Genetic predisposition to hepatocellular carcinoma in alcoholic cirrhosis: The NCAN-PNPLA3-lipid connection?

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Single nucleotide polymorphisms (SNPs) are nucleotide variations occurring at the DNA level in each cell of a human being. In association with environmental factors, SNPs model the phenotypic diversity in humans but are also involved in susceptibility to several illnesses including cancer [1]. The association between SNPs and hepatocellular carcinoma (HCC) has been tested in case-control and prospective cohorts on a hypothesis-driven basis in candidate gene studies. In this setting, numerous variants affecting inflammatory pathways, oxidative stress, iron metabolism or DNA repair mechanisms have been linked with HCC development in cirrhotic patients [2]. In addition, genome-wide association studies (GWAS) used to blindly test the association between thousands of SNPs and HCC have identified several new variants in genes such as MICA, STAT4, HLA-DQ, and DEPDC5 thought to modulate HCC predisposition [2]. However, these unsupervised GWAS approaches have only been conducted in Asian populations, with liver cancer related to hepatitis B or C virus (HBV or HCV) infection by far the most common clinical setting. In contrast, despite the high incidence of HCC in alcoholic cirrhosis in Europe and its continuing increase in developing countries [4], the genetic determinants of alcoholic carcinogenesis have been poorly investigated and only with candidate gene approaches [3].

Components of the metabolic syndrome such as obesity or diabetes mellitus and their hepatic consequences, particularly steatosis, are associated with an increased risk of HCC occurrence in patients with cirrhosis [5]. These features might be only cofactors in viral carcinogenesis, during which the direct oncogenic effects of HBV or HCV are well demonstrated [6], but their implication in liver cancer development in patients with nonalcoholic steatohepatitis (NASH) or alcoholic liver disease (ALD) is pivotal [7,8]. However, a direct link between the amount of lipid accumulation in the liver and development of HCC has never been clearly demonstrated, which suggests a more subtle than direct effect of hepatic triglyceride overload on carcinogenic mechanisms. Indeed, increased fatty acid synthesis and accumulation of lipid droplets are frequent in transformed hepatocytes [9] and likely interfere with cellular signalling pathways by altering regulation of gene transcription implicated in the oncogenic process [10].

The identification of the SNP rs738409 in the adiponutrin/patatin-like phospholipase 3 (PNPLA3) gene by GWAS of patients with NASH and ALD provided a robust link between this variant associated with intracellular triglyceride accumulation and alcohol-induced liver cancer in European populations [11]. In parallel, recent GWAS identified other loci, including neurocan (NCAN), associated with liver fat content [12] and progression of nonalcoholic fatty liver disease (NAFLD) [13]. Some of the variants were associated with distinct changes in serum lipid levels, which suggest different and specific impacts on lipid metabolism and NAFLD progression. In particular, the T allele of NCAN rs2228603 was reported to promote hepatic triglyceride accumulation as well as reduced serum triglyceride and low-density lipoprotein cholesterol levels, which may seem counterintuitive at first sight [12].

In this issue of the Journal of Hepatology, Nischalke et al. [14] report on their well-designed case-control study testing the association of NCAN polymorphism and susceptibility to HCC in German patients with alcoholic cirrhosis. The authors describe a significant association between the T allele of NCAN rs2228603 polymorphism and HCC in these patients (odds ratio [OR] 2.29). This study presents the advantage of meeting several methodological quality criteria. In particular, the association seemed to be restricted to alcoholic carcinogenesis because HCV-infected patients harbouring the T allele did not show increased prevalence of liver cancer. Moreover, a validation set of ALD patients confirmed the association between NCAN rs2228603 and HCC. The authors also took into account variations in PNPLA3, and were thus able to observe higher rates of HCC among carriers of both the NCAN-T and PNPLA3-G risk variants as compared with carriage of only one or none of these genetic traits (OR 1.891 and 4.575, respectively). Finally genotype–phenotype correlations in liver samples highlighted a possible involvement of the extracellular matrix NCAN in ALD progression, although the mechanisms of carcinogenesis remain to be clarified.

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**Editorial**

*NCAN* encodes for a chondroitin sulphate proteoglycan that accumulates in the extracellular matrix [13]. However, the mechanism that links *NCAN* and lipid homeostasis remains elusive. The *NCAN* locus contains at least 20 genes in a 500-kb region on chromosome 19p13 [15]. A finer mapping of this region with genome-wide exome chip genotyping recently revealed *TM6SF2* rs58542926 as a distinct locus in strong linkage disequilibrium with *NCAN* that is also implicated in hepatic triglyceride accumulation and NAFLD progression [16]. Indeed, the p.Glu167Lys *TM6SF2* polymorphism seems to compete with the *NCAN* polymorphism in this region as a culprit for NAFLD susceptibility. Subsequent validation in patients with NASH confirmed its effect on fibrosis progression and suggested a possible impact on HCC development, although issues of low power with insufficient sample size must be acknowledged [17]. The extent to which *NCAN* and/or *TM6SF2* variants act as direct modifiers of liver fat content and possibly carcinogenesis warrants further explorations.

Interestingly, in the Nischalke et al. study, the *NCAN* rs2228603 polymorphism and *PNPLA3* I148M variant were independently associated with increased prevalence of HCC among two genotyped cohorts and had additive value in stratifying patients by presence of liver cancer. This approach highlights the current challenge of deciphering how the combination of inherited factors might collectively define an individual genomic risk prediction of liver cancer in cirrhotic patients. Taken together, these data also underline the potential impact of lipid metabolism and steatosis in liver carcinogenesis. Clearly, the knowledge of a genetic predisposition to HCC in alcoholic cirrhosis and especially the *NCAN* polymorphism adds a new level to our understanding of the mechanisms of liver carcinogenesis related to excessive alcohol intake. Dissecting the complex genetic regulations of lipid metabolism and its possible influence on hepatocarcinogenesis might reveal specific targets for future therapies based on host susceptibility. However, whether *PNPLA3*, *NCAN* or *TM6SF2* variants promote HCC emergence by creating a favourable pro-carcinogenic environment or by specifically triggering the oncogenic process is still enigmatic. Mechanistic studies should unravel specific impaired biological pathways that might account for the repeated reports describing the specific associations between these host factors and the emergence of liver cancer in ALD patients.

In addition, the evaluation of the clinical impact of this genetic heterogeneity on patient care requires validation in prospective cohorts of cirrhotic patients regularly screened for HCC. Such studies would bypass the usual biases of case–control studies and take into account all confounding factors affecting the course of cirrhosis. The identification of SNPs could allow for better predicting HCC occurrence in these patients, help stratify populations in various HCC risk classes and identify subgroups that might benefit from chemopreventive procedures or specific screening strategies based on inter-individual susceptibility. Moreover, downstream of SNPs and constitutional variants, somatic genetic alterations draw the mutational landscape of hepatocellular carcinoma [18]. Future studies will link genetic variations at the constitutional level with somatic genetic alterations or molecular subclasses observed in one cancer type, as described with the different molecular subtypes of breast cancer [19,20]. Associated with somatic genetic alterations of HCC, constitutional SNPs will be important determinants used to predict tumour recurrence after curative procedures, response to targeted therapies and drug toxicity in the future.

**Conflict of interest**

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**References**


