29](#_ENREF_28)]. When it comes to HCC, contradictory and inconclusive results were found. Some studies have reported a correlation between the COX2-765G/C and HBV-related HCC risk[[30-32](#_ENREF_31)], but other studies reported that there is no such correlation exists[[26](#_ENREF_27),[33](#_ENREF_34),[34](#_ENREF_35)]. It has been reported that these inconsistent results possibly due to limited sample sizes and ethnic variation included in those studies. The COX-2 + 8473T/C is associated with oral and breast cancers[[35](#_ENREF_36),[36](#_ENREF_37)], but is not associated with HCC[[37](#_ENREF_38)]. Recent meta- analysis study by Chen *et al*[[26](#_ENREF_27)] on Chinese, Turkish and Egyptian population, have concluded that COX-2 -1195G/A might be associated with HCC risk, but COX-2-765G/C and COX-2+847T/C are not.

***Interleukin IL- 1alpha and 1beta***

Interleukin 1 beta (IL-1β) is one of the potent pro-inflammatory cytokines and has many different biological functions, including cell survival, proliferation, and anti-apoptosis[[38](#_ENREF_39), [39](#_ENREF_40)]. IL-1β is also reported to inhibit interferon-induced antiviral activity[[40](#_ENREF_41)] and is assumed to be closely associated with the pathogenesis of chronic hepatitis C. Several polymorphisms of an IL-1 gene that are thought to affect IL-1β production have been reported[[41](#_ENREF_42)]. -31T SNPs of IL-1β have been shown to enhance IL-1β transcriptional activity[[42](#_ENREF_43)] and several studies reported that -511C/-31T is a risk factor for the development of cancer and liver diseases[[43-45](#_ENREF_44)]. Wang *et al*[[41](#_ENREF_42)] showed that IL-1β-31 polymorphism 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 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 different carcinomas including HCC[[45-52](#_ENREF_46)]. In addition, HBV and HCV reduce E-cadherin expression and promote the 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](#_ENREF_54)]. Several studies demonstrated that CDH1-347 SNPs is significantly associated with HCC risk[[52](#_ENREF_53),[54-57](#_ENREF_55)]. However, the correlation between CDH1-160 SNPs reveals conflicting results. Some studies[[58](#_ENREF_59),[59](#_ENREF_60)] have shown that the CDH1-160 SNPs carriers had an increased risk of prostate and bladder cancer while others showed that it is not associated with the development of prostate, HCC, colorectal or gastric cancer[[60](#_ENREF_61)].

***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](#_ENREF_62)]. PPAR γ has been shown to be associated with type 2 diabetes mellitus (T2DM)[[62](#_ENREF_63)]. PPAR γ contains two isoforms, PPAR γ1 and PPAR γ2 and several variants in the PPAR γ gene have been identified[[63](#_ENREF_64)]. The A allele pf PPAR γ2 is associated with a significantly decreased development of T2DM[[64](#_ENREF_65)]. The relationship between PPAR and HCC is not clear. Although experimental studies have shown that PPAR may have a role in HCC[[65](#_ENREF_66),[66](#_ENREF_67)], implications of these finding is not clear. Koytak *et al*[[66](#_ENREF_67)] have investigated the effect of PPAR α L162V polymorphism on clinical outcome in a patient with HCC caused by hepatitis viruses. They concluded that there is a relationship between PPAR α L162V polymorphism and HBV-induced HCC and is associated with advanced HCC. This polymorphism was shown to enhance PPAR α transcriptional activity and is associated with lipid abnormalities and an increased body mass index[[67-70](#_ENREF_68)].

#### **Tumor necrosis factor alpha-inducible protein 3**

Tumor necrosis factor alpha-inducible protein 3 (TNFAIP3), a cytoplasmic zinc finger protein with ubiquitin-modifying activity, has been shown to inhibit NF-κB activity and TNF-mediated apoptosis[[71-74](#_ENREF_72)]. TNFAIP3 polymorphisms have been linked to inflammatory, autoimmune and malignant diseases. A Recent study has reported that no association between TNFAIP3 rs2230926 polymorphism and susceptibility of chronic HBV infection or the progression of HBV-related diseases[[75](#_ENREF_76)].

***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](#_ENREF_77)]. CTLA-4 polymorphisms are associated with several autoimmune diseases, including thyroid and liver diseases[[77](#_ENREF_78),[78](#_ENREF_79)]. It has been shown that SNPs in CTLA-4 may be associated with HBV progression and viral persistence[[79](#_ENREF_80)]. CTLA-4 SNPs can be used as a marker for predicting treatment outcome in chronic HCV- infected patients[[80-82](#_ENREF_81)].

***Tumor necrosis factor alpha***

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](#_ENREF_84), [84](#_ENREF_85)]. It has been suggested that genetic polymorphisms of TNFα might contribute to the pathogenesis of liver diseases, infectious diseases and inflammatory disorders[[43](#_ENREF_44), [85](#_ENREF_86)]. For example, TNFα SNPs affect TNFα production leading to greater risk of HCC. The polymorphism at the site -1031T/C, -863 C/A, -857 C/T, -376, -308 G/A and -238G/A of the TNFα promoter is associated with the outcome of HBV infection and disease progression[[86-89](#_ENREF_87)].

***Interleukin 10***

Interleukin 10 (IL10) is an important anti-inflammatory cytokine produced in macrophages. Three SNPs in the IL10 gene promoter, at -1082, -819 and – 592, are associated with IL10 production and secretion by the peripheral blood monocytes. It has be shown that IL10 -592 A/C polymorphism was associated with susceptibility to HBV infection[[90](#_ENREF_91)].

***Glutathione S-transferases***

Glutathione S-transferases (GSTs) enzymes play an important role in maintaining cellular defense mechanism against the effects of reactive oxygen and various exogenous toxins and have been shown to be overexpressed in several cancers[[91](#_ENREF_92),[92](#_ENREF_93)]. Deletion polymorphism of GST genes results in diminished enzyme activity leading to the insufficient defense of cells from metabolites and free radical, elevated concentration of endogenous mutagens and high risk of various tumors, including HCC[[93-96](#_ENREF_94)]. 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](#_ENREF_98)]. For example, Meta-analysis studies have been shown that GSTM1, GSTP1, and GSTT1 are associated with an increased HCC risk[[100](#_ENREF_101),[101](#_ENREF_102)] .

***Epidermal growth factor***

Epidermal growth factor (EGF) and its respective EGF receptor (EGFR) signaling are an important regulator of proliferation and pathogenesis of many kinds of human carcinomas[[102](#_ENREF_103),[103](#_ENREF_104)]. Upon ligand binding, the two EGFR domains undergo trans-autophosphorylation at specific tyrosine residues[[104](#_ENREF_105)]. These phosphotyrosines are recognized by Src homology 2 domain containing proteins[[105](#_ENREF_106)] and activates a diverse signaling network that includes the RAS/extracellular signal-regulated kinase pathway[[106](#_ENREF_107)], the phosphatidylinositol 3-kinase pathway[[107](#_ENREF_108)] and the Janus kinase/Signal transducer and activator of transcription pathway[[108](#_ENREF_109)].

Activation of EGF has also been shown to be required for hepatocyte growth during liver regeneration[[109](#_ENREF_110)]. In addition, many viruses like Epstein barr virus and HBV can tweak EGF receptor expression in their favor[[110-112](#_ENREF_111)]. The role of EGF polymorphism has been explored in numerous meta-studies[[113-116](#_ENREF_114)] and shown to be highly associated with susceptibility to hepatocellular carcinoma[[117](#_ENREF_118)]. Prominent among these is the EGF+61A>G transversion (rs4444903) that is shown to regulate the expression of EGF gene[[118](#_ENREF_119), [119](#_ENREF_120)]. This single nucleotide polymorphism (SNP) is found in 5’ UTR of EGF gene and shown in vitro cell lines to enhance the stability of EGF mRNA[[119](#_ENREF_121)]. The G/G allele is associated with higher serum levels of EGF compared with A/A allele patients[[119](#_ENREF_121), [120](#_ENREF_122)]. Numerous follow-up studies have validated the positive association of this G/G and G/A genotype with HCC in diverse genetic populations[[117](#_ENREF_118),[121-123](#_ENREF_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 that is deleted or mutated in 50% of all human tumors[[124](#_ENREF_126)]. P53 is also referred to as the guardian of the genome because it can activate DNA repair pathways[[125](#_ENREF_127)], arrest cell cycle at the G1/S regulation checkpoint[[126](#_ENREF_128)] or initiate apoptosis if the damage can’t be repaired[[127](#_ENREF_129)]. All these important networks converge at the active form of p53 which, is kept in check by MDM2. The addition of ubiquitin subunits at critical lysine residues transfers the active p53 to 26S proteasome for degradation along with MDM2[[1](#_ENREF_130)28, [129](#_ENREF_131)]. In addition, the mere binding of MDM2 can block p53 mediated transactivation functions[[130](#_ENREF_132)]. The activity of MDM2 protein is equally important to regulate this DNA repair-cell cycle-apoptosis nexus in check and variation in expression levels of this protein is shown to have serious consequences for a cell or organism[[131](#_ENREF_133)]. Bond *et al*[[132](#_ENREF_134)] has shown that a particular 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 MDM2 promoter for Sp1 transcription factor[[133](#_ENREF_134)] and thus enhances levels of MDM2 protein in the cell.

The positive association of this SNP 309T>G (rs 2279744) in MDM2 gene with hepatocellular carcinoma is shown by numerous ethnic based studies[[134-136](#_ENREF_135)] as well as meta-analysis studies[[137](#_ENREF_139),[138](#_ENREF_140)]. This epidemiological finding together with functional assays of MDM2 levels points to the relevance of MDM2 SNP 309T>G polymorphism as an important player in the 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](#_ENREF_141)]. The 280 aa mature TIM-3 is selectively expressed on CD4+ Th1 and CD8+Tc1 cells but not on CD4+ Th2cell[[140](#_ENREF_142)]. It interacts with its ligand galectin-9 and drive death Th1 T cells[[141](#_ENREF_143), [142](#_ENREF_144)]. Blocking Tim3 mediated signaling rescues dysfunctional CD4 and CD8+ T cell specific adaptive immune responses[[143](#_ENREF_145)]. Tim3 is upregulated on CD4 and CD8+ T cells in chronic HBV infected individuals[[144](#_ENREF_146)].

Numerous potential SNPs (−1541C/T, −1516G/T, −882C/T, −574G/T and +4259T/G) in TIM3 have been tested for association with chronic HBV and HCC[[145](#_ENREF_147)]. TIM3−1516 G/T (rs10053538) polymorphism has been shown to predispose individuals to cirrhosis and/or HCC[[146](#_ENREF_148),[147](#_ENREF_149)]. One study reported that TIM3 SNPs do not have a functional effect[[148](#_ENREF_150)] whereas others report a significant effect of these TIM3 polymorphic variants[[149](#_ENREF_151)]. 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 repairs of DNA damages like pyrimidine dimers, photo products, chemical adducts and cross-links[[150](#_ENREF_152),[151](#_ENREF_153)]. XPC requires association with HR23B in order to recognize damaged DNA[[152](#_ENREF_154)]. The protein HR23B is a human homolog of Saccharomyces cerevisiae RAD23 and binding of XPC-HR23B to a DNA lesion unwinds the helix[[153](#_ENREF_155)]. The XPA protein can then bind and the whole repair machinery of NER can be recruited onto the damaged base.

Many studies have looked at the association of XPC sequence variants and cancer risk[[154-158](#_ENREF_156)]. Three most common studied SNPs in literature are: PAT–/+[[159](#_ENREF_161)], Lys939Gln (A33512C, rs2228001)[[155](#_ENREF_157)] and Ala499Val (C21151T, rs2228000)[[160](#_ENREF_162)]. 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](#_ENREF_163)] and to lung cancer[[162](#_ENREF_164)], but no studies are yet found on its association with HCC risk. The XPC codon Lys939Gln alleles on the other hand significantly increased HCC risk[[163](#_ENREF_165), [164](#_ENREF_166)]. The Ala499Val variant homozygous genotype is a risk factor for bladder cancer[[158](#_ENREF_160)] but has not been studied for HCC.

**Interleukin 16**

IL16 is a pro-inflammatory cytokine and was initially called lymphocyte chemoattractant factor[[165](#_ENREF_167)]. It can activate a diverse set of immune cells like CD4+ T cells, monocytes, macrophages, eosinophils and dendritic cells[[166-169](#_ENREF_168)]. In addition to inducing activation and chemotaxis of immune cells, IL-16 can upregulate IL-2 receptor[[170](#_ENREF_172)] and HLA-DR4 expression[[171](#_ENREF_173)]. Upon CD4 receptor binding, IL16 signaling increase intracellular calcium and inositol triphosphate and translocation of protein kinase C from cytosol to plasma membrane[[172](#_ENREF_174),[173](#_ENREF_175)]. Moreover, IL16 can stimulate the production of further pro-inflammatory mediators like L1β*,* IL6*,* IL15 and TNF-α, *e.g.*, by monocytes[[174](#_ENREF_176)] thereby initiating and/or sustaining the inflammatory response.

Genetic polymorphism in IL16 has recently been reported and shown to affect susceptibility to a range of cancers like colorectal, gastric, prostate cancer and nasopharyngeal carcinoma[[175-178](#_ENREF_177)]. Data about hepatocellular carcinoma and IL16 polymorphism is scarce in literature and only two studies could be found that have tested the three SNPs (rs11556218 T>G, rs4778889 T>C, and rs4072111 C>T)[[179](#_ENREF_181)]. In the study by Li et al., no association with HCC was found for all three SNPs (rs11556218T/G P = 0.511, rs4072111C/T P = 0.308 rs4778889T/C P = 0.070)[[180](#_ENREF_182)]. The other study by Sara et al. did not include HCC patients to test the SNPs. The study, however, had chronic hepatitis b patients that showed a positive association of rs11556218 T>G, the negative association of rs4778889 T>C and positive association of rs4072111 C>T polymorphisms with patients’ susceptibility to chronic hepatitis B infection[[179](#_ENREF_181)].

# *Genome-wide association studies*

# Numerous Genome-wide association studies (GWAS) have been done with chronic HBV and HCC patients to identify novel susceptible loci contributing to disease[6, [181-186](#_ENREF_183)]. Among these, strong association has been 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, TCF19, HLA-C, UBE2L3, LTL, 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. Transcription factor 19 (TCF19) as the name suggests is an important transcription factor during cell cycle G1/S transition[[187](#_ENREF_190)]. Ubiquitin-conjugating enzyme E2 (UBE2L3) is a typical E2 ligase that accepts ubiquitin from E1 complex and transfers it to targeted proteins[[188](#_ENREF_191)]. Leukocyte telomere length (LTL) has been associated with risk to developing many malignancies[[189](#_ENREF_192)] and LTL related SNPs are potential targets for such GWAS studies. Feredoxin1 (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](#_ENREF_193)]. In addition, it is involved in steroid, vitamin D, and bile acid metabolism[[191](#_ENREF_194)].

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

# *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 like cell growth[[192](#_ENREF_195)], differentiation[[193](#_ENREF_196)], extracellular matrix synthesis[[194](#_ENREF_197)], hematopoiesis[[195](#_ENREF_198)], angiogenesis[[196](#_ENREF_199)], and cellular apoptosis[[197](#_ENREF_200)]. TGF-β1 is one of TGF-β isoforms and is upregulated in HCC tissues correlating with carcinogenesis and prognosis of HCC[[198](#_ENREF_201),[199](#_ENREF_202)]. TGF-β1 also suppresses HBV replication by reducing hepatocyte nuclear factor-4-alpha[[200](#_ENREF_203)]. Thus the relevance of this cytokine and its single nucleotide polymorphism among HBV-associated HCC are of paramount importance.

# Seven polymorphisms have been described in literature for TGF-β1 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](#_ENREF_204)]. Numerous studies have looked at the association of these SNPs in HCC[[202-205](#_ENREF_205)]. There are contrasting reports with some studies reporting a positive association of −509C>T (rs1800469) with HCC risk[[206](#_ENREF_209)] whereas another report weak or no association[[204](#_ENREF_207)]. The Arg25Pro change at +915G/C (rs1800471) is also not correlated with any HCC risk[[207](#_ENREF_210)]. The mutation in codon 10 (Leu>Pro) is very strongly correlated with HCC according to one study[[208](#_ENREF_211)]. There is still limited information about other polymorphisms of TGF-β1 and further studies are required to make a conclusive mark for HCC. Table 1 shows the list of polymorphic genes and their contribution to HCC.

**DISCUSSION**

In this article, we discuss the association of the HBV genotype and 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. The whole transcriptome analyses of 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 development of liver cancer and 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 mutation as HBV infection plays an important role in the development of host genetic mutations, due to the impairment in the DNA repair process. To elucidate the ole of HBV-related genetic variations, researchers used traditional biological methods to identify genetic mutations. Most recently, advanced techniques such as next generation sequencing (NGS) 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-1alpha and 1beta, E-cadherin (CDH1), PPARγ, TNFAIP3, CTLA-4, TNFα, IL10, GSTM1/GSTT1 Deletion Oxidative stress, EGF, MDM2, Tim3), XPC, *Interleukin 16,*TGFβ, 1p36.22, 11q22.3, 6p21, 8p12 and 22q11.21 candidate SNPs in GWAS. The association of each locus with the outcome of the 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 that are involved in the development of HCC. Further studies are needed to evaluate and understanding the role of host-HBV interaction in HBV-related HCC for generating effective diagnosis and therapeutic treatments.

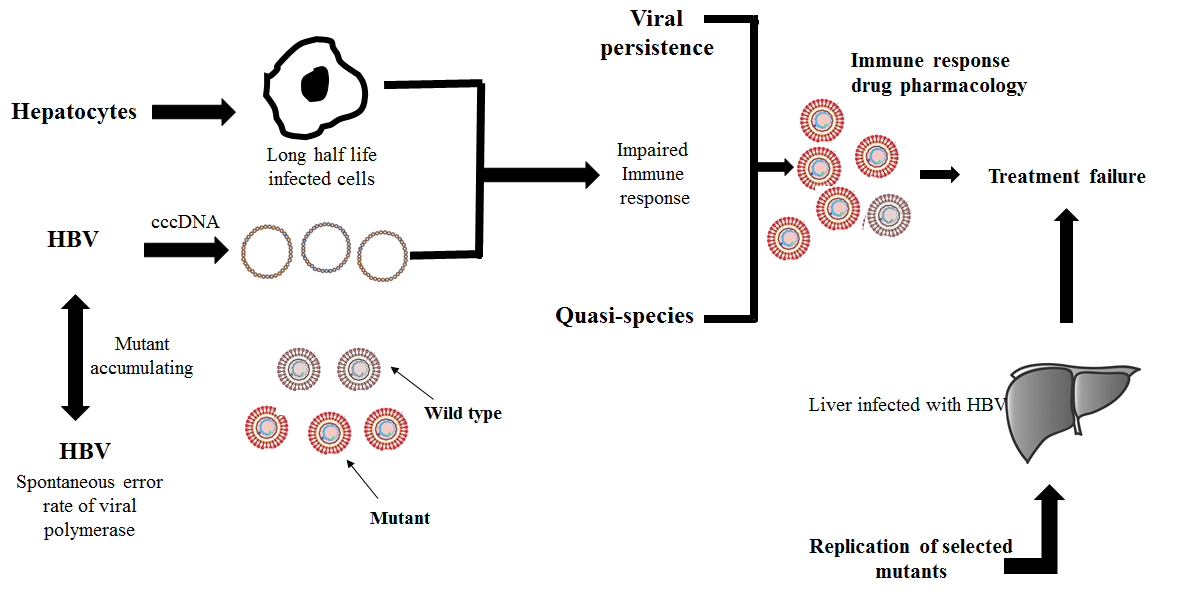
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# Table 1 List of polymorphic genes and their contribution to hepatocellular carcinoma

|  |  |  |  |
| --- | --- | --- | --- |
| Polymorphism | Genotype | Significance | Reference |
| COX-2 | -1195G>A,-765G>C+8473T>C | *P* < 0.00[[209](#_ENREF_212)]*P* < 0.05[[31](#_ENREF_32)] 0.41[[209](#_ENREF_212)]*P* = 0.83[[209](#_ENREF_212)] | He *et al*, 2012[[31](#_ENREF_32)], Chen *et al*, 2015 [[209](#_ENREF_212)] |
| IL-1a, b | 511C>T-31C>T | *P* = 0.02[[41](#_ENREF_42)]*P* = 0.02[[41](#_ENREF_42)] | Wang *et al*, 2003[[41](#_ENREF_42)] |
| CDH1 | -347G>A | *P* = 0.171[[210](#_ENREF_213)] <0.05[[60](#_ENREF_61)] | Li *et al*, 2007[[210](#_ENREF_213)] Chien *et al*, 2011[[60](#_ENREF_61)] |
| PPARγ | L162V | *P* = 0.071[[66](#_ENREF_67)] | Koytak *et al*, 2008[[66](#_ENREF_67)] |
| TNFAIP3 | F127C | *P* = 0.15[[211](#_ENREF_214)] | Zhang *et al*, 2015[[211](#_ENREF_214)] |
| TNFα | -1031T/C,-863 C/A,-857 C/T,-308 G/A-238G/A | *P* = 0.85[[86](#_ENREF_87)]*P* = 0.006[[86](#_ENREF_87)]*P* = 0.09[[86](#_ENREF_87)]*P* = 0.046[[86](#_ENREF_87)]*P* = 0.003[[86](#_ENREF_87)] | Wei *et al*, 2011[[86](#_ENREF_87)] |
| GST | GSTM1+GSTT1 | *P* = 0.001[[212](#_ENREF_215)] | Liu *et al*, 2013 [[212](#_ENREF_215)] |
| EGF | +61A>G | *P* < 0.001[[117](#_ENREF_118)] | Jiang *et al*, 2015 [[117](#_ENREF_118)] |
| MDM2 | 309G>T | *P* = 0.001[[133](#_ENREF_135)] | Ezzikouri *et al*, 2009 [[133](#_ENREF_135)] |
| TIM3 | −1516 G>T | *P* = 0.001[[146](#_ENREF_148)] | Li *et al*, 2013 [[146](#_ENREF_148)] |
| XPC | K939Q | *P* = 0.001[[163](#_ENREF_165)] | Long *et al*, 2010 [[163](#_ENREF_165)] |
| 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 × 10−18 *P*= 4.3 × 10−8  *P*= 0.0266  *P* = 0.0067  *P* = 1.71 × 10−12 | Al-Qahtani *et al*, 2013 [[181](#_ENREF_183)] |
| TGFβ1 | −509C>T  R25P  L10P | *P* = 0.01[[206](#_ENREF_209)] and 0.318[[207](#_ENREF_210)]  *P* = 0.472[[207](#_ENREF_210)]  *P* < 0.02[[208](#_ENREF_211)] | Qi *et al*, 2009 [[206](#_ENREF_209)], Hosseini Razavi *et al*, 2014 [[207](#_ENREF_210)] and Kim *et al*, 2003[[208](#_ENREF_211)] |



**Figure 1 Mechanisms of selection and emergence of hepatitis B virus drug-resistant mutants.**