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Risk of HCC: Genetic heterogeneity and complex genetics

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Hepatocellular carcinoma (HCC) is a common form of cancer that arises from hepatocytes and whose risk may be affected by several known environmental factors, including hepatitis viruses, alcohol, cigarette smoking, and others. Rare monogenic syndromes, such as alpha1-antitrypsin deficiency, glycogen storage disease type I, hemochromatosis, acute intermittent and cutanea tarda porphyria, as well as hereditary tyrosinemia type I are associated with a high risk of HCC. Several common conditions or diseases inherited as polygenic traits e.g. autoimmune hepatitis, type 2 diabetes, a family history of HCC, hypothyroidism, and non-alcoholic steatohepatitis also show an increased risk of HCC compared to the general population. Overall, the genetic susceptibility to HCC is characterized by a genetic heterogeneity; a high individual risk of HCC may thus be caused by several unlinked single gene defects, whose carriers are rare in the general population, or by more common conditions inherited by complex genetics.

Introduction

Hepatocellular carcinoma (HCC) ranks among the five most common cancers worldwide [1,2]. This tumour, which arises from hepatocytes, is often associated with liver cirrhosis resulting from chronic liver diseases. Among the environmental risk factors, the prevalence of chronic hepatitis B (HBV) and C (HCV) virus infections is directly linked to the incidence of HCC. Countries in Southeast Asia and sub-Saharan Africa, where HBV infection is endemic, have the highest rates of HCC, but HBV-related liver cancer cases also occur in western countries [1,2]. Chronic carriers of HBV have up to a 30-fold increased risk of HCC [3–5]. In western countries, the main risk factor of HCC is represented by HCV infection, whose prevalence has increased over the past decades, accompanied by a higher incidence and mortality from HCC [5,6]. A large number of cohort and case–control studies have shown that alcohol consumption causes liver cirrhosis and is an independent risk factor for primary liver cancer [7–9]. Epidemiological studies reported elevated HCC risks associated with exposure to aflatoxins after adjustment for HBV exposure [10]. Cigarette smoking has been causally associated with the risk of HCC [8,11]. A multiplicative effect of heavy smoking and heavy drinking in HCC development has been reported [8].

In addition to environmental risk factors, individual genetic predisposition may play a role in the risk of HCC as suggested by the fact that in a relevant percentage of HCC cases, i.e., about 20% of cases diagnosed in the United States, no known predisposing risk factors, including alcohol use or viral hepatitis, can be identified [6]. The role of genetic factors in the risk of HCC is supported by strong evidence from rodent models, which have enabled the identification of the number and chromosomal location of loci affecting genetic susceptibility to chemically induced hepatocarcinogenesis in both mice and rats (reviewed in [12,13]).

Here, we review current evidence from epidemiological/genetic studies in human populations, which argues for the important role of monogenic and polygenic factors in determining the risk of HCC development. Table 1, which includes estimated risk of HCC according to particular genetic factors, summarizes this evidence.

Monogenic risk factors for HCC

Alpha1-antitrypsin deficiency

Alpha1-antitrypsin (AAT) deficiency is an autosomal recessive disease that results from several mutations in the SERPINA1 (also known as PI) gene located on chromosome 14q32.1 (Table 1). This gene encodes a serine protease inhibitor, which is synthesized at high levels in the liver and whose biochemical function is the inhibition of neutrophil elastase. The common allele is designated PIM, and the most common deficiency variants are designated PIS (Glu264Val, frequency 0.02–0.04 in Caucasians, expressing 50–60% of AAT) and PIZ (Glu342Lys, frequency 0.01–0.02 in Caucasians, expressing 10–20% of AAT). Because both parental alleles are expressed, inheritance of a normal allele protects against the effect of the second "at-risk" allele, and severe AAT deficiency develops only when the individual bears two at-risk alleles [14].

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Abbreviations: HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; AAT, alpha1-antitrypsin; OR, odds ratio; AIP, acute intermittent hepatic porphyria; PCT, porphyria cutanea tarda; AIH, autoimmune hepatitis; HLA, human leukocyte antigen; IGF, insulin-like growth factor; GWAS, genome-wide association studies; HBsAg, HBV surface antigen; NASH, non-alcoholic steatohepatitis; AFB1, aflatoxin B1; GST, glutathione S-transferase; Hcs, hepatocarcinogenesis susceptibility; Hcr, hepatocarcinogenesis resistance.

Table 1. Genetic risk factors and genetic syndromes associated with the development of hepatocellular carcinoma.

Factor/syndrome	Gene symbol	Chromosome	Position[a]	Mode of inheritance[b]	Relative risk[c]	Reference
Alpha1-antitrypsin deficiency	SERPINA1	14	93.9	AR	5.0	[15]
Autoimmune hepatitis	UN[d]	Multiple		Polygenic	>20	[39]
Diabetes, type 2	UN[d]	Multiple		Polygenic	2.5	[41]
Family history	UN[d]	Multiple		Polygenic	4.7	[47]
PAPSS1 locus	UN[d]	4	108.8	AD	3.4	[50]
Glycogen storage disease						
Type Ia	G6PC	17	38.3	AR	NA[e]	
Type Ib	SLC37A4	11	118.4	AR	NA[e]	
Hemochromatosis	HFE	6	26.2	AR	20	[24,25]
Hypothyroidism	UN[d]	Multiple		Polygenic	2.9	[52]
Non-alcoholic steato hepatitis (NASH)	UN[d]	Multiple		Polygenic	NA[e]	
Porphyria						
Acute intermittent	HMBS	11	118.5	AD	>30	[28,29]
Cutanea tarda	UROD	1	45.3	AD	5.3	[32]
Tyrosinemia I	FAH	15	78.2	AR	NA[e]	

[a] In megabases; Ensembl release 54.
[b] For syndromes, AR, autosomal recessive; AD, autosomal dominant or co-dominant.
[c] Fold change in odds ratios or standardized mortality ratios with respect to the general population.
[d] UN, unknown.
[e] Not available.

Patients with AAT deficiency can develop pulmonary emphysema and liver disease. The mechanism of disease is probably related to the altered protease/anti-protease balance. Indeed, liver injury leading to liver cirrhosis in individuals with the PIZZ genotype presumably results from toxic effects of the abnormal SERPINA1 molecule accumulating within the endoplasmic reticulum of liver cells. However, only 12–15% of individuals with this genotype develop liver disease, suggesting a role for modulating factors (genetic or environmental). AAT deficiency is associated with an increased risk of HCC, especially in males, with an odds ratio (OR) of 5.0 observed in Swedish patients with AAT deficiency as compared with the general population [15] (Table 1).

Glycogen storage disease type I

Glycogen storage disease type I (Von Gierke's disease) is caused by the impairment of glucose-6-phosphatase (G6Pase) activity, with consequent excess glycogen storage in the liver. Two subtypes of this disease are recognized: type Ia, in which there is a complete absence of G6Pase; and type Ib, in which there is a deficiency of the glucose-6-phosphate translocase (G6PT) at the endoplasmic reticulum membrane [16] (Table 1). The clinical features are generally similar in both subtypes: hepatomegaly, fasting hypoglycemia, lactic acidosis, hyperlipidemia, hyperuricemia, and growth retardation [16]. Mutations in G6Pase and G6PT account for ~80 and ~20% of glycogen storage disease type I cases, respectively, and the disease is inherited as an autosomal recessive trait [16]. Liver functions are usually normal or show only minor deviations, and cirrhosis does not develop. By their second or third decade of life, patients with type I glycogen storage disease develop hepatocellular adenomas with a prevalence increasing with age and ranging from 16% to 75% (total of 129 cases with adenomas out of 487 patients in seven literature series; mean prevalence 26%) [17,18]. A number of glycogen storage disease type I patients develop HCC [19,20] (Table 1).

Hemochromatosis

Hemochromatosis is a common inherited disorder of iron metabolism, characterized by excessive gastrointestinal iron absorption and by consequent increased iron storage in all organs except for the brain and nervous tissue. Fibrous tissue reaction develops at the site of iron deposition; limited liver dysfunction is present in early stages but may develop into hepatic cirrhosis followed by HCC. The hemochromatosis gene (HFE) is located on chromosome 6p21.3 and hemochromatosis is inherited as an autosomal recessive trait (Table 1). About 90% of individuals with hemochromatosis are homozygous for a founder mutation that leads to a single-base change resulting in the substitution of tyrosine for cysteine at position 282 (C282Y) of the HFE protein [21,22]. While the C282Y mutation in the HFE gene is quite prevalent, with 0.5% of Caucasian adults revealing homozygosity for the mutation in a general screening, approximately 30% of homozygous individuals do not present the clinical features of hemochromatosis [23]. The risk of HCC in hemochromatosis patients is approximately 20-fold higher than in the general population [24,25].

Porphyrias

Hepatic porphyrias are a group of inherited diseases resulting from defects in the heme biosynthesis pathway. Acute intermittent hepatic porphyria (AIP), the most common form of porphyria, is clinically characterized by occasional acute attacks of abdominal pain, gastrointestinal dysfunction, and neuropsychiatric symptoms. Cirrhosis is not frequent in patients with AIP, but morphologic abnormalities of hepatocytes at liver biopsy and altered liver biochemical function have been reported [26]. The disease is inherited as an autosomal dominant trait and is related to a deficiency in enzymatic activity of hydroxymethylbilane synthase (HMBS) (also known as porphobilinogen deaminase) resulting from several coding or non-coding mutations in the HMBS gene, which maps on chromosome 11q23.3 [26,27]. Compared with the total population, the risk of HCC is increased >30-fold in AIP patients [28,29] (Table 1).

Familial porphyria cutanea tarda (PCT) is transmitted as an autosomal dominant trait. The disease is due to several missense or insertion/deletion types of mutations in the uroporphyrinogen decarboxylase gene (UROD), causing deficiency of the relevant enzyme activity [30,31]. UROD maps on chromosome 1p34. PCT

is associated with subacute hepatitis and liver cirrhosis [32]. Several early studies that preceded the discovery of HCV indicated a 100- to 200-fold relative risk of HCC in PCT patients [33,34], whereas a more recent study reported lower risk estimates, i.e., 5.3 [32] (Table 1). A meta-analysis of the prevalence of HCV infection in PCT patients concluded that HCV infection is the most common triggering factor for PCT, since HCV infection is found in approximately 50% of PCT patients, i.e. a much higher rate than that reported in the general population [35]. This suggests a pathogenic role for HCV in inducing PCT or increasing the susceptibility of patients to other triggering factors such as iron overload or alcohol abuse.

Tyrosinemia type I

Hereditary tyrosinemia type I is an autosomal recessive disorder caused by a deficiency of the last enzyme in the catabolic pathway of tyrosine, fumarylacetoacetate hydrolase (FAH), located on chromosome 15q23–q25 [36] (Table 1). The disease is a devastating disorder of childhood that causes liver failure, neurologic crises, rickets, and HCC. The accumulation of tyrosine catabolic intermediates due to the enzymatic deficit is believed to be the cause of the disease, resulting either in acute hepatic failure in infancy or in a chronic liver disease associated with cirrhosis and HCC development [36]. The risk of HCC is very high, with about 40% of patients who survive beyond 2 years of age developing HCC in childhood [37].

Polygenic risk factors for HCC

Autoimmune hepatitis

Autoimmune hepatitis (AIH) is a fairly uncommon disease that results from the progressive destruction of the hepatic parenchyma through a loss of immune tolerance towards hepatocytes; the origin of such immune deregulation remains unknown. In AIH patients, liver histology shows portal and periportal inflammation. AIH does not follow a Mendelian pattern of inheritance, and no single genetic locus has been identified in disease causation [38]. A significantly elevated risk of hepatobiliary malignancies, consisting mostly in HCCs, has been found in AIH patients [39] (Table 1). Confirmed associations with autoimmune hepatitis are limited to polymorphisms at the human leukocyte antigen (HLA) locus on chromosome 6p21.3 [38]. Several small studies have proposed candidacy of chromosomal regions outside the HLA as modifiers of AIH risk and outcome, but the associations of these regions have not yet been confirmed.

Diabetes

In type 2 diabetes, which is associated with the insulin-resistance syndrome, it has been hypothesized that autocrine stimulation of the insulin-like growth factor (IGF) pathway as a result of the high insulin concentrations in these patients might promote hepatocarcinogenesis [40]. Accordingly, a meta-analysis of results mainly pertaining to type 2 diabetes and derived from different populations, different geographic locations, and a variety of control groups, observed a pooled HCC risk estimate of 2.5; either in cohort studies or in a subset of case–control studies showing low statistical heterogeneity [41] (Table 1). Several genome-wide association studies (GWAS) have identified ~20 loci that modulate risk of type 2 diabetes. Most of the loci have been implicated in regulation of insulin secretion in response to increase in insulin resistance or body weight. The increased risk associated with each risk variant is small [42,43].

In type 1 diabetes, the risk for HCC remains controversial, with some studies reporting an increased HCC risk in these patients, whereas other studies do not confirm such associations. For example, Adami et al. [44] observed a significant association between type 1 diabetes (defined by a history of diabetic ketoacidosis) and HCC risk; the standardized incidence ratios was 4.1 for men and of 1.8 for women. A case–control study of insulin-dependent and non-insulin-dependent diabetes also revealed a similar excess risk of HCC (OR~4) [45]. In contrast, another study detected no excess risk of HCC associated with type I diabetes [46].

Family history of HCC

In Sweden, where the prevalence of environmental risk factors for HCC is low, family history of HCC has been described, and heritable factors would likely contribute to the risk of HCC, possibly modified by environmental factors [47] (Table 1). Since familial aggregation may depend on environment rather than on shared genes, the Swedish study tested the family environmental risk by estimating the spouse HCC risk; however, no spouse-case correlation was observed for liver or biliary cancer, suggesting that the environmental effects shared between spouses are small and that the study detected true genetic effects modulating HCC risk.

A study on pedigree from China found that familial aggregation could be explained by the interaction of HBV infection and a major gene [48] and, recently, a locus providing genetic susceptibility to HCC has been mapped on chromosome 4q25 in Chinese families [49]. A subsequent family-based association analysis to finely map this linkage region in these families with HCC and HBV surface antigen (HBsAg)-positive index cases pointed to a linkage near the 3'-phosphoadenosine 5′-phosphosulfate syntase-1 (PAPSS1) gene [50] (Table 1). Functional characterization of the PAPSS1 candidate gene and identification of functional variants await further studies.

Hypothyroidism

Hypothyroidism is the most common thyroid disorder in the adult population, particularly among older women; overall, its prevalence is about 4% but it reaches 12.1% for those 80 years or older [51]. A recent case–control study to investigate the association between hypothyroidism and HCC risk showed that a long-term history of hypothyroidism (>10 years) was associated with a statistically significant high risk of HCC in women, after adjusting for demographic factors, diabetes, hepatitis, alcohol consumption, cigarette smoking, and family history of cancer [52] (Table 1). These findings may be explained by the essential role of thyroid hormones in lipid mobilization, lipid degradation, and fatty acid oxidation. No confirmed associations between genetic polymorphisms and risk of hypothyroidism are available.

Non-alcoholic steatohepatitis

Non-alcoholic steatohepatitis (NASH) is a common liver disease in which hypothyroidism has been implicated, since it may cause

hyperlipidemia and weight gain [53]. NASH may progress to cirrhosis and it has recently been associated with an increased risk of HCC [54], although a precise risk estimates from population-based studies are not yet available (Table 1). HCC was a significant independent risk factor for mortality in NASH patients, with hazard ratio of 7.9 [55]. Genetic associations between several polymorphisms and NASH have been reported, but none have been replicated in large studies.

Evidence for the biological plausibility of a causal link between NASH and HCC comes from a study in mice showing that ablation of the NEMO subunit of the IkappaB kinase (IKK) gene in liver parenchymal cells led to the spontaneous development of HCC preceded by chronic liver disease resembling human NASH; control mice did not develop NASH or hepatocellular tumours [56]. A strain–diet interaction in mice has also been demonstrated, with susceptible mice showing morphological characteristics of NASH (steatosis, hepatitis, fibrosis and cirrhosis), dysplasia, and HCC upon long-term feeding with a high-fat diet [57].

Polymorphisms associated with exposure to liver toxicants

The food contaminants aflatoxins, produced by the common fungus Aspergillus, are potent hepatocarcinogens and represent an important risk factor for HCC in some geographical regions. Aflatoxin B1 (AFB1) undergoes metabolic activation in the liver by cytochrome P450 enzymes to a reactive AFB1-8,9-*exo*-epoxide that can bind to DNA to form the pro-mutagenic AFB1-N7-guanine adduct. The principal detoxification pathway involves glutathione S-transferase (GST)-mediated conjugation of the reactive 8,9-epoxide to reduced glutathione [58]. Thus, genetic polymorphisms in the enzymes of activation and inactivation pathways may modulate the levels of pro-mutagenic aflatoxins, implicating these polymorphisms in HCC risk.

The major CYP enzymes involved in human aflatoxin metabolism are CYP3A4 and CYP1A2. The CYP3A5 polymorphisms show association with levels of the mutagenic AFB1-*exo*-8,9-epoxide [59], but no data are available on the association between these polymorphisms and HCC risk. CYP1A2 genetic polymorphisms reportedly show no significant association with HCC risk in the overall population [60].

GSTM1 and GSTT1 exhibit a deletion polymorphism resulting in the absence of protein in individuals homozygous for the deletion. The overall results of studies on GSTs suggest a small excess risk of HCC in individuals with GSTT1-null and possibly also with GSTM1-null genotypes, although chance could not be excluded due to the observed inter-study heterogeneity [61].

Ethanol, the active compound of alcohol beverages and associated with HCC risk, is metabolized to the carcinogenic and mutagenic acetaldehyde mainly by alcohol dehydrogenase (ADH) and cytochrome p4502E1 (CYP2E1). This metabolite is then detoxified by aldehyde dehydrogenase 2 (ALDH2). The overall analysis of susceptibility to HCC and polymorphisms of the CYP2E1 gene revealed no significant association [62]. Results on possible associations between ADH and ALDH2 polymorphisms and risk of HCC remain controversial [63,64].

Ethanol also increases formation of reactive oxygen species, and polymorphisms affecting pro- and anti-oxidant enzymes have been studied in association with risk of alcoholic cirrhosis and of HCC. A recent study showed that a combination of myeloperoxidase and manganese superoxide dismutase polymorphisms increases the risk of HCC in patients with alcoholic cirrhosis [65].

A common mechanism might underlie both environmentally and genetically induced HCC

Cirrhosis usually results as a reaction to past or ongoing liver necrosis. Hepatocellular necrosis leads to regeneration, cell turnover and proliferation of hepatocytes. Inflammation accompanying the hepatocellular necrosis stimulates fibroplasia. These processes produce cirrhosis accompanied by further reactive proliferation of hepatocytes. Chronic HBV/HCV infection or alcohol abuse lead to liver cirrhosis [66]. A close association exists between HCC and cirrhosis, with more than 70% of HCC cases developing in cirrhotic livers, and cirrhosis is a strong predisposing factor for HCC, with OR = 27.5 [66,67].

It is worth noting that the human monogenic disorders of AAT deficiency [15], hemochromatosis [21], porphyrias [32], and tyrosinemia type I [36], which are all associated with an increased risk of HCC, are also associated with the development of cirrhosis. Moreover, several polygenic conditions associated with an increased risk of HCC are also predisposing conditions for liver cirrhosis, such as AIH [39], diabetes mellitus (which may be the cause or the consequence of cirrhosis) [68], and NASH [54]. Thus, the increased risk of HCC may not be directly linked to genetic disorders, but instead single germ-line mutations or conditions regulated by complex genetics may cause chronic damage (liver cirrhosis) of the target organ, in turn causing the oncogenic mutations and/or promoting preexisting endogenous or virus- or chemical-induced mutations that lead to HCC. Indeed, experimental rodent models suggest that conditions of hepatic necrosis and regeneration, similar to those occurring in human liver cirrhosis, may promote carcinogen-induced hepatocarcinogenesis [69]. Therefore, cirrhosis from any cause appears to be the common pathway by which several risk factors exert their hepatocarcinogenic effect (Fig. 1).

Discussion

Besides the established main role of hepatitis virus infections and of alcohol consumption in the risk of HCC, several genetic factors and/or syndromes also play an important role. Family-based

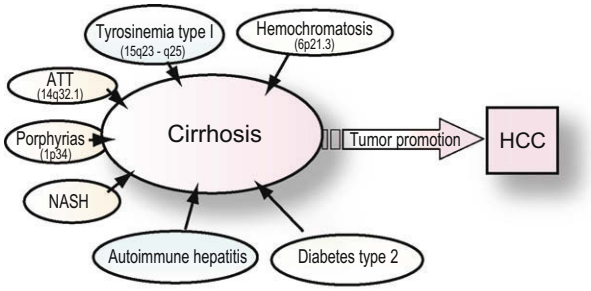

Fig. 1. Common mechanism by which several monogenic syndromes, whose causative gene mutations and chromosome positions are indicated, as well as several conditions under polygenic control, increase the risk of HCC. The single genetic defects and the polygenic conditions cause liver damage and necrosis, resulting in liver cirrhosis that favors accumulation and/or promotion of somatic mutations and of genetic damage and thus representing the ultimate risk factor for HCC.

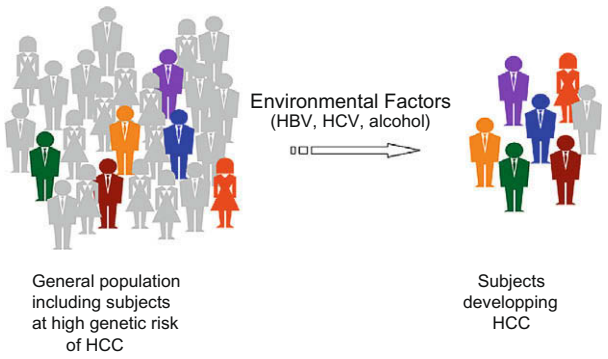

Fig. 2. Proposed model of individual susceptibility to HCC. In the general population, individuals carrying rare syndromes or a combination of susceptibility alleles (polygenic conditions) are at high genetic risk of HCC. The different colors indicate different genetic conditions providing high susceptibility to HCC, thus depicting a model characterized by genetic heterogeneity (Left). Individuals, either genetically susceptible or not, may be exposed to environmental risk factors for HCC (e.g., hepatitis virus infections, high alcohol consumption) that may induce or favor HCC development (Right). Alternatively, some genetic syndromes may cause HCC development in the absence of environmental risk factors and the latter may cause HCC by themselves.

studies suggest that a genetic locus on chromosome 4, encoding the candidate PAPSS1 gene, may modulate individual risk of HCC in HBV-positive subjects of the Chinese population [50]. The role of PAPSS1 genetic variants in HCC risk in the general population, in other countries, and in the absence of HBV infection remains to be established.

The prevalence in the general population of monogenic genetic syndromes associated with a high risk of HCC (e.g., AAT deficiency, hemochromatosis, and others) is generally low, resulting in an overall minor attributable risk of HCC, although these syndromes may provide a high risk at the individual level. In addition to these rare syndromes, other relatively common genetic conditions characterized by polygenic inheritance, such as type 2 diabetes, hypothyroidism, and NASH, are associated with an increased risk of HCC (Table 1).

Overall, present evidence suggests a scenario of individual HCC risk that is modulated by complex genetics where "strong" variants in several unlinked genes as well as several polygenic conditions may provide a high lifetime risk of HCC development. Thus, genetic heterogeneity appears to play a major role in the individual predisposition to HCC in humans (Fig. 2).

Genetic heterogeneity also appears to operate in rodent models in which hepatocarcinogenesis susceptibility (Hcs) or resistance (Hcr) loci control predisposition to hepatocellular tumours. Indeed, in three genetic crosses with different mouse strains, 3–4 unlinked loci per cross were mapped, with no overlap among crosses [70–72]. Similar observations of strain-combination-specific, non-overlapping sets of loci have been reported in rat hepatocarcinogenesis [73,74].

Most of the complex genetic factors have not yet been identified, and future large family- and population-based studies on clinically well-characterized HCC cases may improve our knowledge of the role of complex genetics in this common neoplastic disease. Also, a better understanding of the genetic mechanisms underlying the individual predisposition to HCC will lead to improvements in the prevention, early diagnosis, and treatment of this disease.

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