

A REVIEW ON GENETIC POLYMORPHISM IN HEPATOCELLULAR CARCINOMA

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ABSTRACT: Hepatocellular carcinoma (or HCC) is also referred to as Primary liver cancer. It is states as fifth most common cancer in men and the seventh in women globally, and it is the third leading cause of death. It has been proved that Chronic hepatitis virus infection, such as hepatitis B virus (HBV) and hepatitis C virus (HCV), Alcohol, Aflatoxin, male gender, and liver cirrhosis have been shown to be the major risk factors for HCC. The risk of HCC is also influenced by genetic history. Genetic association studies are essential for epidemiological investigations since they can classify candidate genome regions linked to specific diseases. Genetic variation is commonly represented by single nucleotide polymorphisms (SNPs). The existence of single nucleotide polymorphisms (SNPs) has been linked to the development of HCC in numerous studies. Liver carcinogenesis is a complex and multi- factorial process, in which both environmental and genetic features interfere and contribute to malignant transformation. However, large genetic epidemiology studies in the field of cancer diseases have suggested the limited ability of polymorphic traits, alone, to refine individual prognosis. Several decades of intense research have generated large amounts of data on the genetic susceptibility of HCC, yet the empirical findings have been mixed and inconclusive regarding HCC susceptibility related to SNPs. More studies with large sample sizes, detailed data regarding established risk factors for HCC.

Index Terms : Environmental risk factors, Genetic polymorphism, Genetic variants, Hepatocellular carcinoma, SNPs.

I. INTRODUCTION

Hepatocellular carcinoma (or HCC) is also referred to as Primary liver cancer. It is states as fifth most common cancer in men and the seventh in women globally. Hepatocellular carcinoma is the world's fifth most common cancer and third leading cause of cancer death. The most common form of primary liver cancer, hepatocellular carcinoma (HCC), has been the world's most insecure public-health threat, which leads to a cancer-related death with limited early detection and therapeutic option. Liver carcinogenesis is a complex, multi-factorial process that interferes and contributes to malignant transformations with environmental and genetic features. Genetic association studies are essential for epidemiological investigations since they can classify candidate genome regions linked to specific diseases. The existence of single nucleotide polymorphisms (SNPs) has been linked to the development of HCC in numerous studies. Single nucleotide polymorphisms (SNPs) have been inconsistently associated with hepatocellular carcinoma (HCC) risk. This meta-analysis aimed to synthesize relevant data on SNPs associated with HCC. It has been proved that Chronic hepatitis virus infection, such as hepatitis B virus (HBV) and hepatitis C virus (HCV), Alcohol, Aflatoxin, male gender, and liver cirrhosis have been shown to be the major risk factors for HCC. The risk of HCC is also influenced by genetic history. The epidemiology of liver cancer is made complex by the difficulty to separate the large number of secondary tumors from primary liver cancers [1]. In most populations, hepatocellular carcinoma (HCC) is the most commonly affected type of primary liver neoplasm, with other forms including adult cholangiocarcinoma originating from the intrahepatic biliary ducts, angiosarcoma originating from the intrahepatic blood vessels, and childhood hepatoblastoma [2]-[4].

II. ENVIRONMENTAL RISK FACTORS

2.1 Hepatitis Infection

Chronic HBV and HCV infections are the most significant risk factors for HCC worldwide [2],[4],[5]. There is a strong geographic correlation between the prevalence of chronic HBV infection and the incidence of HCC. HBV infection is thought to be responsible for 54 percent of all liver cancers worldwide [8]. Several epidemiological studies conducted in more than 25 countries over the last few decades have provided conclusive evidence for a causal role of chronic HBV infection in HCC [5]. In most epidemiological studies, the estimated risk of developing HCC among HCV-infected subjects compared to uninfected subjects ranges between 20 and 30 [5]. There is evidence that heavy alcohol consumption and HCV infection have a strong interaction on HCC risk [6],[9],[10]. An interaction between HBV and HCV infections in the development of HCC has also been revealed, with combined infection leading to an RR of HCC greater than 50 [7],[11]. The mechanisms by which HCV causes liver cancer are unknown. HCV, as a non-integrating virus, is unlikely to play a direct role in the initiation of HCC. Because the majority of HCV-associated HCC occurs in the presence of cirrhosis [12], HCV infection may cause cancer via an indirect mechanism of immune-mediated damage and subsequent liver cell turnover [5]. Thus, the development of HCV- related malignancy requires a long period of hepatocellular damage progressing from chronic hepatitis to cirrhosis to HCC. Heavy alcohol consumption raises the risk of HCC in people with HCV-related cirrhosis.

2.2 Alcohol Drinking

Heavy alcohol consumption is linked to an increased risk of primary liver cancer [13],[14], though not as strongly as cancers of the upper aero-digestive tract [13]. Many case-control studies provide the majority of the evidence linking heavy alcohol consumption to an increased risk of HCC [12]. The largest cohorts that provide alcohol and HCC results were conducted in Asian countries. A recent meta-analysis of 19 prospective studies with a total of 4445 incident cases and 5550 deaths from liver cancer found pooled RRs of 1.16 (95% CI) between alcohol drinkers of 3 drinks per day and 1.22 (95%CI) between drinkers of 6 drinks per day, compared to non-drinkers, and suggested relationship with increasing alcohol intake in drinkers [15]. An evaluation on the risk of cancer at various locations related to light drinking alcohol (up to a drink daily), based on seven cohort studies and 13 case control studies [16], provided a pooled RR of 1.03 (95% CI) for liver cancer. Furthermore, summary RR-estimations were 1,12 (95% CI) for cohort and 2,79 (95% CI) for case control reports for >50 grams of alcohol each day (approximately >4 drinks per day) derived. There was not an increased risk of liver cancer in lights (drinkers<12.5 g/day, about <1 drink/day) and in moderates (drinkers <50 grams/day).

2.3 Aflatoxin

Aflatoxin is a mycotoxin that is produced by *Aspergillus* fungi and mainly produced in foodstuffs like corn and peanuts when stored in warm humidity. Many people in low-income countries are exposed to a large proportion of aflatoxin in a chronic way [17]. Food contamination with aflatoxin is a high-risk factor for the development of HCC in Sub-Saharan Africa and East Asia. There are four main aflatoxins (B1, B2, G1 and G2), the most potent hepato-carcinogen was aflatoxin B1 (AFB1) in animal studies. AFB1 is metabolized to an ABB1-exo-8,9-epoxide, an active intermediate which may bind to DNA and cause mutation and damage to the tumor suppressor gene p53. This mutation has been seen in 30% to 60% of HCC tumors in people living in aflatoxin endemic zones [18], compared to cases in which the exposure to aflatoxin is low in the United States or Europe. Evidence from epidemiological studies suggests that the exposure to aflatoxins interacts with the increase in the risk of HCC and chronic HBV infection. According to a meta-analysis, in areas where aflatoxin contamination and chronic HBV infection are common, these two risk factors interact exponentially in HCC risk, with subjects exposed to both risk factors having a very high risk of HCC [19].

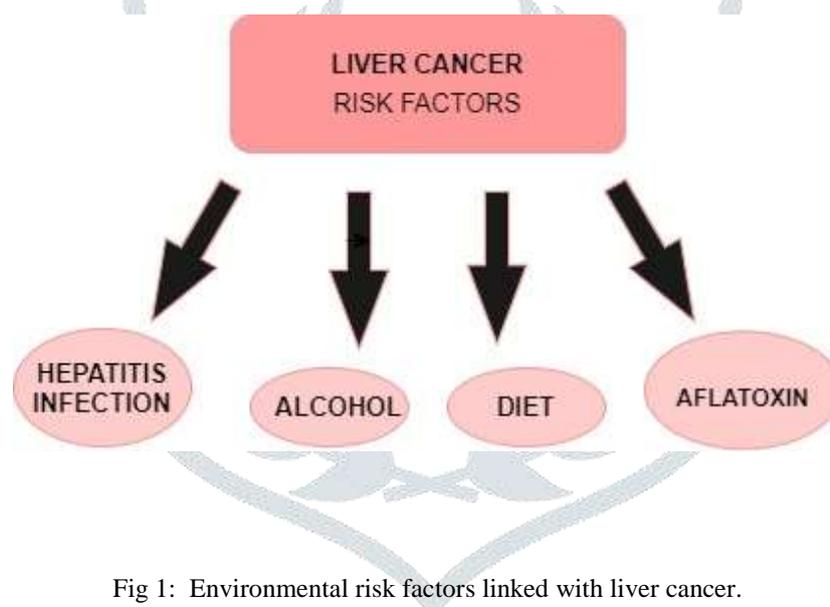


Fig 1: Environmental risk factors linked with liver cancer.

III.GENETIC ASSOCIATION OF GENES INVOLVED IN HCC

Genetic variation is commonly represented by single nucleotide polymorphisms (SNPs), which are inherited single base changes in exon or intron regions. While the majority of SNPs are functionally neutral, some have been discovered to modify gene expression and function or to be in linkage disequilibrium (LD) with causal loci linked to cancer risk and/or prognosis. Many gene SNPs derived from distinct pathways, such as tumor suppressors, inflammation, hepatic metabolism, DNA repair, and microRNA-mediated silencing, have been identified to affect individual susceptibility to HCC.

The aim of this analysis was to look at all of the significant SNPs linked to HCC susceptibility. Since there is a lack of evidence to suggest which genetic model is most suitable for identifying SNP-HCC associations, different approaches to selecting the most appropriate genetic models of inheritance and measuring the reliability of the associations have been used instead of assuming the underlying genetic model. In order to summarize and clarify the gene-HCC association results, we collected SNPs on which the study number was more than three and to do the meta-analyses. As we aimed to provide some clear information on this field, we only reported candidate SNPs that showed overall significant association to HCC.

3.1 Glutathione S-Transferases in HCC

Glutathione S-transferases (GSTs) is a superfamily gene of phase II metabolic enzymes involved which purify oxidative agents, primarily tobacco smoke, stress products and carcinogenic substances such as benzopyrene and other polycyclic aromatic hydrocarbons. GSTs are also involved in the induction of other enzymes and proteins needed for cellular functions including DNA repair [20]. GSTM1 and GSTT1 are the most thoroughly researched genes in the GST gene superfamily. Polymorphic deletion variants in the GSTM1 and GSTT1 genes result in either a functional enzyme (non-deletion alleles or heterozygous deletion, GSTM1-1 and GSTT1-1) or a total absence of the enzyme (homozygous deletion alleles, GSTM1-null and GSTT1-null) [21]. As a result, these enzymes may be linked to the risk of HCC. Significant efforts have been made in recent years to investigate the links between GSTT1 and GSTM1 null polymorphisms and HCC risk in various populations. One such meta-analysis included 34 studies with a total of 4,463 cases and 6,857 controls. In a combined analysis, the null genotypes of GSTM1 (OR = 1.29, 95%; P = 0.01) and GSTT1 (OR = 1.43, 95 %; P <10-5) were found to have significantly increased HCC risks [22].

3.2 DNA Repair Genes and HCC

Genetic polymorphisms in DNA repair genes may significantly affect variation in DNA repair capacity and may play a major role in carcinogenesis. Several DNA repair systems are involved in nucleotide excision repair (NER). The NER has been linked to the development of several cancers [23]-[26]. Two major repair genes involved in NER are XRCC1 and XPD. Variations in the repair efficiency of DNA damage are associated with mutations and polymorphisms in DNA repair genes, and this repair deficit may increase the risk of cancer [27]. The two most common XRCC1 polymorphisms are Arg194Trp and Arg399Gln, and the two most common XPD polymorphisms are Asp312Asn and Lys751Gln. The genotype distributions of XRCC1 Arg194Trp, XRCC1 Arg399Gln, XPD Lys751Gln, and XPD Asp312Asn in cases and controls were significantly different. When compared to the wide-type genotype, XRCC1 194Trp/Trp was strongly associated with an increased risk of HCC cancer, with an adjusted OR (95 % CI) of 2.26. Individuals with the XRCC1 399Gln/Gln mutation had an increased risk of HCC. The association between the SNPs and the risk of HCC was investigated using conditional logistical regression analysis, with frequency matched by age and sex. (OR=1.74, 95%CI). The XPD 751Gln/Gln and Gln allele genotypes were linked to a significantly increased risk of HCC (OR=3.51 and 1.42, respectively). Polymorphisms in XRCC1 Arg194Trp, XRCC1 Arg399Gln, and XPD Lys751Gln were linked to HCC risk in the Chinese population, according to the results of this study. These data suggest that XRCC1 and XPD polymorphisms may have functional significance in HCC [28].

On the other hand, Aflatoxin B1 (AFB1) is a significant environmental carcinogen that can cause DNA damage and play a role in the development of hepatocellular carcinoma (HCC). A lack of DNA repair capacity caused by polymorphisms in DNA repair genes may play a key role in the development of HCC tumors. However, the role of DNA repair gene polymorphisms and AFB1 in the risk of hepatocellular carcinoma is unknown. A study investigated, whether six polymorphisms (rs25487, rs861539, rs7003908, rs28383151, rs13181, and rs2228001) in DNA repair genes (XPC, XRCC4, XRCC1, XPD, XRCC7, and XRCC3) interacted with AFB1, and the gene-environmental interactive role in HCC risk. HCC patients had higher AFB1 exposure compared to the control group [odds ratio (OR) = 2.08 for moderate AFB1 exposure level and OR = 6.52 for high AFB1 exposure level. A higher risk of HCC was also observed in those with DNA repair gene mutations (risk values were from 1.57 to 5.86). These results indicated that AFB1 may interact with DNA repair risk genotypes in the risk of HCC [29].

3.4 MicroRNA Encoding Genes in HCC

MicroRNAs (miRNAs) are a type of small non-coding RNA that acts as a post-transcriptional regulator of gene expression and has been linked to the initiation and progression of cancer [30]. MicroRNAs (miRNAs), a class of endogenous small non-coding RNAs, regulate a wide range of biological functions, including cell proliferation, differentiation, apoptosis, genome rearrangements, and transcriptional regulation [34],[35]. A study hypothesis showed that genetic polymorphisms in miRNAs could be functional and were involved in the development of HCC [34],[35]. Most studies support the idea that the functional polymorphisms in miRNAs can assist an individual to develops chronic HBV infection-related HCC [31],[32]. The current meta-analysis focused on three novel polymorphisms in miRNA-encoding genes: miR-146a G > C (rs2910164), miR-196a-2 C > T (rs11614913), and miR-499 T > C. (rs3746444). To confirm that the observed association was an independent risk factor for HCC rather than a predisposition to HBV infection, allele/genotype distributions were compared between the case (HBV-related HCC patients) and control groups (healthy controls without HBV infection). A quantitative summary on the study of the links between the polymorphisms of the miRNA gene and the risks associated with HCC or HBV. The study acknowledged of this meta-analysis show that the miR-146a and miR-196a-2 polymorphisms were related with HCC risks, and that these associations varied across ethnic groups, genders, and HBV status [35].

3.5 Aldehyde Dehydrogenase-alcohol metabolism enzyme

The two classes of alcohol metabolism enzymes, Alcohol dehydrogenase (ADH), which oxidizes ethanol to acetaldehyde, and aldehyde dehydrogenase (ALDH), which oxidizes acetaldehyde to acetate, both have functional polymorphisms that may alter the rate of synthesis of the toxic metabolite acetaldehyde or decrease its further oxidation [36]. ALDH exists in multiple forms in the liver and other tissues of mammals, including humans, with a diverse range of aldehydes as substrates [37],[38]. Although the cytosolic ALDH1A1, mitochondrial ALDH1B1, and ALDH2 are known to participate in acetaldehyde metabolism, only ALDH2 has a very high affinity (Km <5 µM) for acetaldehyde, making it the most important isozyme in vivo for the oxidation of acetaldehyde produced from ethanol [39],[40]. ALDH2 gene was investigated in several studies and the link between the genotype and development of alcoholism and cancer growth is established alcohol metabolism and single nucleotide polymorphisms (SNPs);[41], [42],[43]. In the study, a human liver tissue was used in different cell organelles and the overall metabolism of different

aldehydes was investigated. A study has found that the ALDH2*2 allele is not affected equally by any type of aldehyde, and metabolism of different aldehydes was investigated. A study has found that the ALDH2*2 allele is not affected equally by any type of aldehyde, and metabolism in the areas of ageing, sex, smoking, alcohol and mild liver abnormality.

Table 1: Gene polymorphism that influence progression of liver fibrosis

GENE	PROTEIN FUNCTION	GENOTYPE	LIVER DISEASE	REFERENCE
IL-10	Anti-inflammatory	-627 C→A	ALD	44
TGF-β1	Profibrogenic	Codon25 pro→ARG	HCV	45
IL-1β	Pro-inflammatory	-511 C→T, -3953 T→C	ALD/PBC	46,47
IL-1 receptor	Pro-inflammatory	VNTR Intron2	ALD/PBC	47
ADH	Ethanol metabolism	ADH2 c1 c2 c3 alleles	ALD	48,49,50
		ADH3 c1 c2 c3 alleles		
ALDH	Ethanol metabolism	ALDH2 c2/c2 alleles	ALD	50,51
CYP2E1	Ethanol metabolism	c1/c1,c2/c2 alleles	ALD	52,49,53,51
	ROS generation			
CD14	Receptor LPS	-159 C→T	ALD	55

IV.CONCLUSION

Liver carcinogenesis is a complex and multi-factorial process, in which both environmental and genetic features interfere and contribute to malignant transformation. However, large genetic epidemiology studies in the field of cancer diseases have suggested the limited ability of polymorphic traits, alone, to refine individual prognosis. Several decades of intense research have generated large amounts of data on the genetic susceptibility of HCC, yet the empirical findings have been mixed and inconclusive regarding HCC susceptibility related to SNPs. More studies with large sample sizes, detailed data regarding established risk factors for HCC, and high quality are warranted to verify the findings of this study and further evaluate the effect of gene-gene and gene-environment interactions in determining HCC risk.

ACKNOWLEDGMENT

The authors acknowledge the help provided by Department of Life Sciences, Institute of Applied Medicines and Research, Ghaziabad, India.

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