

2015 Advances in Cirrhosis

## Genetic, metabolic and environmental factors involved in the development of liver cirrhosis in Mexico

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**Supported by** Promep-University of Guadalajara (UDG-CA-478, to Panduro A).

**Conflict-of-interest statement:** The authors declare no conflicts of interest.

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Received: April 28, 2015  
Peer-review started: May 6, 2015  
First decision: July 13, 2015  
Revised: July 29, 2015  
Accepted: September 14, 2015

Article in press: September 14, 2015  
Published online: November 7, 2015

### Abstract

Liver cirrhosis (LC) is a chronic illness caused by inflammatory responses and progressive fibrosis. Globally, the most common causes of chronic liver disease include persistent alcohol abuse, followed by viral hepatitis infections and nonalcoholic fatty liver disease. However, regardless of the etiological factors, the susceptibility and degree of liver damage may be influenced by genetic polymorphisms that are associated with distinct ethnic and cultural backgrounds. Consequently, metabolic genes are influenced by variable environmental lifestyle factors, such as diet, physical inactivity, and emotional stress, which are associated with regional differences among populations. This Topic Highlight will focus on the genetic and environmental factors that may influence the metabolism of alcohol and nutrients in the setting of distinct etiologies of liver disease. The interaction between genes and environment in the current-day admixed population, Mestizo and Native Mexican, will be described. Additionally, genes involved in immune regulation, insulin sensitivity, oxidative stress and extracellular matrix deposition may modulate the degree of severity. In conclusion, LC is a complex disease. The onset, progression, and clinical outcome of LC among the Mexican population are influenced by specific genetic and environmental factors. Among these are an admixed genome with a heterogenic distribution of European, Amerindian and African ancestry; a high score of alcohol consumption; viral infections; a hepatopathogenic diet; and a high prevalence of obesity. The variance in risk factors among populations suggests that intervention strategies directed towards the prevention and management of LC should be tailored according to such population-based features.

**Key words:** Genomic medicine; Polymorphisms; Viral hepatitis; Obesity; Nonalcoholic steatohepatitis; Risk factors

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**Core tip:** Liver cirrhosis is a global health problem. The onset, progression, and clinical outcome of liver cirrhosis are influenced by several hereditary and lifestyle factors. Worldwide, interactions between genetic and environmental factors involved in liver cirrhosis may be associated with ethnic-based variations. Globally, in populations with admixed genomes, such as the Mexican population, individualized medicine represents a new challenge for hepatologists and gastroenterologists.

Ramos-Lopez O, Martinez-Lopez E, Roman S, Fierro NA, Panduro A. Genetic, metabolic and environmental factors involved in the development of liver cirrhosis in Mexico. *World J Gastroenterol* 2015; 21(41): 11552-11566 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v21/i41/11552.htm> DOI: <http://dx.doi.org/10.3748/wjg.v21.i41.11552>

## INTRODUCTION

Liver cirrhosis (LC) is a chronic illness caused by multiple, long-term injuries to the liver<sup>[1]</sup>. Globally, LC represents the 14<sup>th</sup> leading cause of mortality<sup>[2]</sup> but is the 12<sup>th</sup> leading cause of mortality in the United States<sup>[1]</sup> and the 4<sup>th</sup> leading cause in Central Europe<sup>[3]</sup> and Mexico<sup>[4]</sup>. In general, the main etiologies of LC are chronic alcohol abuse, followed by viral infections (hepatitis C and B viruses) and nonalcoholic fatty liver disease (NAFLD), including nonalcoholic steatohepatitis (NASH)<sup>[5]</sup>. Other causes that occur in a lesser extent are autoimmune hepatitis, obstructive cholestasis, hereditary hemochromatosis, alpha-1-antitrypsin deficiency, Wilson's disease and drug toxicity<sup>[6]</sup>.

Liver cirrhosis is characterized by the degeneration and necrosis of hepatocytes, the replacement of liver parenchyma with fibrotic tissues and regenerative nodules and loss of liver function<sup>[7]</sup>. The impaired liver architecture induces intrahepatic vascular distortion and portal hypertension, which manifests in major complications, such as ascites, upper gastrointestinal bleeding, jaundice and hepatic encephalopathy<sup>[8]</sup>. However, regardless of the etiological factors, the susceptibility and degree of liver damage may be influenced by genetic polymorphisms that are associated with particular ethnic backgrounds<sup>[9]</sup>. Consequently, genes involved in various metabolic pathways are influenced by distinct environmental lifestyle factors, such as diet, physical inactivity, and emotional stress<sup>[10]</sup>.

Thus, this Topic Highlight will focus on the genetic and environmental factors that may influence the metabolism of alcohol and nutrients in the setting of

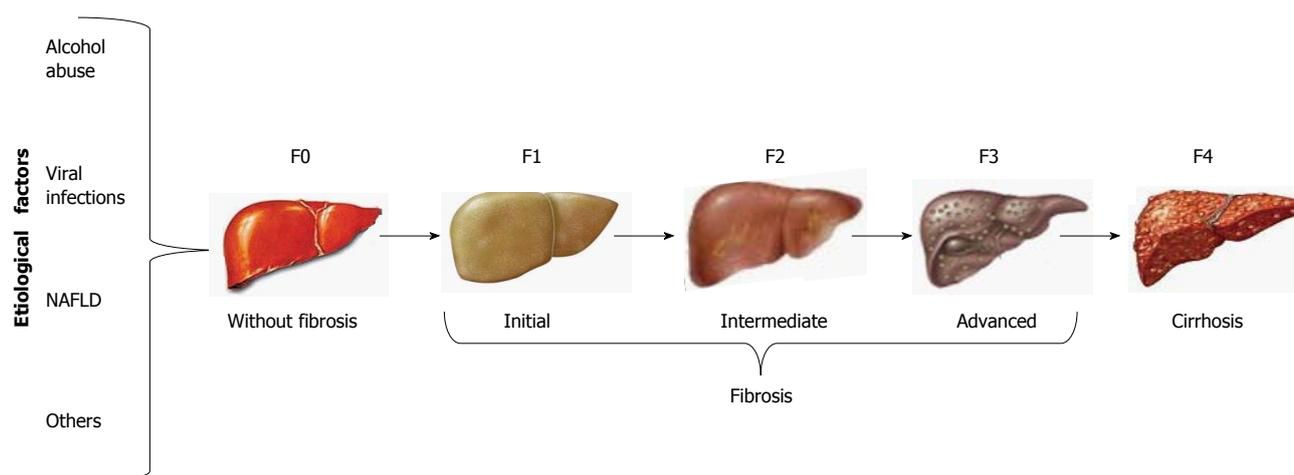
distinct etiologies of liver disease. Additionally, genes involved in immune regulation, insulin sensitivity, oxidative stress and extracellular matrix deposition may modulate the degree of severity. The interaction between genes and environment in the current-day admixed population, Mestizo and Native Mexican, will be described. The inheritance of a heterogenic distribution of European, Amerindian and African ancestry in this population<sup>[11,12]</sup> may play a central role in the clinical outcome of liver disease in conjunction with specific environmental factors.

## CELLULAR AND MOLECULAR MECHANISMS INVOLVED IN THE PATHOGENESIS OF LIVER CIRRHOSIS

Hepatic fibrogenesis is a key factor for the progression of liver damage as a result of an excessive healing response triggered by acute and chronic liver injury associated with the continuous deposition of extracellular matrix (ECM), mainly fibrillary collagen<sup>[13]</sup>. The accumulation of ECM is due to both increased synthesis and decreased degradation that contributes to the loss of hepatocyte microvilli and endothelial fenestrations, resulting in LC and liver failure<sup>[14,15]</sup>. Hepatic fibrosis is driven by a population of activated fibrogenic cells known as myofibroblasts (MFs)<sup>[16]</sup>. The hepatic stellate cells (HSCs) are the primary source of MFs, orchestrating the deposition of ECM in normal and fibrotic liver, and activation of the immune response<sup>[17]</sup>. However, recent research has revealed that several cell types contribute to MF formation, including portal fibroblasts and bone marrow-derived mesenchymal cells<sup>[18]</sup>.

The clinical assessment of cirrhosis and the staging of fibrosis have given rise to a number of non-invasive techniques that have been validated as surrogate tests for liver biopsy, such as the most recently developed transient elastography (FibroScan; Echosens, Paris, France). By this method, shear wave velocity correlates with liver stiffness, which is staged from F0 to F4, regardless of the etiological agent of liver fibrosis (Figure 1)<sup>[1]</sup>.

Regarding the cellular and molecular mechanisms of LC, activation of HSCs involves two main stages (Figure 2). The first stage of initiation renders the cells responsive to diverse agents of liver injury, which results from the paracrine stimulation of neighboring cells, such as hepatocytes, circulating leukocytes, platelets and endothelial and Kupffer cells (KCs). Such stimuli include reactive oxygen species (ROS) and inflammatory cytokines. Others effectors are transcriptional factors, such as the three types of peroxisome proliferator-activated receptors (PPAR- $\alpha$ , - $\beta$  and - $\gamma$ ), c-Myb, nuclear factor kappa B (NF- $\kappa$ B), Kruppel-like factor 6 (KLF6) and the CCAAT/enhancer binding protein- $\beta$  (C/EBP $\beta$ ). In addition, growth factors, mainly transforming growth factor beta 1 (TGF- $\beta$ 1), platelet-derived growth factor (PDGF), epidermal growth factor (EGF) and insulin-like growth factor 1



**Figure 1 Stages of liver fibrosis.** Liver fibrosis may be evaluated by liver biopsy and non-invasive methods. Regardless of etiological factors, liver fibrosis encompasses 3 stages until the development of cirrhosis. NAFLD: Nonalcoholic fatty liver disease.

(IGF-1), play an important role in the activation of HSCs<sup>[19,20]</sup>.

Once the HSCs are activated, the perpetuation stage encompasses phenotypic changes in cell biology, such as proliferation, contractility, fibrogenesis, matrix degradation, chemotaxis, retinoid loss, cytokine release and white blood cell chemoattraction. These events are regulated in an autocrine and paracrine manner by proinflammatory, pro-fibrogenic and pro-mitogenic signals to exacerbate the accumulation of ECM<sup>[20]</sup>. Finally, if the causal agent is eliminated, liver injury may be resolved. In this case, activated HSCs limit the fibrogenic response through the up-regulation of genes involved in apoptosis, enhanced immune surveillance and the increased secretion of ECM-degrading enzymes<sup>[21]</sup>.

## GENETIC, METABOLIC AND ENVIRONMENTAL FACTORS INVOLVED IN LIVER DISEASE

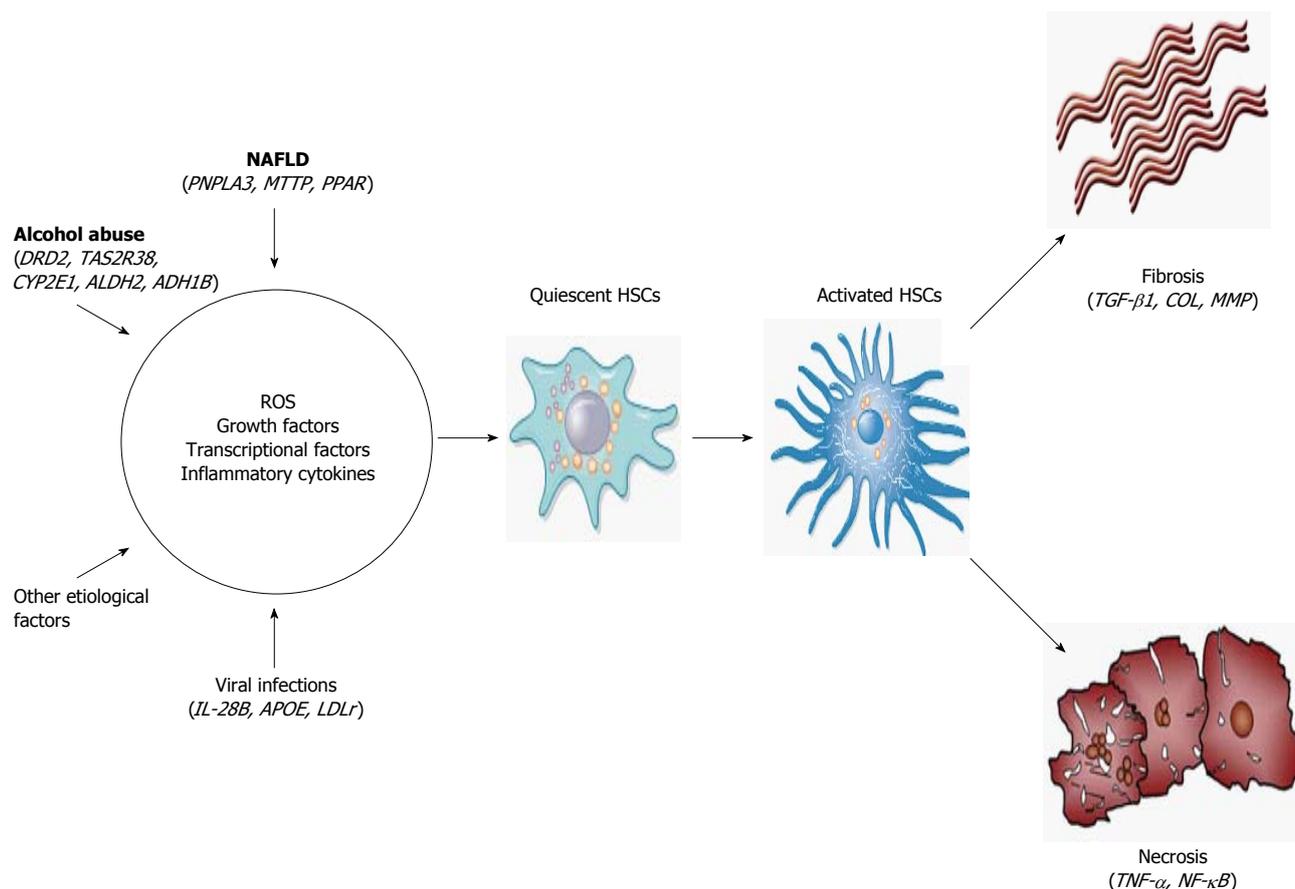
### **Alcoholic liver disease**

Overconsumption of alcohol is directly associated with liver disease and affects millions of individuals worldwide<sup>[22]</sup>. It is estimated that a consumption of > 40 g of alcohol/d in men and > 20 g of alcohol/d in women over a period of 10 years significantly increases the risk of LC<sup>[23]</sup>. Alcohol-induced liver disease pathogenesis involves alcohol-metabolizing enzymes that alter the levels of acetaldehyde and ROS; these enzymes are known to have variable allelic distribution worldwide (Table 1)<sup>[24]</sup>. High levels of ROS diminish antioxidant activity, leading to oxidative damage of proteins, lipids, and DNA, which serve as antigens for eliciting the host immune response<sup>[25]</sup>. In addition, oxidative stress can modify intracellular signaling cascades related to an inflammatory state<sup>[26]</sup>. The resulting oxidative damage and subsequent mitochondrial and autophagy dysfunction lead to

energy depletion, the accumulation of cytotoxic mediators and cell death<sup>[27]</sup>. Furthermore, acetaldehyde promotes bacterial lipopolysaccharide (LPS) translocation from the gut to the liver, which in turn stimulates Kupffer cells to release proinflammatory cytokines<sup>[28]</sup>. Additionally, acetaldehyde alters lipid homeostasis by disrupting lipoprotein transportation from the liver, decreasing  $\beta$ -oxidation of fatty acids and increasing its biosynthesis; resulting in hepatic steatosis<sup>[29]</sup>. Moreover, acetaldehyde is involved in fibrogenesis because this metabolite stimulates the synthesis of collagen and ECM components through the activation of the TGF- $\beta$ 1/SMAD3 signaling pathway<sup>[30]</sup>. Finally, acetaldehyde and ROS can form DNA adducts that are prone to mutagenesis and carcinogenesis<sup>[31]</sup>.

Furthermore, in alcoholic liver disease (ALD), additional genetic factors involved in alcohol dependence and alcohol abuse have been intensively studied. Among these factors are the dopamine receptor D2 (*DRD2*); the bitter taste receptor (*TAS2R38*); and the liver enzymes alcohol dehydrogenase class I, beta polypeptide (*ADH1B*), cytochrome P450, family 2, subfamily E, polypeptide 1 (*CYP2E1*) and aldehyde dehydrogenase 2 family (*ALDH2*). Moreover, polymorphisms of lipid metabolizing genes, such as apolipoprotein E (*APOE*), fatty acid-binding protein 2 (*FABP2*), patatin-like phospholipase domain-containing 3 (*PNPLA3*) and peroxisome proliferator-activated receptor  $\gamma$ 2 (*PPAR- $\gamma$ 2*) have been associated with the severity of ALD. Others genes related to the process are inflammatory tumor necrosis factor alpha (*TNF- $\alpha$* ), nuclear factor kappa-light-chain-enhancer of activated B cells (*NF- $\kappa$ B*), CXC chemokine ligand 1 (*CXCL1*) and CD14 endotoxin receptor (*CD14*) (Table 1).

Additionally, environmental cultural factors involved in ALD may vary among populations. In Spain, drinking moderate amounts of red wine is part of the traditional Mediterranean diet and has been associated with reduced all-cause mortality<sup>[32]</sup>. Mexico has a strong Spanish cultural influence; however, the Mexican



**Figure 2 Hepatic fibrogenesis.** Different etiological factors induce production of several stimuli to HSCs activation. Activated HSCs promote fibrosis and necrosis of hepatocytes. These pathogenic processes can be modulated by genetic polymorphisms involved in each stage of the pathophysiological process. HSC: Hepatic stellate cells; DRD2: Dopamine receptor D2; TAS2R38: Bitter taste receptor; CYP2E1: Cytochrome P450, family 2, subfamily E, polypeptide 1; ALDH2: Aldehyde dehydrogenase 2 family; ADH1B: Alcohol dehydrogenase class I, beta polypeptide; PNPLA3: Patatin-like phospholipase 3; MTP: Microsome triglyceride transfer protein; PPAR-γ2: Peroxisome proliferator-activated receptors; IL-28B: Interleukin-28B; APOE: Apolipoprotein E; LDLr: Low-density lipoprotein receptor; TGF-β1: transforming growth factor beta 1; COL: Collagenases; MMP: Matrix metalloproteinase; TNF-α: Tumor necrosis factor alpha; NF-κB: Nuclear factor kappa B; ROS: Reactive oxygen species.

population did not inherit this Mediterranean alcohol drinking pattern. Instead, the Mexican population has a pattern of alcohol consumption that differs from what has been reported in other regions worldwide<sup>[24]</sup>. Specifically, in West Mexico, young people consume 80 to 360 g of alcohol (mainly beer) over the weekends in a period of 10 years. In the next decade, alcohol consumption eventually increases from 360 to 640 g of alcohol per day, including beer and a combination of beer and distilled beverages, such as tequila. Finally, 3-5 years later, the amount of alcohol increases up to 720 g daily, mainly tequila<sup>[24,33]</sup>, until LC clinically manifests<sup>[34,35]</sup>. This pattern of alcohol consumption is consistent with the age-related onset of alcohol-induced LC previously reported<sup>[36]</sup>. The average peak age for LC onset has been reported to be 45 years; however, one group reported an average age of 30 years, which may be the earliest onset ever reported most likely due to genetic susceptibility<sup>[36]</sup>. Genetic polymorphisms in the *CYP2E1*, *APOE*, and *FABP2* genes have been associated with the early onset of LC in the population of West Mexico (Table 1). However, the distribution of these genetic polymorphisms

has demonstrated ethnic differences. Interestingly, the *APOE\*2* risk allele is highly frequent in the Caucasian population<sup>[12]</sup>, whereas the *CYP2E1\*c2* risk allele prevails among Amerindians<sup>[37]</sup>. Other factors may affect the development of alcoholic liver damage, including dose, duration and type of alcohol consumption; drinking pattern; gender; obesity; iron overload; and diet<sup>[24]</sup>. Consistently, patients with chronic alcohol abuse had a higher intake of cholesterol, sodium and simple carbohydrates than other groups with liver disease, which may accelerate hepatocellular injury<sup>[38]</sup>.

Furthermore, certain polymorphisms that are associated with Amerindian ancestry may have placed the current-day Mestizo population at a higher risk of genetic susceptibility to alcoholism. The novel AVV haplotype of *TAS2R38*, which has not been identified in other populations, was associated with alcohol abuse in the population of West Mexico<sup>[39]</sup>. Globally, Mexico has the highest frequency of the allele A1 in *DRD2*, which has been correlated with alcohol addiction<sup>[24]</sup>. The identification of these factors has contributed to an integrative understanding of ALD in Mexico. However,

**Table 1** Genetic polymorphisms associated with alcohol dependence, alcohol abuse and liver disease

Gene	Risk allele	Association	Population	Ref.
Alcohol-metabolizing enzymes				
<i>CYP2E1</i>	CYP2E1*c2	Higher susceptibility to LC; decompensated liver function	Mexican (Mestizo), West Mexico	[110]
<i>ADH1B</i>	ADH1B*2	Higher risk to LC	Japanese	[111]
<i>ADH1B</i>	ADH1B*1	Alcohol dependence	European, Asian	[112-114]
<i>ALDH2</i>	ALDH2*1	Higher susceptibility to LC	Japanese	[111]
Alcohol dependence genes				
<i>DRD2</i>	Taq I A1	Alcohol dependence	European, East Asian	[115]
<i>TAS2R38</i>	AVV haplotype	Higher alcohol intake	Mexican, (Mestizo), West Mexico	[39]
Lipid metabolism				
<i>APOE</i>	APOE*2	Hypertriglyceridemia and increased development of early LC	Mexican (Mestizo), West Mexico	[36]
<i>FABP2</i>	Ala54	Earlier onset of LC	Mexican (Mestizo), West Mexico	[116]
<i>PNPLA3</i>	M148	Alcoholic liver disease and clinically evident LC	Mixed European and Native American, Mexico City	[117,118]
<i>PPAR-γ2</i>	Ala12	Increased risk to develop severe steatohepatitis and fibrosis	German	[119]
Immune response				
<i>TNF-α</i>	-238 A	Higher prevalence of LC	Spanish	[120]
<i>NF-KB</i>	ATTG deletion	Higher prevalence of LC	Spanish	[121]
<i>CXCL1</i>	rs4074 A	Higher prevalence of LC	German	[122]
<i>CD14</i>	-159 T	Advanced liver disease, hepatitis and especially with LC	Finnish	[123,124]

LC: Liver cirrhosis.

further large-scale studies that involve distinct ethnic groups are needed to determine how genetics may influence the onset and progression of LC.

## VIRAL HEPATITIS

### Hepatitis C virus

The hepatitis C virus (HCV) is a hepatotropic single-stranded RNA virus of the *Flaviviridae* family<sup>[40]</sup>. HCV infection is one of the most common causes of chronic liver disease worldwide, with an estimated prevalence of 3% or 170 million infected people<sup>[41]</sup>. Latin America has one of the lowest prevalences (1.23%); however, this prevalence varies between different regions<sup>[42]</sup>. In Mexico, 400000 to 1400000 individuals are infected with HCV. Of these individuals, 200000 to 700000 present with active viremia<sup>[43]</sup>. HCV has been classified into six main genotypes with a heterogeneous global distribution. HCV genotypes 4, 5 and 6 are common in Africa and South East Asia, whereas genotypes 2 and 3 are more frequent in European countries<sup>[44]</sup>. However, the most predominant HCV genotypes in Mexico are 1a and 1b<sup>[45]</sup>, which have been associated with increased resistance to treatment with pegylated interferon and ribavirin. These HCV endemic differences are explained in part by the prevalent routes of transmission in each region. In West Mexico, the predominant risk factors for HCV transmission are blood transfusions from infectious donors and surgeries with contaminated surgical instruments<sup>[46]</sup>. In contrast, in North America, injection drug use is the major route of HCV infection<sup>[47]</sup>.

Approximately 18%-34% of patients with acute HCV infection undergo spontaneous clearance through a sustained, vigorous and virus-specific CD4<sup>+</sup> T-cell

response in peripheral blood<sup>[48]</sup>. However, in cases of persistent HCV infection, the virus evades the host innate immune response<sup>[49]</sup>. This condition may potentially increase the risk of progression to hepatic fibrosis, cirrhosis and hepatocellular carcinoma (HCC) over 20-30 years of HCV infection<sup>[50]</sup>. HCV is a non-cytopathic virus; therefore, the related liver damage is mainly caused by the host immune response. The potential mechanisms of LC include portal lymphoid infiltration, focal and bridging necrosis, and degenerative lobular lesions, which may be amplified by the accumulation of specific T cells that are recruited by adhesion molecules and chemokine expression<sup>[51]</sup>.

Studies in West Mexico have found that cytokines influence the extent of HCV development in patients infected with genotype 1a. Our data reveal that chronic infection results in an increased secretion of interleukin 8 (IL-8) and the chemokine (C-C motif) ligand 5 (CCL5), whereas patients who spontaneously cleared HCV exhibited augmented levels of interleukin 1 alpha (IL-1α), interleukin 13 (IL-13), interleukin 15 (IL-15), TNF-α, TGF-β1 and the chemokine (C-C motif) ligand 8 (CCL8)<sup>[52]</sup>. This finding correlates with studies conducted in regions where the virus is endemic and suggests that variations in the profile of cytokines involved in the immune response may contribute to either the ability to clear HCV or to the long-term persistence of HCV and thus the potential development of LC<sup>[53]</sup>.

Chronic HCV infection causes numerous pathogenic changes in the liver, including iron overload, steatosis, insulin resistance, the induction of endoplasmic reticulum stress, the unfolded protein response, oxidative stress, mitochondrial dysfunction and altered

growth control<sup>[54-56]</sup>. Other factors are significantly associated with the progression of fibrosis in chronic HCV carriers. These factors include the duration of infection, advanced age, male sex, heavy alcohol use (> 50 g/d), HIV coinfection, diabetes and a low CD4 count<sup>[57-59]</sup>. Moreover, physical inactivity, obesity, and related lipid alterations may play a critical role in the progression of fibrosis<sup>[42]</sup>. Recently, we found that approximately 65% of HCV-infected patients in West Mexico have a sedentary lifestyle, and approximately 70% of these patients are overweight or obese<sup>[38]</sup>. Because overnutrition may influence the course of infection, the analysis of distinct cohorts, including obese and non-obese individuals, should be conducted to characterize the influence of this factor on LC development.

In addition to environmental and viral features, host genetic factors are important contributors to the modulation of HCV outcomes<sup>[42]</sup>. Diverse polymorphisms in genes involved in lipid metabolism have been described, such as apolipoprotein B (*APOB*), *APOE*, LDL receptor (*LDLR*), microsomal triglyceride transfer protein (*MTTP*) and *PNPLA3*. Polymorphisms in several immune regulatory genes have been demonstrated to influence HCV outcomes, including *CXCL1*, interleukin 28B (*IL-28B*), *TGF-β1* and *TNF-α*; and matrix metalloproteinase 1 (*MMP-1*), 3 (*MMP-3*) and 9 (*MMP-9*). Additionally, genetic polymorphisms that have been implicated in the metabolism of homocysteine (methylentetrahydrofolate reductase, *MTHFR*), iron (hemochromatosis gene, *HFE*), and vitamin D (vitamin D receptor, *VDR*) have been reported (Table 2). Finally, a meta-analysis demonstrated that two polymorphisms in *IL-28B* (rs12979860 CC and rs8099917 TT) were strong predictors of sustained virological response in patients on pegylated interferon and ribavirin treatment<sup>[60]</sup>.

### Hepatitis B virus

The hepatitis B virus (HBV) is a noncytopathic, hepatotropic virus of the *Hepadnaviridae* family<sup>[61]</sup>. HBV infection is a public health problem, in which nearly 400 million people suffer chronic HBV infection<sup>[62]</sup>. In Mexico, epidemiological studies have indicated that at least 15 million adults may have been exposed to HBV during their lifetime<sup>[63]</sup>, and up to 300000 individuals may be active carriers<sup>[64]</sup>. Globally, geographical areas with a high endemicity of HBV infection include Asian countries, regions in South America with indigenous peoples and Alaska<sup>[65,66]</sup>. In contrast, Mexico is considered a region of low endemicity<sup>[43]</sup>, which is associated with predominant HBV genotypes H and G<sup>[67]</sup>, low hepatitis B surface antigen (HBsAg) seroprevalence<sup>[64]</sup>, and low viral loads<sup>[63]</sup> but a high prevalence of occult B infection (OBI) among native Mexican groups (Nahuas and Huichol)<sup>[68]</sup>. OBI is diagnosed based on a negative serum hepatitis B surface antigen (HBsAg) test, the presence of HBV DNA in

the liver and very low HBV DNA levels in serum<sup>[69]</sup>. Therefore, given these features, the detection of HBV infection in Mexico may be underestimated in the setting of HBV-induced chronic liver disease.

The outcome of HBV infection is the result of complex interactions between HBV and the host immune system<sup>[53,70]</sup>. A study of cytokine sera profiles in native Mexican groups revealed that OBI patients displayed increased interleukin 2 (IL-2) secretion and a characteristic inflammatory profile (reduction in IL-8 and *TNF-α*, and increased levels of *TGF-β1*)<sup>[71]</sup>. This finding correlates with the accepted role of *TGF-β1* in the progression of liver disease<sup>[72]</sup>, whereas the high secretion of IL-2 suggests that OBI may be modulated by IL-2. Experimental data indicate that cytotoxic T cells are the main cell type responsible for the inhibition of viral replication and for hepatocyte lysis<sup>[73]</sup>.

Moreover, HBV genotypes influence the natural course of infection and related liver damage. Regarding the distribution of HBV genotypes, HBV genotype H in native and Mestizo Mexicans and genotype F in native Latin Americans are linked to a less severe natural course of disease and a faster resolution of infection<sup>[74]</sup>. This finding may be due to a high degree of immune adaptation to the virus in these populations. Nonetheless, in Mestizo Americans, genotype F is commonly associated with acute and chronic liver disease with a tendency toward HCC<sup>[74]</sup>.

Additionally, HBV is associated with metabolic alterations in host cells, which lead to hepatic steatosis, oxidative stress, inflammation, and carcinogenesis. The main mechanisms include the transcriptional up-regulation of genes involved in the biosynthesis of lipids, phosphatidylcholine, and hexosamine; as well as modifications in cell proliferation and differentiation. Together, such changes promote HBV replication and liver damage<sup>[75]</sup>. Other factors, such as alcohol abuse (> 60 g/d) for at least 10 years, central obesity, insulin resistance, diabetes and environmental hepatotoxins, including tobacco smoke and aflatoxins, may increase the progression rate of liver injury in chronic HBV-infected patients<sup>[76]</sup>. In addition, genetic polymorphisms modulate the outcome of HBV infection. These polymorphisms include interleukin 10 (*IL-10*), *IL-28B*, *TGF-β1* and the collagenases, type I, alpha 1 (*COL1A1*) and type III, alpha 1 (*COL3A1*) (Table 3).

### Other viral hepatitis

Recently, we described a high seroprevalence of the hepatitis E virus (HEV) in serum samples from cirrhotic patients in whom no etiological agent was found<sup>[43]</sup>. Consequently, this finding suggests a potential role of HEV in LC development and is consistent with the description of HEV-related cirrhosis in immunocompromised patients<sup>[77]</sup>. Further epidemiological studies are warranted among the Mexican population to elucidate the plausible influence of HEV in liver disease.

**Table 2 Genetic polymorphisms associated with the outcomes of hepatitis C virus infection**

Gene	Risk allele	Association	Population	Ref.
Lipid metabolism				
<i>APOB</i>	-516 C	Increased susceptibility of HCV infection	Chinese	[125]
<i>APOE</i>	APOE*3	Viral persistence	Northern European	[126]
<i>LDLr</i>	rs2738459 C, rs2569540 G, rs1433099 A, rs11672123 A	Higher viral load in genotypes 1 and 4	Spanish	[127]
<i>MTTP</i>	-493 T	Higher degree of steatosis, HCV RNA serum levels and hepatic fibrosis	Native Italian	[128,129]
<i>PNPLA3</i>	M148	Higher risk for steatosis and fibrosis progression	European: Belgian, German and French	[130]
Immune response mediators				
<i>CXCL1</i>	rs4074 A	Higher risk for LC	German	[131]
<i>IL-28B</i>	rs12979860 T	Higher risk for LC and HCC	Native Italian and Chinese	[132,133]
<i>TGF-β1</i>	-509 T	Higher risk for LC and HCC	Egyptian	[134]
<i>TNF-α</i>	-308 A	Higher risk for LC and HCC	Egyptian	[134]
Fibrogenesis				
<i>MMP-1</i>	-1607 2G	Higher prevalence of LC	Japanese	[135]
<i>MMP-3</i>	-1171 5A	Lower age at LC diagnosis and a higher Child-Pugh score	Japanese	[135]
<i>MMP-9</i>	-1562 C	Higher prevalence of LC	Japanese	[135]
Nutrient metabolism				
<i>MTHFR</i>	677 T	Hyperhomocysteinemia and higher degree of steatosis and fibrosis	Italian	[136]
<i>HFE</i>	63 D	Higher likelihood of LC	Taiwanese	[137]
<i>VDR</i>	CAA haplotype (rs1544410 C, rs7975232 A, rs731236 A)	Higher fibrosis progression and LC	Swiss	[138]

LC: Liver cirrhosis; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma.

**Table 3 Genetic polymorphisms associated with the outcomes of hepatitis B virus infection**

Gene	Risk allele	Association	Population	Ref.
Immune response mediators				
<i>IL-10</i>	-592 C	Significant increased risk of LC	Asian	[139]
<i>IL-28B</i>	rs12979860 C	Increased risk for developing LC	Asian	[140]
<i>TGF-β1</i>	10 T	Higher prevalence of LC	Chinese	[141]
<i>TGF-β1</i>	-509 C	Higher susceptibility to LC	Chinese	[142]
Fibrogenesis				
<i>COL1A1</i>	TC haplotype (-1997 T, -1363 C)	Higher prevalence of LC	Chinese	[143]
<i>COL3A1</i>	rs3106796 A	Higher prevalence of chronic hepatitis, LC and HCC	Koreans	[144]

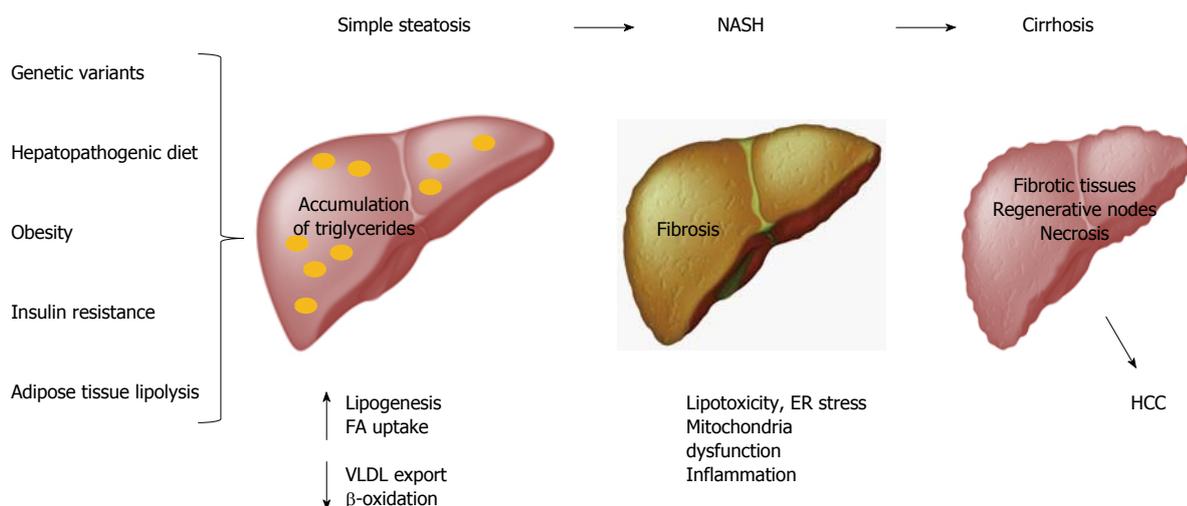
LC: Liver cirrhosis; HCC: Hepatocellular carcinoma.

## NAFLD

Obesity is considered the main factor associated with multiple metabolic disorders, such as NAFLD, which comprises simple steatosis, NASH, cirrhosis and HCC<sup>[78,79]</sup>. Hepatic steatosis is defined by the presence of cytoplasmic triglyceride (TG) droplets in more than 5% of hepatocytes as a result of an imbalance between lipid input and output<sup>[80,81]</sup>. The abnormal accumulation of TGs in the liver induces lipotoxicity, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and inflammation, which all result in fibrosis (Figure 3)<sup>[82,83]</sup>. Conventionally, international guidelines and intervention strategies have been proposed for the treatment of NAFLD/NASH. However, because disparities in genetic and environmental factors among populations were not considered, the application of these strategies may not be feasible for all populations

worldwide. Therefore, intervention strategies for the prevention and management of such obesity-related diseases should be based on a regionalized genome-based diet by focusing on the specific ancestry of each population and the convenience of consuming traditional ethnic food<sup>[11]</sup>.

Currently, Mexico is one of the countries with the highest number of obese individuals, which is closely related to dietary factors and physical inactivity<sup>[84]</sup>. The diet in West Mexico is hepatopathogenic because of its high content of fat derived mainly from the habitual consumption of meat, fried foods and sausages<sup>[11,38]</sup>. Interestingly, we have observed that a genetic variant in the fat taste *CD36* receptor may play an important role in this condition<sup>[85]</sup>. High-fat diets are associated with an increase in body weight, the upregulation of blood glucose levels, the progression of steatosis, and marked inflammation of the liver<sup>[86]</sup>. Moreover,



**Figure 3 Nonalcoholic fatty liver disease pathogenesis.** The spectrum of NAFLD includes simple steatosis, NASH, LC and even HCC. Risk factors such as obesity, hepatopathogenic diet, insulin resistance and adipose tissue lipolysis lead to accumulation of triglycerides. This abnormality can stimulate lipotoxicity, ER stress, mitochondria dysfunction and inflammation, promoting fibrosis. Chronic fibrogenesis causes histological changes in the liver that lead to LC, which in turn may evolve to HCC. NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis; LC: Liver cirrhosis; HCC: Hepatocellular carcinoma; FA: Fatty acids; VLDL: Very low-density lipoprotein; ER: Endoplasmic reticulum.

more than 70% of the Mexican population frequently consumes soda, which increases fructose input<sup>[38]</sup>. Fructose promotes steatosis, insulin resistance, necroinflammation, and fibrosis<sup>[87-89]</sup>. In contrast, our diet is deficient in n-3 polyunsaturated fatty acids (PUFA) and antioxidants, which favors oxidative stress and lipid alterations<sup>[90]</sup>. Finally, inadequate dietary behaviors, such as missing breakfast and a lack of feeding schedules, are common among the Mexican population<sup>[38]</sup> and have been linked to obesity<sup>[91]</sup>.

Other interactions between genes and environmental lifestyle factors that favor changes in the body mass index have been studied in West Mexico. Dietary modifications consisting of a lower intake of saturated fat (< 7%) significantly decreased body mass index, waist circumference, waist-to-hip ratio, and reactive C protein in *FABP2* Thr<sup>54</sup> allele carriers compared to Ala54 allele carriers<sup>[92]</sup>. Additionally, recent studies in an obese cohort demonstrated that the expression of adiponectin levels may be modulated by changes in lifestyle regardless of the presence of an adiponectin (*ADIPOQ*) 11391G/A polymorphism<sup>[93]</sup>.

However, despite the strong correlation between obesity and NAFLD, approximately 5% of morbidly obese patients do not develop NAFLD<sup>[94]</sup>. This finding supports the role of genetic factors in the development of NAFLD and NASH (Table 4). These factors may include polymorphisms in genes that affect lipid metabolism, such as apolipoprotein C3 (*APOC3*), *PNPLA3*, *MTTP*, and phosphatidylethanolamine N-methyltransferase (*PENM*). Polymorphisms in genes that affect insulin sensitivity, such as *ADIPOQ*, adiponectin receptors 1 and 2 (*ADIPOR 1* and *ADIPOR 2*), *PPAR-γ*, *PPAR-γ* coactivator 1α gene (*PPARGC1A*) and *PPAR-α*, may play a role in the development of NAFLD and NASH. Additionally,

regulatory genes of oxidative stress, including glutamate cysteine ligase (*GCLC*), inducible nitric oxide synthase (*NOS2*), and manganese superoxide dismutase (*SOD2*), have been implicated. Genes related to immune regulation, including signal transducer and activator of transcription 3 (*STAT3*), *TNF-α*, *IL-8* and interleukin-6 (*IL-6*); as well as *MTHFR* and *HFE* have been described. Finally, other less common genes that have been associated with the development of NAFLD and NASH include ATP-binding cassette subfamily C member 2 (*ABCC2*, also known as multidrug resistance protein 2, *MRP2*) and angiotensin II type I receptor (*AGTR1*)<sup>[95]</sup>.

## HCC

Globally, HCC is the most common form of liver cancer, the sixth most prevalent cancer and the third most frequent cause of cancer-related death<sup>[96]</sup>. Nearly 75% of HCC cases are attributed to chronic HBV and HCV infections in high endemic regions<sup>[97]</sup>. Therefore, the particular characteristics of these viruses and the genetic structure and environmental factors that prevail in each population may explain the epidemiological differences in HCC worldwide. Regions with higher incidence rates of this malignant disease include sub-Saharan Africa, Eastern Asia, followed by Southern European countries<sup>[32]</sup>. However, HCC is rare in other geographical areas, such as North and South America, Northern Europe, Oceania, and Mexico<sup>[98]</sup>. The low incidence of HBV-related HCC among the Mexican population is associated with a low steady HBsAg seroprevalence<sup>[64]</sup>. Furthermore, because Mexican patients with alcoholic cirrhosis are young, death occurs earlier due to long-term complications. This fact hinders the study of the association between alcohol consumption and HCC in

**Table 4 Genetic polymorphisms associated with the development of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis**

Gene	Risk allele	Association	Population	Ref.
<b>Lipid metabolism</b>				
<i>APOC3</i>	482 T, 455 C	Higher fasting plasma triglyceride concentration and higher prevalence of NAFLD	Asian Indian	[145]
<i>PNPLA3</i>	M148	Increased hepatic fat levels, hepatic inflammation and fibrosis in NAFLD and NASH patients	Hispanic, African American, European American, Finnish, Argentinean, Italian	[146-150]
<i>MTTP</i>	-493 G	Higher intrahepatic triglycerides content. Higher incidence and progression of NASH	French, Japanese	[151,152]
<i>PEMT</i>	M175	Higher prevalence of NAFLD and NASH	Hispanic, African American, European American, Asian	[153,154]
<b>Insulin resistance/sensitivity</b>				
<i>ADIPOQ</i>	45 T, 276 T	Higher prevalence of NAFLD. Lower postprandial adiponectin and higher postprandial triglyceride, VLDL, and FFA in NASH patients	Italian	[155]
	45 G, 276 G	Higher prevalence of NAFLD, severe fibrosis and insulin resistance in females	Japanese	[156]
<i>ADIPOR1</i>	-8503 A, -1927 C	Lower insulin sensitivity and higher liver fat	German	[157]
<i>ADIPOR2</i>	rs767870 T	Increased hepatic fat and biochemical surrogates of NAFLD	Finnish	[158]
<i>PPAR-γ</i>	161 T	Higher susceptibility of NAFLD	Chinese	[159]
<i>PPARGC1A</i>	rs2290602 T	Higher occurrence of NAFLD	Japanese	[160]
<i>PPAR-α</i>	Val227	Higher prevalence of NAFLD and anthropometrical indicators of obesity	Chinese	[161]
<b>Oxidative stress</b>				
<i>GCLC</i>	-129 T	Higher prevalence of NASH	Brazilian	[162]
<i>NOS2</i>	rs1060822 T	Higher fibrosis index in NAFLD patients	Japanese	[163]
<i>SOD2</i>	1183 T	Higher prevalence of NASH	Japanese	[152]
<b>Immune response mediators</b>				
<i>STAT3</i>	rs6503695 T, rs9891119 A	Higher prevalence of NAFLD	Argentinean	[164]
<i>TNF-α</i>	-238 A	Higher prevalence of NAFLD and NASH	Italian, Chinese	[165,166]
<i>IL-8</i>	-251 A	Disease progression in NASH	Turkish	[167]
<i>IL-6</i>	-174 C	Higher risk for NAFLD and NASH	Italian	[168]
<i>MTHFR</i>	1298 C, 677 C	Higher prevalence of NASH	Turkish	[169]
<i>HFE</i>	282 Y	More hepatic fibrosis in NASH patients. Higher prevalence of NAFLD	Australian	[170-172]
<i>ABCC2/MRP2</i>	rs17222723 T, rs8187710 A	NAFLD disease severity	Argentinean	[173]
<i>AGTR1</i>	rs3772633 G, rs3772627 C, rs3772622 A	Higher prevalence of NASH	Japanese	[174]

NAFLD: Nonalcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis.

Mexico because the average age of death from HCC is at least one or two decades after the clinical diagnosis of LC<sup>[98]</sup>. Similarly, epidemiological studies have indicated a positive correlation between liver cancer and the consumption of several foodstuffs contaminated with aflatoxins and fumonisins, including maize, cereals, ground nuts and tree nuts<sup>[99]</sup>. These mycotoxins are potent liver carcinogens through the formation of pro-mutagenic DNA adducts. Nonetheless, the process of "nixtamalization" in the elaboration of Mexican tortillas since pre-Hispanic times<sup>[100]</sup> inactivates up to 95% of aflatoxins in corn (maize), which may exert a protective effect against the development of HCC<sup>[101]</sup>.

## EPIGENETIC FACTORS

Epigenetic changes affect gene expression without altering the underlying DNA sequence<sup>[102]</sup>. These changes include DNA methylation, histone modifications, chromatin remodeling, and microRNAs (miRs), which

are essential for the proper maintenance of cellular homeostasis<sup>[103]</sup>. However, such processes are regulated by environmental factors, including diet, alcohol, drugs, exercise and stress<sup>[104]</sup>. Growing evidence suggests that epigenetic alterations are correlated with a wide range of chronic disorders, including liver diseases. Diverse miRs have been implicated in the development and progression of NAFLD by disrupting lipid and glucose metabolism, insulin resistance, the unfolded protein response, mitochondrial damage, ER stress, oxidative stress, cellular differentiation, inflammation and apoptosis<sup>[105,106]</sup>. Moreover, the reduction of histone expression promotes the differentiation of HSCs to myofibroblasts, thereby enhancing the fibrogenesis process<sup>[107]</sup>. Interestingly, alcohol directly stimulates changes in chromatin structure, which induces the trans-differentiation of HSCs and the increased expression of ECM proteins<sup>[108]</sup>. Global DNA hypomethylation and the dysregulated expression of non-coding RNAs and epigenetic regulatory genes have

been found to trigger carcinogenesis of hepatocytes<sup>[109]</sup>. Taken together, these findings support the need to evaluate epigenetic factors in distinct populations and their relationship to the severity of liver damage.

## CONCLUSION

LC is a complex disease. The onset, progression, and clinical outcome of LC are influenced by genetic polymorphisms that are associated with particular ethnic backgrounds and their interaction with environmental factors, such as lifestyle. Currently, chronic alcohol abuse is the main etiological factor of LC in Mexico, which is associated mainly with cultural and genetic aspects. To date, HCV genotypes 1a and 1b favor chronicity, liver damage and therapeutic failure among Mexicans. In contrast, the more favorable natural course of HBV infection in the native Mexican population may be linked to an evolutionary immune adaptation to HBV genotype H. Finally, the hepatopathogenic diet and the high prevalence of obesity in our population contribute to the onset and progression of NAFLD. These findings highlight the influence of genetic and environmental factors in the development of LC, which may be different than those reported in other regions of the world. Therefore, these factors represent a challenge for hepatologists and gastroenterologists in Mexico and worldwide because they require the incorporation of personalized genomic medicine into current medical practices. However, the development of intervention strategies according to individual or population-based features will have a substantial impact on the prevention, management and treatment of LC.

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ISSN 1007-9327

