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Genetic Polymorphisms Associated with Liver Disease Progression in HIV/HCV-Coinfected Patients

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Abstract

The pathogenic mechanisms of the accelerated progression of liver injury in HIV/HCV coinfection are incompletely understood. The progression of liver disease is variable between individuals having similar risk factors, suggesting that genetic background is an important contributor. The aim of this review is to give a summary of all single nucleotide polymorphisms associated with the severity of liver disease in patients coinfected with HIV and HCV reported in the literature. Therefore, a systematic search for articles published was made, 17 of which were selected for this review. In summary, a large number of single nucleotide polymorphisms have been associated with the severity of liver disease in HIV/HCV-coinfected patients. These genes are involved in different biological processes, including seven that correspond to cytokine genes* (IFNL3-4, CXCL9-11, IL15, TNF), *two to receptor genes* (IL7R, TLR8), *and three are genes related to metabolism* (PNPLA3, FTO, GSTM1). *In addition, two combinations of polymorphisms (cirrhosis risk score and mitochondrial haplogroups) have also been related to severity of liver disease in HIV/HCV-coinfected patients. Although determinants other than genetics, such as environmental and viral factors, may be implicated in liver disease progression, information about genetic variation might be useful in clinical practice, allowing prioritization of patients with a genetic background that predispose to a worse evolution of HCV-related liver disease. **(AIDS Rev. 2017;19:3-15)**

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Key words

Genetic polymorphism. HCV/HIV coinfection. Liver fibrosis. Cirrhosis. Liver-related disease.

Introduction

Hepatitis C virus (HCV) infection affects nearly 150 million people worldwide and is a leading cause of chronic liver disease, ranging from mild chronic hepatitis to end-stage cirrhosis and hepatocellular carcinoma[1]. In these patients, coinfection with HIV is quite common (20-30% worldwide)[2]. The success of combination antiretroviral therapy has made chronic hepatitis C (CHC) an important comorbidity and a major cause of death in HIV/HCV-coinfected patients[3,4]. Additionally, HIV infection modifies the natural history of CHC in HIV/HCV-coinfected patients, with a higher probability of liver fibrosis progression, cirrhosis, and end-stage liver disease than in HCV-monoinfected patients[5,6]. Roughly 34% of patients increase at least one METAVIR fibrosis stage over 2.5 years[7].

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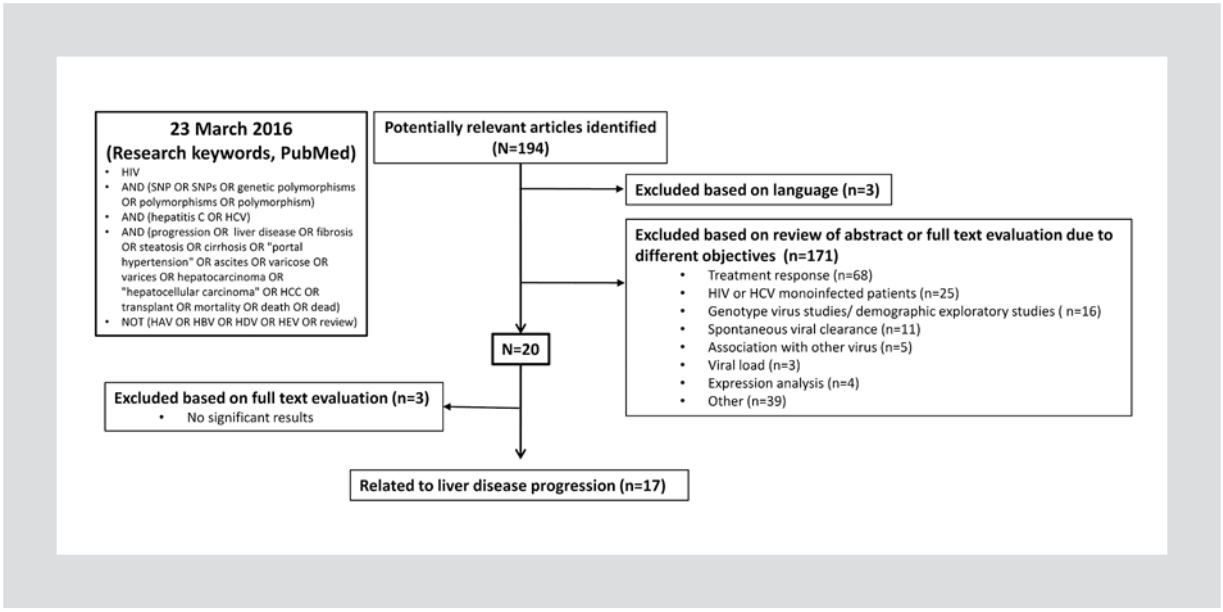

Figure 1. *Flow-chart of systematic search of articles included in this review. SNP: single nucleotide polymorphism.*

The pathogenic mechanisms of the accelerated progression of liver injury in HIV/HCV coinfection are incompletely understood. Immunity has a crucial role in HCV persistence and tissue damage during CHC[8]. The interferons (IFN) are the central cytokines involved in this process, and are able to induce an antiviral state by the transcription activation of hundreds of genes denominated IFN-stimulated genes. The IFN-stimulated genes show antiviral effect across different steps of the viral life cycle, but they also induce activation of the immune system and increase the degree of liver inflammation. Moreover, enhanced oxidative stress may also increase profibrogenic cytokine expression and secretion. Thus, the elevated expression of proinflammatory cytokines in the liver may promote fibrosis development[5].

In recent years, the development of direct-acting antivirals (DAA) as therapy for HCV infection has allowed to achieve increased efficacy, shorter treatment periods, and decreased adverse events in HIV/HCV-coinfected patients[9]. However, the current high cost of these mediations is limiting their availability in all countries and across all liver fibrosis stages. Consequently, it is very important to predict the progression of liver disease in order to prioritize the administration of DAAs. A helpful strategy is to pinpoint genetic biomarkers that are able to predict disease progression to prioritize the administration of DAAs in those patients more susceptible to have a worse prognosis.

The progression of liver disease is variable between individuals with similar risk factors, suggesting that a genetic background is an important contributor[10]. Apart from the well-known single nucleotide polymorphisms (SNP) around the *interleukin 28B (IL28B)* gene[11], other SNPs have also been shown to have an important role[12]. The aim of this review is to give a summary of all SNPs associated with the severity of liver disease in HIV/HCV-coinfected patients that have been described in the literature. Therefore, a systematic search for articles published was made, 17 of which were selected for this review (Fig. 1).

Markers of severity of liver disease in chronic hepatitis C

Hepatic biopsy is the classic "gold standard" to diagnosis CHC. It allows measuring the necroinflammatory activity grade and the stage of fibrosis and steatosis. Several scoring systems have been proposed for assessing liver injury and there is no general consensus on the best system. One of the most widely used is the METAVIR score[13], which has a 5-point fibrosis scale from F0 (no fibrosis) to F4 (cirrhosis) and 4-point necroinflammatory activity scale from A0 (no activity) to A3 (severe activity). Moreover, steatosis is common in HIV/HCV-coinfected patients[14], and has been linked to higher liver fibrosis

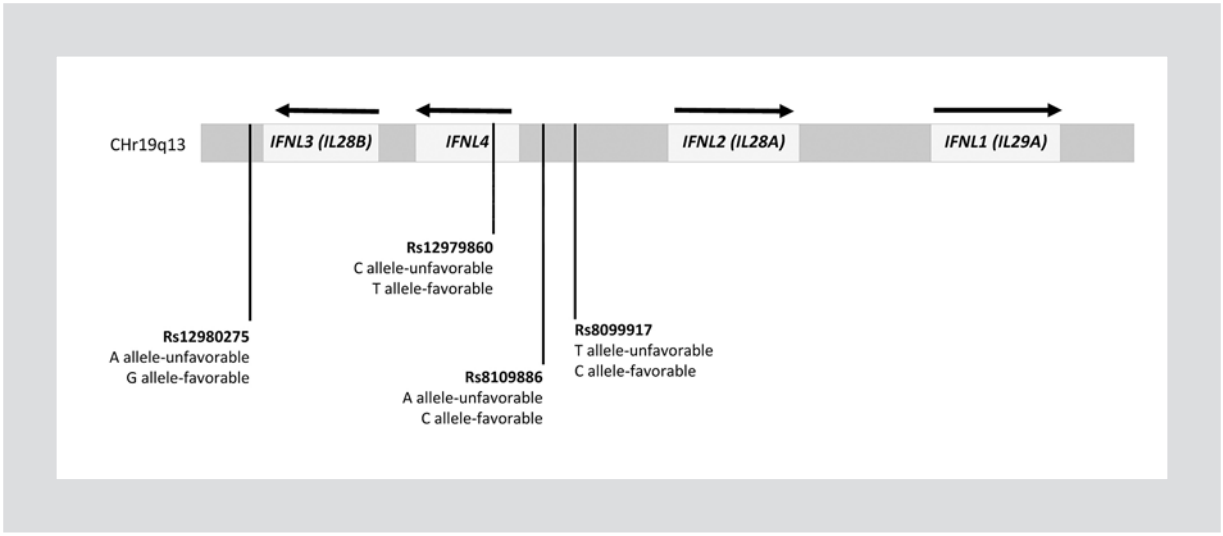

Figure 2. *Interferon (IFN)-λ3 and IFN-λ4 variants on chromosome 19, which have been related to severity of liver disease in HIV/HCV-coinfected patients.*

progression rates[15]. Frequently, steatosis is evaluated according to the existence of hepatocytes containing visible macrovesicular fat droplets (> 10%). However, liver biopsy is associated with several drawbacks such as invasiveness, sampling error, cost, and inter/intra-observer variability.

Nowadays, several non-invasive diagnostic methods have been developed for determining liver fibrosis, including the aspartate aminotransferase-to-platelet ratio index (APRI), FIB-4 index, and transient elastography (FibroScan)[16]. The most widely studied indirect fibrosis marker is the APRI, which provides an accurate assessment of significant fibrosis and cirrhosis in HCV-monoinfected patients[17] and is slightly less accurate in HIV/HCV-coinfected patients[18]. The APRI cutoff for the correct identification of at least significant fibrosis (F ≥ 2) is APRI ≥ 1.5[17]. The FIB-4 score was developed to correctly identify advanced fibrosis (F ≥ 3) in HIV/HCV-coinfected patients, and it is calculated with regard to age, platelet count, aspartate aminotransferase (AST), and alanine aminotransferase (ALT)[19]. The FIB-4 cutoff for the correct identification of patients with at least advanced fibrosis (F ≥ 3) is FIB-4 ≥ 3.25[19]. Transient elastography quantifies the liver stiffness by an elastic shear wave passing through liver tissue. Liver stiffness is expressed as kilopascals (kPa) and correlates with fibrosis stage in CHC[20]. Transient elastography is the best validated of the non-invasive techniques, with excellent accuracy for detecting advanced fibrosis and cirrhosis in HIV/HCV-coinfected patients[16]. Several cut-offs have been proposed for the different stages of fibrosis, although no general consensus has been reached.

Genetic polymorphisms at genes of cytokines and chemokines

IFNL3 and IFNL4 polymorphisms

In recent years, a large number of SNPs around the *IL28B* gene (in both the interferon lambda 3 *[IFNL3* or *IL28B]* and the interferon lambda 4 *[IFNL4]* gene) have been described as predictors of spontaneous HCV clearance and CHC treatment outcome[11,21]. Thus, *IFNL3* and *IFNL4* polymorphisms seem to be related to stronger immune response, which could be mediating a certain protective effect against HCV infection, but also they could promote greater liver damage associated to higher expression of inflammatory cytokines and more rapid fibrosis progression[22,23].

Only four polymorphisms (rs8109886, rs12979860, rs12980275, rs8099917) have been associated with severity of liver disease in HIV/HCV-coinfected patients (Table 1), all of them around the *IFNL3* and *IFNL4* genes (Fig. 2).

rs12979860

The rs12979860 polymorphism is located within the first intron of *IFNL4* (Fig. 2). This gene encodes for a

Table 1. Genetic polymorphisms at genes of cytokines and chemokines associated with severity of liver disease in HIV/HCV-coinfected patients

Gene	Chr. location	SNP	Prot./Risk allele	Location	Outcome	Ethnicity	HCV-GT	Reference
IFNL4	19q13.2	rs12979860	T/C	intron 1	ALT	Caucasian	1, 3, 4	[25,26]
					AST	Caucasian	1, 4	[26]
					APRI	Caucasian	1, 4	[26]
					Liver stiffness	Caucasian	1	[27]
					Cirrhosis (F4)	Caucasian	1, 3, 4	[25]
IFNL3	19q13.13	rs12980275	G/A	downstream	ALT	Caucasian	3	[28]
					Significant fibrosis (F ≥ 2)	Caucasian	3	[28]
					Fibrosis progression	Caucasian	3	[28]
					Steatosis	Caucasian	1	[28]
					Liver-related death	African American		[32]
IFNL3/IFNL4	19:39252525	rs8099917	G/T	Intergenic	ALT	Caucasian	3	[28]
					Significant fibrosis (F ≥ 2)	Caucasian	3	[28]
					Fibrosis progression	Caucasian	3	[28]
					Steatosis	Caucasian	1	[28]
					APRI (≥ 1.5)	Caucasian	1, 2, 3, 4	[33]
IFNL4	19:39252122	rs8109886	A/G	Upstream	Liver-related death	African American		[32]
CXCL9	4q21.2	rs10336	C/T	3´UTR	APRI	Caucasian	1	[43]
					FIB-4	Caucasian	1	[43]
					Significant fibrosis (F ≥ 2)	Caucasian	1	[43]
					Activity grade	Caucasian	1	[43]
CXCL10	4q21.2	rs3921	C/G	3´UTR	APRI	Caucasian	1	[43]
					FIB-4	Caucasian	1	[43]
					Significant fibrosis (F ≥ 2)	Caucasian	1	[43]
					Activity grade	Caucasian	1	[43]
CXCL11	4q21.2	rs4619915	G/A	3´UTR	APRI	Caucasian	1	[43]
					FIB-4	Caucasian	1	[43]
					Significant fibrosis (F ≥ 2)	Caucasian	1	[43]
					Activity grade	Caucasian	1	[43]
IL15	4q31	rs10833	G/A	3´UTR	Advanced fibrosis (F ≥ 3)	Caucasian	1, 2, 3, 4	[46]
TNF-alpha	6p21.3	rs361525	A/G	upstream	Advanced fibrosis (F ≥ 3)	Caucasian	1,4	[48]
					Cirrhosis (F4)	Caucasian	1, 4	[49]

Chr: chromosome; SNP: single nucleotide polymorphism; Prot: protective; GT: genotype; ALT: alanine aminotransferase; AST: aspartate aminotransferase; IFNL: interferon lambda; CXCL: chemokine (C-X-C motif) ligand; IL: interleukin; TNF: tumor necrosis factor; APRI: AST/platelet ratio; FIB-4: fibrosis-4 score; UTR: untranslated region.

protein of moderate similarity with *IFNL3,* which also induces IFN-stimulated genes and generates antiviral response in hepatoma cells[24]. The major allele (C) of rs12979860 has been related to increased values of ALT, AST, and APRI. The rs12979860 CC carriers had higher ALT levels in two cohorts of Spanish HIV/HCV-coinfected patients[25,26]. Regarding AST, patients with rs12979860 CC genotype had higher AST levels, whereas rs12979860 CT/TT genotype was a protective factor[26]. Furthermore, the rs12979860 CC genotype has been associated with higher odds of having values of APRI ≥ 1.5, while the rs12979860 CT/TT genotype was protective against APRI ≥ 1.5 (OR: 0.03; 0.002-0.41)[26]. Only Lutz, et al. did not find a significant association of rs12979860 genotypes with ALT and APRI levels in HIV/HCV-coinfected patients, probably due to the reduced number of patients (n = 86) and the fact that they only tested the genetic additive model and not the dominant[27].

The rs12979860 CC genotype has also been related to liver cirrhosis (F4) in HIV/HCV-coinfected patients. Barreiro, et al. found that rs12979860 CC genotype was associated with a higher odds of cirrhosis (> 14.5 kPa; F = 4; OR: 2.32; 1.22-4.41)[25]. However, in a longitudinal study over 25 months, Lutz, et al. found that liver stiffness in HIV/HCV-coinfected patients with the *IFNL4* rs12979860 C allele did not show further progression, while liver stiffness slightly increased in T allele carriers infected with HCV-GT1[27].

rs12980275

The rs12980275 polymorphism is located downstream of the *IL28B* gene (Fig. 2). Guzmán-Fulgencio, et al.[28] showed that patients with rs12980275 A allele had higher odds of having significant fibrosis (F ≥ 2; OR: 6.3; 1.5-26.4) and higher fibrosis progression (fibrosis progression rate ≥ 0.075 fibrosis units/years; OR: 1.64; 1.03-2.61). In addition, considering the HCV genotype, patients infected with HCV-GT3 and with rs12980275 A allele had higher odds of having values of ALT ≥ 80 IU/l (OR: 4.12; 1.09-15.6) and reduced odds for liver steatosis (OR: 0.22; 0.09-0.50) in HCV-GT1 patients. This last finding, though it might seem counterintuitive, is in agreement with a previous study in HCV-monoinfected Japanese patients[29], and it could have important clinical implications because persistent fatty liver disease may be a problem for HCV-GT1 patients with rs12980275 G allele even with successful HCV clearance[30,31]. In another study, Sarkar, et al. found also a protective effect of rs12980275 G allele in a cohort of HIV/HCV-coinfected women from different ethnicities[32]. The rs12980275 GG genotype was associated with lower risk of liver-related death (including hepatic decompensation or hepatocellular carcinoma) (adjusted hazard ratio [aHR] = 0.36; 0.14-0.90). Moreover, the rs12980275 G allele showed a higher frequency in African American women, which is in accordance with the slower fibrosis progression of these patients.

rs8099917

The rs8099917 polymorphism is located upstream of the *IFNL4* gene (Fig. 2). Guzmán-Fulgencio, et al.[28] have also found that the rs8099917 T allele was related to higher odds of attaining values of ALT ≥ 80 IU/l (OR: 1.78; 1.01-3.17), significant fibrosis (F ≥ 2; OR: 1.93; 1.11-3.60) and rapid fibrosis progression rate (FPR: ≥ 0.075 fibrosis units/years; OR: 2.08; 1.12-3.88). Besides, considering the HCV genotype, patients infected with HCV-GT1 and with rs8099917 T allele also had reduced odds for liver steatosis (OR: 0.39; 0.16-0.99). In another article, Moqueet, et al. observed that individuals who had developed significant fibrosis (APRI ≥ 1.5) were also more likely to carry rs8099917 TT genotype compared to patients that carry rs8099917 TG/GG genotype (aHR: 1.79; 1.24-2.57)[33].

rs8109886

The rs8109886 polymorphism is located upstream of the *IFNL4* gene (Fig. 2). The rs8109886 AA genotype was associated to a lower risk of liver-related death (aHR: 0.67; 0.45-0.99) in 794 coinfected women from three different ethnicities (African American, Caucasian, and Hispanic), but this association was no longer significant after adjusting for ethnicity[32].

CXCL9-11 polymorphisms

The chemokines such as the IFN-gamma-inducible protein (IP-10/CXCL10), IFN-gamma-induced monokine (MIG/CXCL9), and IFN-inducible T-cell alpha chemo attractants (I-TAC/CXCL11) may promote the lymphocyte migration from the periphery to liver parenchyma, causing the development of liver fibrosis in response to HCV infection[34]. In fact, high serum CXCL9-11 levels have been related to a higher degree of hepatic damage and are able to predict fibrosis stage in patients infected with HCV-GT1 in

Table 2. Genetic polymorphisms at receptor genes associated with severity of liver disease in HIV/HCV-coinfected patients

Gene	Chr. location	SNP	Prot./Risk allele	Location	Outcome	Ethnicity	HCV-GT	Reference
IL7R	5p13	rs3194051	A/T	exon 8, missense	APRI	Caucasian	1, 2, 3, 4	[58]
					FIB-4	Caucasian	1, 2, 3, 4	[58]
					Advanced fibrosis (F ≥ 3)	Caucasian	1, 2, 3, 4	[58]
	5p13	rs987106	A/T	intron 6	Advanced fibrosis (F ≥ 3)	Caucasian	1, 2, 3, 4	[58]
	5p13	rs6897932	T/C	exon 6	Activity grade	Caucasian	1, 2, 3, 4	[58]
TLR8	Xp22	rs3764880	G/A	exon 1, missense	Non-progression (F0)	Caucasian	1	[69]
	Xp22	rs1013151	T/C	intron 2	Non-progression (F0)	Caucasian	1	[69]
	Xp22	rs5744069	T/G	intron 2	Non-progression (F0)	Caucasian	1	[69]

Chr: chromosome; SNP: single nucleotide polymorphism; Prot: protective; GT: genotype; IL7R: interleukin-7 receptor; TLR8: toll-like receptor 8; APRI: AST/platelet ratio; FIB-4: fibrosis-4 score.

HCV-monoinfected and HIV/HCV-coinfected patients[35-37]. The *CXCL9-11* genes are located on human chromosome 4 in a cluster among several CXC chemokine genes[38]. The SNPs in this region are in strong linkage disequilibrium and have been related to severity of viral infections such as enterovirus-71[39], hepatitis B[40,41], and hepatitis C[42].

Pineda-Tenor, et al. (Table 1) reported that the homozygosity for minor alleles at *CXCL9* rs10336 (T), *CXCL10* rs3921 (G), and *CXCL11* rs4619915 (A) was linked to higher values of APRI and FIB-4, and higher odds of achieving values of APRI ≥ 1.5 and FIB-4 ≥ 3.25 in HIV/HCV-coinfected patients[43], particularly in patients infected with HCV-GT1. They also observed that patients infected with HCV-GT1 and with rs10336 TT, rs3921 GG, and rs4619915 AA had higher odds of having significant fibrosis (F ≥ 2) and severe activity grade (A3). Besides, the TGA haplotype (unfavorable alleles) was related to higher odds of having values of APRI ≥ 1.5 and FIB-4 ≥ 3.25, and having significant fibrosis (F ≥ 2) and severe activity grade (A3)[43].

IL15 polymorphisms

Another gene associated with advanced fibrosis is interleukin 15 *(IL15),* which is essential for the activation and function of cells involved in the response against HCV infection[44]. The IL15 has been related to inflammatory response in HIV/HCV-coinfected patients, where its expression has been positively associated with immune activation in peripheral T-cells and hepatic stellate cells[45].

Jimenez-Sousa, et al. (Table 1) reported that patients with *IL15* rs10833 AA genotype had increased odds of developing advanced fibrosis (aOR: 2.30; 1.15-4.61), mainly in males (aOR: 2.24; 1.04-4.86), patients with HCV RNA < 500,000 IU/ml (aOR: 5.14; 1.32-19.8), and patients with *IL28B* rs12980275 AG/GG genotypes (aOR: 2.51; 1.02-6.20)[46]. Furthermore, the rs10833 AA genotype was also associated with higher serum levels of HGF, sICAM-1, and sVCAM-1 than AG/GG carriers. The *IL15* rs10833 polymorphism, located at the 3´UTR region, could be part of micro RNA (miRNA) binding sites. The authors observed by *in silico* analyses that rs10833 A allele generates putative target sites for several miRNAs, whereas the presence of rs10833 G allele disrupts these target sites and generates others. Therefore, the rs10833 polymorphism might play an important role in regulatory mechanisms.

TNF-alpha polymorphisms

Tumor necrosis factor alpha (TNF-α) seems to affect liver fibrosis by stimulating hepatic stellate cells[47]. Two polymorphisms at *TNF*-α have been studied (rs361525 and rs1800629) in relation to liver disease in HIV/HCV-coinfected patients, but only rs361525 (G > A) was significantly associated with liver fibrosis

and cirrhosis (Table 1)[48,49]. This SNP consists of a G to A substitution at position –238 in the proximal promoter of the TNF-α gene, which seems to affect TNF-α transcriptional activity[50]. In a first study, Corchado, et al. found patients with the rs361525 GG genotype, which showed significantly higher values of liver stiffness than those with genotypes GA/AA ($p < 0.001$)[48]. A second study performed in Caucasian patients by the same research group showed patients carrying rs361525 GG allele, which had higher frequency of cirrhosis (97 vs. 77%; $p=0.025$)[49]. However, there are some controversial results about these findings in HCV-monoinfected patients because rs361525 A allele has been associated with a higher risk of cirrhosis[51] and other authors did not find any association[52].

Genetic polymorphisms located on receptor genes

IL7R polymorphisms

Interleukin-7 (IL-7) is required for T-cell development, maintaining and restoring homeostasis of mature T-cells, and it is a critical factor in maintaining or inducing an effective antiviral $CD4^+$ and $CD8^+$ T-cell response[53]. The responsiveness of IL-7 is dependent on the expression of the IL-7 receptor *(IL7R)*. Several *IL7R* polymorphisms seem to affect the expression of *IL7R* and the immune response[54], particularly in HIV infection[55-57].

Guzman-Fulgencio, et al. have described an association between *IL7R* SNPs and severity of liver disease (Table 2)[58]. The homozygosis for major rs3194051 A allele has been associated with higher APRI values (OR: 2.52; 1.10-5.77) and values of FIB-4 (≥ 3.25; OR: 4.01; 1.17-13.71) in HIV/HCV-coinfected patients[58]. Moreover, the *IL7R* polymorphisms are also among those that are related to severity of liver disease in hepatic biopsy. The T allele at rs987106 and G allele at rs3194051 on *IL7R* gene were associated with higher odds of having advanced fibrosis (F ≥ 3; OR: 3.09; 1.32-7.22 and OR: 2.73; 1.22-5.87, respectively). Furthermore, the authors found that *IL7R* rs6897932 CC genotype was associated with higher odds of having severe activity necroinflammatory grade (A3; OR: 4.16; 1.19-14.59)[58].

The rs987106 TT, rs3194051 GG, and rs6897932 CC genotypes have been associated to higher plasma levels of the soluble isoform of IL7R (sCD127)[59,60]. Thus, elevated levels of sCD127 in plasma limit the bioavailability of circulating IL7 levels, and therefore reduce IL7 effects on development, survival, and proliferation of $CD4^+$ T-cells. Furthermore, unfavorable alleles of these three *IL7R* polymorphisms (rs6897932 C, rs987106 T, rs3194051 A) have been related to low $CD4^+$ T-cells and rapid AIDS progression in Caucasian naive HIV-infected patients[61]. In this regard, low CD4 counts are associated with accelerated liver fibrosis progression in HIV/HCV-coinfected patients[62]. Thus, it is possible that unfavorable *IL7R* genotypes (rs6897932 CC, rs987106 TT, rs3194051 AA) could lead to an increased risk of severe liver disease due to regulation of sCD127 levels by decreasing $CD4^+$ cells count and enhancing AIDS progression in HIV/HCV-coinfected patients[63].

TLR8 polymorphisms

Toll-like receptors (TLRs) are highly conserved sensors of microbial and endogenous danger signals, which play a key role in HCV recognition and activation of innate immunity[64]. In particular, TLR8 seems to be critical for clarifying RNA viruses. The *TLR8* gene is located at chromosome X, and encodes for an intracellular receptor that recognizes double-stranded RNA from viruses in endosomal compartments. The TLR8 has been related to an altered innate immune response and susceptibility to HCV infection[65,66] and progression of HIV disease[67,68].

Three *TLR8* polymorphisms (rs3764880, rs1013151, rs5744069) were related to non-fibrosis (F0), mainly in men coinfected with HIV and HCV-GT1 (Table 2). Fernandez-Rodriguez, et al.[69] found that the rs3764880 G allele was a protective allele on fibrosis progression in patients coinfected with HIV and HCV-GT1 (OR: 5.65; 1.26-25.36), possibly due to a putative enhanced immune activation and a better control of HCV infection. Another two polymorphisms, rs1013151 and rs5744069, were also associated to non-fibrosis (F0) both in male patients (OR: 4.49; 1.08-18.62 and OR: 6.17; 1.45-26.20, respectively) and HCV-GT1 patients (OR: 5.79; 1.44-23.32 and OR: 8.01; 2.16-35.65, respectively).

The *TLR8* rs3764880 is a missense polymorphism located at exon 1 that modifies the start codon and it results in a different TLR8 isoform with a shorter signal peptide[68], which seems to be related to increased expression of TLR8 and NF-kappa B activation[70]. The *TLR8* rs1013151 located at intron 2 seems to harbor different transcription start sites depending on the

Table 3. Genetic polymorphisms at genes related to metabolism that have been associated with severity of liver disease in HIV/HCV-coinfected patients

Gene	Chr. location	SNP	Prot./Risk allele	Location	Outcome	Ethnicity	HCV-GT	Reference
PNPLA3	22q13.31	rs738409	C/G	exon 3, missense	FIB-4	Caucasian	1, 2, 3, 4	[74]
					Advanced fibrosis (F ≥ 3)	Caucasian	1, 2, 3, 4	[74]
FTO	16q12.2	rs9939609	T/A	intron 1	Significant fibrosis (F ≥ 2)	Caucasian	1, 2, 3, 4	[77]
					Steatosis	Caucasian	1, 2, 3, 4	[77]
Haplogroup U*								
MT-CO3	9504	T9504C	Non-U/U	Mitochondria	Cirrhosis (F4)	Caucasian	1, 2, 3, 4	[84]
MT-ND3	10398	A10398G	Non-U/U	Mitochondria	Cirrhosis (F4)	Caucasian	1, 2, 3, 4	[84]
MT-ND4	10873	T10873C	Non-U/U	Mitochondria	Cirrhosis (F4)	Caucasian	1, 2, 3, 4	[84]
MT-ND5	12705	T12705C	Non-U/U	Mitochondria	Cirrhosis (F4)	Caucasian	1, 2, 3, 4	[84]
tRNA Leu	12308	A12308G	Non-U/U	Mitochondria	Cirrhosis (F4)	Caucasian	1, 2, 3, 4	[84]
Haplogroup H†								
MT-CO3	9504	T9504C	H/Non-H	Mitochondria	Advanced fibrosis (F ≥ 3)/ FPR	Caucasian	1, 2, 3, 4	[84]
MT-ND3	10398	A10398G	H/Non-H	Mitochondria	Advanced fibrosis (F ≥ 3)/ FPR	Caucasian	1, 2, 3, 4	[84]
MT-ND4	10873	T10873C	H/Non-H	Mitochondria	Advanced fibrosis (F ≥ 3)/ FPR	Caucasian	1, 2, 3, 4	[84]
MT-ND5	12705	T12705C	H/Non-H	Mitochondria	Advanced fibrosis (F ≥ 3)/ FPR	Caucasian	1, 2, 3, 4	[84]
MT-Cytb	14766	T14766C	H/Non-H	Mitochondria	Advanced fibrosis (F ≥ 3)/ FPR	Caucasian	1, 2, 3, 4	[84]
MT-ND2	4580	G4580C	H/Non-H	Mitochondria	Advanced fibrosis (F ≥ 3)/ FPR	Caucasian	1, 2, 3, 4	[84]
MT-COI	7028	T7028C	H/Non-H	Mitochondria	Advanced fibrosis (F ≥ 3)/ FPR	Caucasian	1, 2, 3, 4	[84]
GSTM1	1p13.3	Null genotype	Null genotype	Not mentioned	Oxidative stress	Caucasian African	–	[86]

*T9504C, A10398G, T10873C, T12705C ,A122308G mitochondrial DNA polymorphisms belong to haplogroup U.
†T9504C, A10398G, T10873C, T12705C, T14766C, G4580C, T7028C mitochondrial DNA polymorphisms belong to haplogroup H.
Chr: chromosome; SNP: single nucleotide polymorphism; Prot: protective; GT: genotype; MT-CO3: mitochondrially encoded cytochrome c oxidase III; MT-ND: mitochondrially encoded NADH dehydrogenase; MT-COI: mitochondrially encoded cytochrome c oxidase I; MT-Cytb: mitochondrially encoded cytochrome b; MT-tRNA: mitochondrially encoded tRNA; PNPLA3: patatin-like phospholipase domain-containing 3; FTO: fat mass and obesity; FPR: fibrosis progression rate.

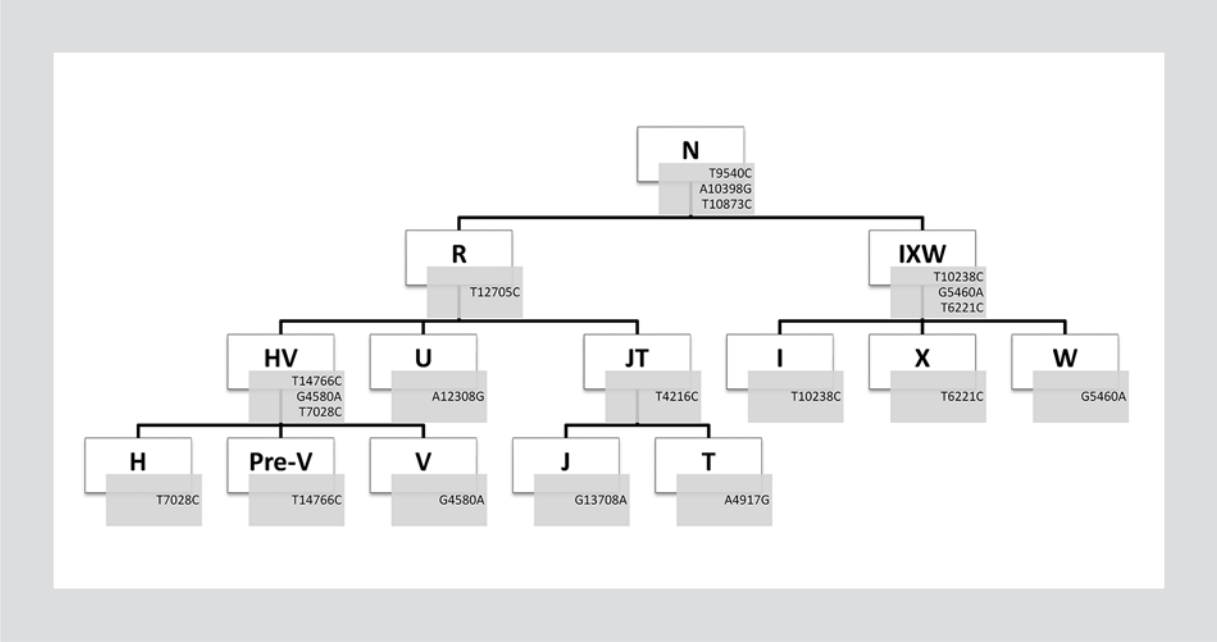

Figure 3. *List of European mitochondrial DNA (mtDNA) haplogroups with their defining mutation.*

present allele[71]. Dissimilar transcription factors related to fibrosis may bind to alternative alleles, which could affect *TLR8* expression[69]. The rs5744069, which is located at intron 2, may generate a target site for the myocyte enhancer factor 2 (MEF2) when the risk allele G is present.

Genetic polymorphisms at genes related to metabolism

PNPLA3 polymorphisms

Polymorphisms at the patatin-like phospholipase domain-containing 3 *(PNPLA3)* gene have been related to liver fibrosis in chronic liver disease[72]. The *PNPLA3* gene, located on chromosome 22, encodes for a protein with lipase activity, which is highly expressed in the liver and adipose tissue. One missense polymorphism (rs738409) located at exon 3 generates an isoleucine to methionine substitution at position 148 of the protein (I148M). This modification results in a loss of PNPLA3 function, which seems to have implications in nonalcoholic steatohepatitis (NASH) and progressive liver fibrosis in HCV-infected patients[73].

Jimenez-Sousa, et al. described an association between *PNPLA3* rs738409 polymorphism and liver fibrosis in HIV/HCV-coinfected patients (Table 3). The *PNPLA3* rs738409 G allele was associated with higher odds of developing advanced fibrosis (FIB-4 ≥ 3.25; OR: 8.77; 1.11-69.0) and F ≥ 3 (OR: 2.15; 1.07-4.35) in HIV/HCV-coinfected patients[74], suggesting that this polymorphism might also play a significant role in the progression of hepatic fibrosis in this group of patients. However, they did not find any association for liver steatosis, possibly due to the fact that steatosis was defined as a dichotomous variable (fatty hepatocytes ≥ 10%).

FTO polymorphisms

The fat mass and obesity-associated *(FTO)* gene located on chromosome 16q12.2 encodes for a nuclear protein whose exact physiological function is unknown, although it seems to be involved in the management of energy homeostasis and in the regulation of body weight[75]. The rs9939609 polymorphism is located at the first intron of *FTO* gene, and the risk allele A, which displays an increased *FTO* expression[76], has been associated with metabolic disturbances (obesity, metabolic syndrome, insulin resistance, type 2 diabetes mellitus).

Pineda-Tenor, et al. described an association between *FTO* rs9939609 polymorphism and liver disease (Table 3). The rs9939609 AA genotype was associated with higher odds of having significant fibrosis (F ≥ 2;

Table 4. Genetic polymorphisms at genes related to cirrhosis risk score (Huang, et al.87), which has been associated with severity of liver disease in HIV/HCV-coinfected patients

Gene	Chr. location	SNP	Prot./Risk allele	Location	Outcome	Ethnicity	HCV-GT	Reference
AZIN	8q22.3	rs62522600	A/G	exon 12, synonymous	Mild fibrosis (F ≥ 1)	Caucasian	1, 2, 3, 4	[88]
TLR4	9q33.1	rs4986791	T/C	exon 4, missense	Mild fibrosis (F ≥ 1)	Caucasian	1, 2, 3, 4	[88]
TRPM5	11p15.5	rs886277	T/C	exon 9, missense	Mild fibrosis (F ≥ 1)	Caucasian	1, 2, 3, 4	[88]
AP3S2	15q26.1	rs2290351	G/A	exon 7	Mild fibrosis (F ≥ 1)	Caucasian	1, 2, 3, 4	[88]
STXBP5L	3q13.33	rs17740066	G/A	exon 19, missense	Mild fibrosis (F ≥ 1)	Caucasian	1, 2, 3, 4	[88]
AQP2	12q13.12	rs2878771	C/G	3´UTR	Mild fibrosis (F ≥ 1)	Caucasian	1, 2, 3, 4	[88]
LOC10192714	Chr1	rs4290029	C/G	exon 1	Mild fibrosis (F ≥ 1)	Caucasian	1, 2, 3, 4	[88]

Chr: chromosome; SNP: single nucleotide polymorphism; Prot: protective; GT: genotype; AZIN; antizyme inhibitor 1; TLR4: toll-like receptor 4; TRPM5: transient receptor potential cation channel subfamily M member 5; AP3S2: adaptor-related protein complex 3 sigma 2 subunit; STXBP5L: syntaxin binding protein 5 like; AQP2: aquaporin 2; LOC101927143: uncharacterized LOC101927143; UTR: untranslated region.

OR: 2.34; 1.02-5.36) and steatosis (OR: 3.65; 1.29-10.36) in a cohort of 261 Spanish HIV/HCV-coinfected patients[77]. Authors suggest that this association could be due to the metabolic disorders related to CHC, since the development of liver fibrosis is strongly associated with obesity/overweight, insulin resistance, and steatosis.

Mitochondrial haplogroups

Mitochondria are essential organelles that provide energy to eukaryotic cells via oxidative phosphorylation and regulate cellular survival via control of apoptosis, while playing a key role in the innate immune response against viral infections[78]. HIV and HCV lead to mitochondrial dysfunction, with increased production of reactive oxygen species (ROS)[79,80].

Mutations in mitochondrial DNA (mtDNA) have been acquired throughout human history, and thus the human population has been subdivided into a number of discrete mitochondrial clades or haplogroups, which are defined on the basis of specific mtDNA polymorphisms[81]. In European Caucasians, four major haplogroups or clusters (HV, U, JT, and IWX) and several minor haplogroups (H, V, pre-V, J, T, Uk, W, X, I, etc.) have been identified (Fig. 3)[81]. MtDNA haplogroups have been directly associated with susceptibility to disorders such as cancer, sepsis, diabetes, and degenerative diseases[82]. In HIV infection, mtDNA haplogroup H has been associated with a low likelihood of AIDS progression and/or severe immunodeficiency[83].

García-Álvarez, et al. described an association between mitochondrial haplogroups and progression of liver disease (Table 3). They found that haplogroup H, within the major haplotype HV, was strongly associated with reduced odds of advanced fibrosis (OR: 0.4; 0.18-0.91), cirrhosis (OR: 0.14; 0.03-0.67) and FPR (OR: 0.47; 0.23-0.95) in a cohort of Caucasian patients[84]. This haplogroup H is associated with higher ATP and ROS production, but the higher production of ROS could enhance the innate immunity and, thus, disease progression will be slower[85]. On the other hand, the major haplogroup U was also strongly associated with an increased odds of cirrhosis (OR: 5.25; 1.76-15.64). This haplogroup U (lower ATP and ROS production) has been related to disruption of oxidative phosphorylation complexes, antioxidant enzyme deficiency, and apoptosis[85].

GSTM1 null-allele

In addition, dysregulation of the redox system through mitochondrial transmembrane potential alteration has

been observed in coinfected patients, probably due to the viral replication via activation of nuclear factor kB and induction of apoptosis of $CD4^+$ T-cells[86]. In this respect, Parson, et al. explored the role of a well-known detoxification enzyme, the glutathione-S-transferase mu 1 *(GSTM1)* (Table 3). This gene, located at 1p13.3, encodes a cytosolic GST of the mu subfamily, which plays a role in the detoxification of the ROS. They found that "null genotype" at *GSTM1* (no transcription of functional copy) was associated to higher oxidative stress in HIV/HCV-coinfected patients, determined by oxidized glutathione, mitochondrial 8-oxo-dG and apoptosis markers[86].

Cirrhosis risk score

Fibrosis progression among HIV/HCV-coinfected patients is highly variable and difficult to predict due to multifactorial interactions between viral and host factors[5]. Host genetic factors may play an important role in fibrosis progression and a cirrhosis risk score (CRS), previously described for HCV-monoinfected patients[87], has been able to predict fibrosis/cirrhosis progression. The CRS signature uses the genetic information of seven SNPs (rs62522600, rs4986791, rs886277, rs2290351, rs17740066, rs2878771, rs4290029) located in different genomic regions *(AZIN, TLR4, TRPM5, AP3S2, STXBP5K, AQP2,* and an intergenic region downstream *DGS1,* respectively).

Fernández-Rodríguez, et al. evaluated this CRS in a cohort of HIV/HCV-coinfected patients (Table 4)[88]. They found that non-progressors (F0) had CRS values significantly lower than progressors ($F \geq 1$; 0.61 vs. 0.67; $p = 0.043$), but the CRS itself seems not to be a good marker for identifying HIV/HCV-coinfected patients who are at high risk of developing liver fibrosis. However, the CRS score coupled with clinical factors (age at HCV infection, IDU, gender, *IL28B* and HCV genotype) had values of area under the receiver operating characteristic curve (AUROC) of 0.739, and it might help to distinguish between non-progressor and progressor patients.

Conclusions

In summary, today a large number of SNPs have been associated with the severity of liver disease in HIV/HCV-coinfected patients. These genes are involved in different biological processes; seven genes correspond to cytokine genes *(IFNL3-4, CXCL9-11, IL15, TNF),* two to receptor genes *(IL7R* and *TLR8),* and three are genes related to metabolism *(PNPLA3, FTO, GSTM1).* In addition, two combinations of polymorphisms (CRS and mitochondrial haplogroups) have also been related to severity of liver disease in HIV/HCV-coinfected patients. Although other factors, such as environmental and viral factors, may be implicated in liver disease progression, the information about genetic variation might be useful in clinical practice. Thus, we could prioritize those patients with a genetic background that predispose to a worse evolution of HCV liver-related disease.

Declaration of interest

Al authors declare no conflicts of interest.

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