*SYSTEMATIC REVIEWS*

# Role of genetic polymorphisms in hepatitis C virus chronic infection

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## Abstract

**AIM:** To analyze the host genetics factors influencing the clinical course and the response to antiviral treatment in patients with chronic hepatitis C (CHC).

**METHODS:** We conducted an electronic search on the PubMed and MEDLINE (2000-2014) databases and Cochrane library (2000-2014). A total of 73 articles were retrieved and their data were extensively evaluated and discussed by the authors and then analyzed in this review article.

**RESULTS:** Several studies associated polymorphisms in the interleukin 28B gene on chromosome 19 (19q13.13) with a spontaneous viral clearance in acute hepatitis C and with the response to pegylated interferon (Peg-IFN)-based treatment in chronic hepatitis C patients. Other investigations demonstrated that inosine triphosphate pyrophosphatase genetic variants protect hepatitis C virus-genotype-1 CHC patients from ribavirin-induced anemia, and other studies that a polymorphism in the patatin-like phospholipase domain-containing protein 3 was associated with hepatic steatosis in CHC patients. Although not conclusive, some investigations suggested that the vitamin D-associated polymorphisms play an important role in the achievement of sustained virologic response in CHC patients treated with Peg-IFN-based antiviral therapy. Several other polymorphisms have been investigated to ascertain their possible impact on the natural history and on the response to treatment in patients with CHC, but the data are preliminary and warrant confirmation.

**CONCLUSION:** Several genetic polymorphisms seem to influence the clinical course and the response to antiviral treatment in patients with CHC, suggesting individualized follow up and treatment strategies.

**Key words:** Single nucleotide polymorphism; Hepatitis

C virus infection; Interleukin 28B; Inosine triphosphate pyrophosphatase; Patatin-like phospholipase domain-containing protein 3

**Core tip:** Some single nucleotide polymorphisms have been associated with the clinical presentation and/or response to antiviral treatment in subjects with chronic hepatitis C (CHC). In this review article the effect of old and new host genetics factors [interleukin 28B, inosine triphosphate pyrophosphatase, patatin-like phospholipase domain, cannabinoid receptor type 2 (CB2-63), vitamin D associated polymorphisms, *etc.*] on the outcome of CHC and the response to antiviral treatment will be presented, analyzed and discussed, to provide some guidance for individualized therapies in clinical practice.

## INTRODUCTION

The World Health Organization estimates that 130-170 million people are infected with hepatitis C virus (HCV) worldwide and that more than 350000 people die of HCV-related liver diseases each year[1]. In addition, HCV chronic infection is recognized as the most common cause of end-stage liver diseases in Western countries[2]. Primary infection causes asymptomatic acute hepatitis C (AHC) in most cases, which, however, progresses to chronicity in about two thirds of the cases, whereas about one third clear the virus spontaneously and recover[3-9]. Patients with chronic hepatitis C (CHC) frequently show the increasing severity of liver fibrosis over time, which leads to liver cirrhosis in nearly a quarter of cases. Hepatocellular carcinoma (HCC) develops in HCV-related liver cirrhosis with a yearly rate around 3%[10-18].

The combination of pegylated interferon (Peg-IFN) and ribavirin (RBV) has been recommended as the treatment of choice for CHC for nearly a decade[19-24]. This treatment provides a sustained clearance of circulating HCV [sustained viral response (SVR)] in nearly half of the patients with CHC due to HCV genotype 1 and in nearly 70% of those with HCV genotype 2 or 3. Several predictors of a favorable/unfavorable response to treatment have been identified. Some viral factors (HCV genotype 1/4 and an on-treatment slow or absent viral clearance) and host factors (male sex, older age, insulin resistance, diabetes, Afro-American ethnicity, presence of cirrhosis and/or steatosis, and high body mass index) have been associated with a poor response to Peg-IFN plus RBV treatment.

More recently, genome-wide association studies (GWAS) investigated the association between single nucleotide polymorphisms (SNPs) and the clinical presentation, course of the disease and response to antiviral treatment. Several studies have associated polymorphisms in the interleukin 28B (*IL28B*) gene on chromosome 19 (19q13.13) with a spontaneous clearance of HCV in AHC and with the response to Peg-IFN plus RBV treatment in CHC[25-28].

Some investigations demonstrated that inosine triphosphate pyrophosphatase (ITPA) genetic variants protect HCV-genotype-1 patients from RBV-induced anemia[29-31] and some other studies that a polymorphism in the patatin-like phospholipase domain (PNPLA3) is associated with hepatic steatosis[32,33].

The addition of a direct-acting antiviral (DAA) NS3 protease inhibitor boceprevir or telaprevir to the traditional combination of Peg-IFN plus RBV has increased the SVR rate in CHC patients with HCV genotype 1% to 70%[34-38], and the replacement of these first generation protease inhibitors with the recently developed second or third generation DAAs to nearly 90%[39-43]. In addition, some IFN-free treatments recently investigated have been shown to eradicate HCV infection in 90% or more of CHC patients. These high rates of HCV eradication should reduce the clinical value of most predictors of response to treatment so far considered, at least in countries where the high cost of second and third generation DAAs will not be an obstacle to their use. Nevertheless, the low toxicity of IFN-free DAA regimens allow the treatment of patients with comorbidities for which IFN-based treatments are contraindicated, those with advanced or decompensated liver cirrhosis and liver transplant recipients, who are all patients who may require individualized treatment possibly based on predictors of a favorable response.

## MATERIALS AND METHODS

In this review article we focus on old and new host genetic factors influencing the outcome of CHC and the response to antiviral treatment to offer some guidance for individualized therapy in clinical practice. We conducted an electronic search on the PubMed and MEDLINE (2000-2014) databases and Cochrane library (2000-2014). A total of 73 articles were retrieved and their data were extensively evaluated and discussed by the authors and then analyzed in this review article.

## RESULTS

### Host IL28B and HCV infection

Several studies performed in the last 4-5 years have demonstrated that two SNPs, the rs12979860C/T and rs8099917T/G, located in the *IL28B* gene in chromosome 19 have a substantial impact on the clinical course of HCV-related liver diseases and on the response

to Peg-IFN-based treatment in CHC. The *IL28B* gene region encodes for an endogenous antiviral cytokine interferon-λ3 involved in both the early stage of the host innate immune response to HCV infection[25,44,45] and, by binding to a cellular class Ⅱ cytokine receptor complex, in the activation of interferon stimulating genes through the JAK-STAT pathway[44,45]. Thus, there is an immunological and virological explanation for the protective effect of the rs12979860CC[25] and rs8099917TT[28] genotypes on the natural course of primary HCV infection and on the response to IFN-based treatment[26-28,46].

### IL28B and AHC

AHC has an asymptomatic course in 50%-90% of cases[3], but primary HCV infection becomes chronic in two-third of the cases, more frequently in men[47] and in asymptomatic cases[48]. Viral factors (genotype, subtypes and quasispecies)[49-53] and host factors (route of transmission, presence or absence of symptoms, initial immune response) have been described as playing a role in the natural history of the illness[25,28,46,54-57]. More recently, the rs12979860CC and rs8099917TT SNPs have been described as independently associated with a spontaneous clearance of HCV[25,28,58,59]. A recent meta-analysis of 8 studies on 2460 patients with HCV chronic infection and 1052 with a spontaneous HCV clearance, 7 studies investigating rs12979860 and 3 rs8099917, confirmed that, at least in Caucasian populations, rs12979860CC and rs8099917TT favor a spontaneous HCV clearance[60].

Early short-term IFN treatment prevents the progression to CHC in the majority of cases, whereas the results are less encouraging when treatment is started 6 mo or more after the onset of AHC[61-63]. Two controlled randomized studies recently published showed a frequent favorable response to a short Peg-IFN treatment starting three months after the onset of AHC[64,65]. Although both rs12979860CC and rs8099917TT have not been associated with a treatment-induced HCV clearance in AHC[58], some authors have suggested that treatment should be started immediately for patients with a non-CC genotype, while it can be delayed for those with the CC genotype, since these subjects may clear HCV spontaneously[59,66].

### IL28B and the natural course of CHC

The influence of IL28B polymorphisms on the progression of CHC remains unclear. The rs8099917TT genotype was found to be associated with more severe liver neuroinflammation and fibrosis in a study from Japan[67], whereas it was not found to be associated with the more severe stages of liver fibrosis in an Italian prospective study[68]. In addition, an association of IL28B polymorphisms with the development of HCC in cirrhotic patients described in an Italian study[69] was not confirmed in a study from Japan showing similar prevalences of rs8099917TT genotype in 69 patients with HCC and in 442 without[70]. Further studies are needed to afford further clarification.

### IL28B and response to antiviral treatment in CHC

The combination of Peg-IFN-alfa-2a or -2b and RBV has been used for nearly a decade to treat patients with CHC. More recently, the first generation DAA NS3 protease inhibitors, boceprevir or telaprevir, have been used in combination with Peg-IFN and RBV to treat patients with HCV genotype 1[34,71-73]. Second and third generation DAAs against HCV have been recently developed[74-76] and interferon-free combinations of these drugs are at present available both in the United States and in some European countries[77].

**IL28B and Peg-IFN plus ribavirin treatment in patients with HCV-genotype 1:** The IL28B genotype SNPs rs12979860 and rs8099917 are reliable predictors of the course of the disease after Peg-IFN and RBV treatment in CHC patients with HCV genotype 1[26-28,46]. In fact, the rs12979860-CC or rs8099917-TT genotypes are detectable in the majority of patients with a favorable response to treatment and patients with these genotypes have a twofold likelihood of achieving SVR[78-81]. These genotypes are more frequent in Asian (73%) than in Caucasian (41%), Hispanic (25%) and African American populations (13%)[26-28,46,79,80]. This different distribution strongly contributes to the racial differences in the response to therapy[79], since the favorable effects of rs12979860-CC and rs8099917-TT are similar for all ethnic groups.

**IL28B and Peg-IFN plus ribavirin treatment in patients with non-1 HCV genotypes:** The association between the IL28B polymorphisms and the response to Peg-INF plus RBV treatment in patients with HCV-genotype 2 and 3 has been investigated by few authors. In a recent study, Eslam *et al*[82] confirmed that rs12979860 CC and rs8099917 TT are independent predictors of SVR also in patients with HCV-genotype 2 or 3. In a study by Sarrazin *et al*[83] the rs12979860 CC genotype, HCV genotype 2 and a young age were found to be significantly associated with SVR in HCV genotype 2/3-infected patients, whereas rs8099917 and rs12980275 were not found to be associated. In addition, the achievement of SVR in patients with RVR was associated with the rs12979860 CC genotype, while no association was found for non-RVR subjects. In a recent study on the impact of SNP rs8099917 and of the amino acid substitutions in the NS5A region on the response to Peg-IFN plus RBV treatment in 286 CHC patients with HCV-genotype 2, SVR was achieved with similar rates in patients with rs8099917TT (76%) and those with TG or GG alleles (72%), whereas it was significantly less frequent in patients with the wild-type IFN sensitivity-determining region (ISDR) than in those with the mutant type (65.9% *vs* 83.5%). On multivariate analysis the only factors related to SVR were a younger age of patients and the ISDR, indicating that in patients with HCV genotype 2, the ISDR sequence variations are significantly associated with the response to Peg-IFN plus RBV treatment[84].

The SNPs rs12979860CC and rs8099917TT were found to be strongly associated with SVR in a large number of genotype-3-infected patients recently investigated by Firdaus *et al*[85].

In a retrospective study on 169 patients with genotype 4 treated with Peg-INF and RBV for 48 wk, Boglione *et al*[86] demonstrated that the combination of rs8099917/rs12979860 polymorphisms is useful to identify possible SVR patients, null-responders and relapsers. In fact, these authors achieved an 88.8% SVR in cases with rs8099917/rs12979860 TT/CC or TT/TC genotypes. Moreover, Youssef *et al*[87] underscored that alpha-fetoprotein increased the SVR predictive strength of IL28B rs12979860 CC polymorphism in Egyptian CHC patients with HCV-genotype 4.

**IL28B and Peg-IFN plus ribavirin and first generation DAA triple therapy:** Triple therapy with Peg-IFN, RBV and a first generation protease inhibitor boceprevir or telaprevir has increased the rates of SVR in HCV-genotype 1 CHC patients to nearly 70%, which reduces the importance of predictors of the response to therapy[71]. Nevertheless, IL28B favorable genotypes may still be useful to identify patients with a greater likelihood of achieving SVR with a first-line, low-cost Peg-IFN and RBV regimen, reserving DAA-based treatment for non-responders and relapsers[72,73], a particularly useful strategy in developing countries.

**IL28B and second and third generation DAAs:** The introduction of the second and third generation DAAs in IFN-based and IFN-free regimens for CHC patients has strongly reduced the need to determine the IL28B genotypes to predict the response to treatment. In fact, a favorable response was obtained in nearly 90% of patients with HCV-genotype 1 treated with sofosbuvir plus Peg-INF and RBV, this rate being slightly lower in patients with cirrhosis. In CHC patients with HCV-genotype 2, the combination of sofosbuvir and RBV given for 12 wk also resulted in SVR of 90% or more, with a slightly lower efficacy in patients with cirrhosis[76]. Other studies showed an SVR rate of nearly 95% in CHC patients treated with IFN-free regimens[74,75], independently of the IL28B status[74,75]. Guedj *et al*[88] found no effect of IL28B on the viral kinetics in HCV-genotype-1 CHC patients treated with sofosbuvir and GS-0938 given alone and in combination for 14 d.

The combination of daclatasvir plus sofosbuvir, with or without RBV, obtained SVR in 98% of both therapy-naïve or - experienced CHC patients with HCV-genotype 1a or 1b (98% and 100%, respectively), with IL28B CC or non-CC (93% and 98%, respectively) and with RBV included or excluded from combination therapy (94% and 98%, respectively)[77]. The data from the above-mentioned studies strongly indicate that we cannot evaluate the influence of *IL28B* genotypes on the response to second or third generation DAA treatments of CHC, due to the high efficacy of these treatments.

*IL28B and HCV recurrence after liver transplantation*
Some investigations showed an association between IL28B polymorphism and response to therapy in patients with a recurrence of HCV infection after liver transplantation. In particular, the highest SVR rates were observed when both donor and recipient showed the same rs12979860CC or rs8099917TT genotypes[89,90]. It has also been reported that the recipients with rs12979860TT genotype showed a more severe histological HCV recurrence after liver transplantation[89].

*PNPLA3 polymorphism and HCV infection*
The *PNPLA3* gene encodes a 481 amino acid protein called adiponutrin, which belongs to the patatin-like phospholipase family. Its progenitor, patatin, was first described in potato tubers and has non-specific lipid acyl-hydrolase activity[91]. The adiponutrin has a molecular mass of 53 kDa and is mainly expressed in both human adipocytes and hepatocytes[92]. The protein presents a sequence similar to that of adipose tissue triglyceride lipase, and has both triglyceride lipase and transcylase activity.

In 2008 two GWAS[32,33] showed a correlation between the rs738409 polymorphism of PNPLA3 and non-alcoholic fatty liver disease. In fact, a C to G mutation causes the substitution of isoleucin at codon 148 with a methionine, whose hydrophobic side-chain inhibits the binding of the substrate to the catalytic site, leading to a reduction in the enzymatic activity of the protein towards glycerolipids. Consequently, triglycerides accumulate, resulting in the development of macrovesicular steatosis.

Hepatic steatosis, frequent in patients with CHC and with the highest rates in those with genotype 3[93], has been associated with a more rapid progression of liver fibrosis[94] and a poor response to IFN-based treatments[95]. Due to these associations several authors investigated the impact of the rs738409 polymorphism of PNPLA3 on the clinical presentation and natural history of CHC (Table 1). The I148M mutation was found to be associated with the degree of steatosis and with the development of cirrhosis in two independent cross-sectional studies investigating, respectively, 537 and 819 patients with CHC[96,97]. These data were confirmed by the Swiss Hepatitis C Cohort Study Group on 626 patients with CHC for all HCV genotypes except genotype 3[98]. Zampino *et al*[99] found a stronger correlation between waist circumference and liver steatosis in homozygous 148M Italian CHC patients carrying non-3 HCV genotypes, but not with carotid atherosclerosis[100]. In addition, the association between another PNPLA3 polymorphism, the rs2896019, and the presence of any degree of steatosis, even severe, was demonstrated in a cross-sectional investigation[101] on 972 patients. Instead, Nakamura *et al*[102] did not find any association between the I148M mutation and the presence of steatosis or cirrhosis development in 260 Japanese patients with CHC; in this study, however, liver

**Table 1 Studies on the role of the rs738409PNPLA3 polymorphisms in hepatitis C virus chronic infection**

| Ref. | No. of patients | Country | Type of study | Liver disease | Outcome (GG *vs* GC + CC) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Steatosis | Severe steatosis | Cirrhosis | SVR | HCC |
| Cai *et al*[98] | 626 | Switzerland | Cross-sectional | Chronic liver disease | OR = 1.880 (95%CI: 1.571-2.250)[1] | OR = 1.578 (95%CI: 1.331-1.870)[1,2] | | | |
| Clark *et al*[101] | 972 | United States | Cross-sectional | Chronic liver disease | OR = 1.62 (95%CI: 1.22-2.14)[3] | OR = 1.78 (95%CI: 1.40-2.27)[3,4] | | No association (*P* = 0.294)[3] | |
| Dunn *et al*[103] | 101 | United States | Cohort | Liver transplantation recipients and donors | | | HR = 2.53, (95%CI: 1.28-5.02)[5,6] | | |
| Guyot *et al*[105] | 253 | France | Cohort | Cirrhosis | | | | No association (*P* = 0.5)[7] | No association (*P* = 0.5) |
| Nakamura *et al*[102] | 260 | Japan | Cross-sectional | 37 Cirrhosis 223 Chronic hepatitis | No association (*P* = 0.935)[8] | | No association (*P* = 0.876)[8] | | |
| Nischalke *et al*[104] | 162 | Germany | Case-control | Cirrhosis | | | | | No association (*P* = 0.386) |
| Trépo *et al*[96] | 537 | Belgium, Germany, France | Cross-sectional | Chronic liver disease | | OR = 2.84 (95%CI: 1.22-6.60)[2] | OR = 2.43 (95%CI: 1.24-4.78)[9] | | |
| Valenti *et al*[97] | 819 | Italy | Cross-sectional/ case-control | 548 Chronic hepatitis 215 Cirrhosis 56 HCC | OR = 1.90 (95%CI: 1.39-2.73) | OR = 2.09 (95%CI: 1.62-2.67)[4] | OR = 1.47 (95%CI: 1.15-1.87) | OR = 0.63 (95%CI: 0.44-0.86)[10] | OR = 2.16 (95%CI: 1.33-3.59)[11] |
| Zampino *et al*[99] | 166 | Italy | Cross-sectional | Chronic hepatitis | Mean steatosis score GG: 1.94 ± 1.6, CG: 1.25 ± 1.2, CC: 1 ± 1.1, *P* < 0.05 | | | | |

[1]GG + GC *vs* CC non-genotype 3; [2]Steatosis > 5%; [3]Rs2896019 GG + GT *vs* TT genotype 1; [4]Steatosis > 32%; [5]GG + GC *vs* CC donors; [6]Occurrence of Ishak staging $\geq$ 3, acute cellular rejection, chronic rejection or fibrosing cholestatic hepatitis during a 620-d (IQR 317-975) follow-up; [7]226 patients; [8]GG+GC *vs* CC, United States diagnosis of steatosis and cirrhosis; [9]F3 or F4; [10]470 patients; [11]325 patients. SVR: Sustained viral response; HCC: Hepatocellular carcinoma.

steatosis was detected only by ultrasound. Interestingly, Dunn *et al*[103] found the I148M mutation to be independently associated with fibrosis progression and graft loss in a prospective study on 101 CHC patients who underwent liver transplantation.

An independent association between the I148M mutation and a poor response to IFN-based therapy was described by Valenti *et al*[97] in 470 patients with CHC; in the same paper these Authors described an association between this SNP and the development of hepatocellular carcinoma. An association between the I148M mutation and HCC development was found in a case-control study on 160 German patients with alcohol-related cirrhosis, but not in a group of 162 patients with HCV-related end-stage liver disease[104]. While confirming this association in alcoholic liver disease, Guyot *et al*[105] found no association between the rs738409 polymorphism and HCC occurrence or between this SNP and the SVR rate of IFN-based therapy in a prospective study on 253 patients with HCV-related cirrhosis. However, a recent meta-analysis including 2503 European patients with cirrhosis, particularly HCV - and alcohol-related, indicated that rs738409 exerts a marked influence on hepatocarcinogenesis[106].

Concluding on this point, further studies are needed to confirm the association between the I148M mutation and a poor response to IFN-based therapy and to establish the mechanisms relating to the role of PNAPL3 on the development of HCC.

### ITPA polymorphisms and HCV infection
Ribavirin has made a strong contribution to the success of old and new combination treatments to eradicate HCV infection[107,108].

This drug, however, induces a dose-related hemolytic anemia that impairs the patients' quality of life and frequently entails a dosage reduction and lowered SVR rates[109-112]. This adverse reaction has been reported as more frequent during the administration of triple combination therapy with Peg-IFN, RBV and telaprevir or boceprevir[108,113].

Erythrocyte hemolysis is considered the main cause of RBV-induced anemia[114]. By reducing adenosine triphosphate (ATP) levels in human erythrocytes, RBV induces a guanosine triphosphate (GTP) depletion followed by the inhibition of the ATP-dependent oxidative metabolism, membrane damage and premature hemolysis of erythrocytes[115,116].

In patients with reduced ITPA activity, however, inosine triphosphate (ITP) accumulates in erythro-

cytes[117-120], replacing the GTP activity and producing adenosine monophosphate[121], thus avoiding the inhibition of the ATP-dependent oxidative metabolism and erythrocyte hemolysis. Therefore, RBV-induced anemia seems primarily to be due to the reduced levels of ATP in erythrocytes consequent to the effect of the drug on GTP[121], and resistance against RBV-related anemia is due to a reduced ITPA activity[115,116].

The genetic bases of these phenomena were first identified in 2010 by Fellay *et al*[29], who in a GWAS found a strong association between the single nucleotide polymorphism rs6051702 and the quantitative hemoglobin reduction at week 4 of Peg-IFN plus RBV treatment. The association was explained by 2 functional variants in the *ITPA* gene (encoding inosinetriphosphatase-ITPase) on chromosome 20: a missense variant in exon 2 (rs1127354, P32T) and a splice-altering single nucleotide polymorphism in intron 2 (rs7270101). The polymorphisms rs1127354 and rs7270101 were found to be associated with a hemoglobin reduction at week 4 of treatment in 304 genotype-1 CHC patients receiving Peg-IFN plus RBV, while the minor alleles of each variant protected against hemoglobin reduction; in particular, a 3g reduction in hemoglobin levels was a rare occurrence in 22 (2%) patients with a reduction in the ITPA activity of less than 30% and in 45% of 212 with normal enzyme activity[30]. These data were confirmed in other investigations both in HCV-genotype-1 patients[31,122-127] and in those with HCV-non-1 genotypes (Table 2)[116,128-132].

There are contrasting opinions on the impact of ITPA polymorphisms in patients treated with telaprevir-based triple therapy since some studies reported an impact of the ITPA polymorphism similar to that observed in patients receiving Peg-IFN plus RBV double therapy (Table 2)[133-135], whereas a recent study did not find ITPA deficiency useful to predict early anemia in patients with advanced fibrosis receiving telaprevir[135]. No information is so far available on the impact of ITPA polymorphisms in patients with CHC treated with a boceprevir-based triple therapy.

### Polymorphisms influencing the vitamin D metabolism and HCV infection

Vitamin D is a steroid hormone exerting its primary role in bone mineral homeostasis. The main source of vitamin D comes from the synthesis of its inactive precursor 7-dehydrocholesterol in the skin during an ultraviolet-B radiation-dependent reaction, whereas only small amounts of vitamin D2 and D3 come from food. Vitamin D from both sources undergoes 25-hydroxylation by hepatic microsomal enzymes and, through a series of other enzymatic reactions, 1,25-dihydroxy-vitamin D3 (calcitriol), the active form of vitamin D, is obtained. A vitamin D receptor (VDR) is expressed in several human cells. It binds to its ligand and plays the role of a transcription factor for numerous target genes. Consequently, vitamin D exerts its effect on several tissues.

An anti-inflammatory and anti-fibrotic role of vitamin D in chronic liver diseases has only recently been hypothesized, mostly on the basis of the observation that nearly two thirds of patients with chronic liver disease present low serum levels of vitamin D[136] associated with a high fibrosis score and low response to Peg-IFN-based therapy[137,138]. A case-control study on 110 patients with CHC showed a significant correlation between the CYP27B1-1260 promoter polymorphism rs10877012 and the SVR rate (Table 3)[139]. Falleti *et al*[140] found a significantly higher likelihood of response to antiviral treatment in patients with a higher "vitamin D pathway functional score", a genetic model they constructed considering for each patient the sum of every functional allele associated with the achievement of SVR, including the rs10877012 and another three polymorphisms, the rs7041 and rs4588 of the *GC* gene and the rs10741657 of CYP2R1. These Authors also demonstrated that the achievement of SVR with Peg-IFN plus RBV treatment in CHC patients with difficult-to-treat HCV genotypes is predicted both by the carriage of the GC-globulin WT isoform and by normal levels of serum vitamin D at the baseline[141]. Baur *et al*[142,143] demonstrated a correlation between the carriage of the *VDR* gene bAt (CCA) genotype, comprising three different polymorphisms of the *VDR* gene, and the SVR rate and cirrhosis development. These data were confirmed in another cross-sectional study, which also showed a relationship between another *VDR* gene polymorphism and the likelihood of response to therapy[144].

Concluding on this point, the studies mentioned above do not allow conclusions to be drawn at present, but they certainly suggest that the vitamin D-associated polymorphisms play an important role in the achievement of SVR with Peg-IFN based treatment in CHC patients.

### Other polymorphisms and HCV infection

Several other polymorphisms have been investigated to ascertain their possible impact on the clinical presentation and natural history of CHC (Table 4). Huang *et al*[145] proposed a risk score based on 7 different SNPs that were highly predictive of the development of cirrhosis in two retrospective series of 420 and 154 Caucasian patients (a training and validation cohort, respectively). This score was demonstrated to be effective in these series of patients and in subsequent large prospective[146,147] and retrospective[148] studies carried out in patients with mild or moderate chronic hepatitis, human immunodeficiency virus (HIV)-HCV coinfected patients[149] and liver transplant recipients[150].

Interesting data also come from studies investigating the genes regulating the immune system. Yee *et al*[151] showed that patients with chronic hepatitis C carrying the IL-6 rs1800795 G allele have a reduced chance of achieving SVR when treated with Peg-IFN plus RBV. These data are in disagreement with those of a previous study[152], which, however, enrolled only HIV-HCV coinfected patients. This polymorphism was also associated with the higher degrees of liver necroin-

**Table 2 Studies on the role of inosine triphosphate pyrophosphatase polymorphisms in hepatitis C virus chronic infection**

| Ref. | No. of patients | Country | Type of study | SNPs | Liver disease/HCV genotype | Therapy | Outcome |
|---|---|---|---|---|---|---|---|
| Thompson et al[30] | 304 | United States | Retrospective | rs1127354 rs7270101 | CHC/1 | Peg-IFN-α-2a + RBV | Hb reduction > 3 g/dL at week 4 ITPase deficiency (both SNPs): OR = 0.26, 95%CI: 0.15-0.4; $P = 2.7 \times 10^{-7}$ |
| Eskesen et al[128] | 457 | Norway | Retrospective | rs1127354 rs7270101 | CHC/2/3 | Peg-IFN-α-2b + RBV | Patients with any degree of reduced ITPAase activity were less likely to have their RBV dose reduced: OR = 0.39, 95%CI: 0.16-0.96, $P = 0.040$ |
| Seto et al[129] | 60 | Hong Kong | Prospective | rs1127354 | CHC/6 | Peg-IFN + RBV | ITPA rs1127354 CA vs CC genotype: lesser degree of anemia throughout therapy $P < 0.05$ for all time points |
| Hai et al[122] | 66 | Japan | Retrospective | rs1127354 | CHC/1 | Peg-IFN + RBV | At multiple regression analysis, age < 60 yr, ITPA CA/AA genotype and serum RBV concentration were significant independent predictive factors for SVR |
| Thompson et al[116] | 238 | United States | Retrospective | rs1127354 rs7270101 | CHC/2/3 | PegIFN-α-2b + RBV | Hb reduction at week 4 ITPase deficiency (both SNPs): $P = 10(-11)$ There was no association between the ITPA variants and SVR |
| Ahmed et al[123] | 102 | Egypt | Prospective | rs1127354 | CHC 1/4 | Peg-IFN + RBV | CC patients had more frequently Hb decline > 3 g/dL than non-CC patients at weeks 8 and 12 ($P = 0.024$ and 0.038, respectively) Reduction of the amount of the planned RBV dose was significantly higher for CC patients than non-CC patients during the first 12 wk (18% ± 12.1% vs 8.5% ± 10.2%, $P = 0.021$) |
| Azakami et al[124] | 830 | Japan | Retrospective | rs1127354 | CHC/1 | Peg-IFN + RBV | Cumulative reduction of ribavirin was significantly more frequent in genotype CC patients than non-CC patients (OR = 1.928, $P = 8.6 \times 10^{8}$) |
| Kurosaki et al[125] | 446 | Japan | Prospective | rs1127354 | CHC/1 | Peg-IFN + RBV | ITPA AA/CA had the lowest incidence of anemia (17%) |
| Matsuura et al[126] | 309 | Japan | Retrospective | rs1127354 | CHC/1 | Peg-IFN + RBV | The incidence of severe anemia, ≥ 3 g/dL reduction or < 10 g/dL of Hb up to week 12 was more frequent in patients with CC (65% and 33%) than in those with CA/AA (25%, 6%); $P < 0.0001$ |
| Rau et al[130] | 216 | Switzerland | Retrospective | rs1127354 rs7270101 | CHC Mixed genotype | Peg-IFN + RBV | ITPA SNP rs1127354 was associated with Hb drop ≥ 3 g/dL during treatment (RR = 2.1, 95%CI: 1.3-3.5) |
| Clark et al[131] | 193 | Australia | Retrospective | rs1127354 rs7270101 | CHC Mixed genotype | Peg-IFN + RBV | More severe ITPA deficiency was associated with a lesser reduction in Hb level ($P < 0.001$), lesser ribavirin dose reduction ($P = 0.005$), lesser EPO use ($P = 0.029$) ITPA deficiency was associated with SVR ($P = 0.041$) |
| Rembeck et al[132] | 354 | Sweden | Prospective | rs1127354 rs7270101 | CHC/2/3 | Peg-IFN + RBV | Reduced ITPAase activity was associated with a decreased risk of anemia ($P < 0.0001$), increased risk of thrombocytopenia ($P = 0.007$), and lower ribavirin concentrations ($P = 0.02$) |
| D'Avolio et al[127] | 167 | Italy | Retrospective | rs1127354 rs7270101 | CHC/1 | Peg-IFN + RBV | Both SNPs were associated with Hb decrease. The carrier of at least one variant in the ITPA was associated with a lower decrease of Hb (-1.1 g/dL), compared to patients without (-2.75 g/dL; $P = 4.09 \times 10$) |
| Suzuki et al[133] | 61 | Japan | Retrospective cohort study | rs1127354 | CHC/1 | Peg-IFN + RBV + telaprevir | Decreases in Hb levels were greater in patients with CC than CA/AA genotypes at week 2 (-1.63 ± 0.92 g/dL vs -0.48 ± 0.75 g/dL, $P = 0.001$), week 4 (-3.5 ± 1.1 vs -2.2 ± 0.96, $P = 0.001$) and at the end of treatment (-2.9 ± 1.1 vs -2.0 ± 0.86, $P = 0.013$) |
| Ogawa et al[134] | 292 | Japan | Prospective, multicenter study | rs1127354 | CHC/1 | Peg-IFN + RBV + telaprevir | Pretreatment predictors of the development of severe anemia: baseline Hb < 135 g/L (HR = 2.53; $P = 0.0013$), estimated glomerular filtration rate < 80 mL/min per 1.73 $m^2$ (HR = 1.83; $P = 0.0265$), ITPA CC genotype (rs1127354) (HR = 2.91; $P = 0.0024$) |
| Aghemo et al[135] | 69 | Italy | Retrospective cohort study | rs1127354 rs7270101 | CHC/1 | Peg-IFN + RBV + telaprevir | During the first 12 wk of TPV triple therapy: grade 3-4 anemia developed in 81% non-ITPA deficient patients vs 67% mildly deficient and 55% moderately deficient patients ($P = NS$); RBV dose reduction in 60% with no deficiency, 58% with mild, 67% with moderate deficiency ($P = NS$); Erythropoietin use in 65% with no deficiency, 58% with mild, 56% with moderate ($P = NS$); need for blood transfusion in 27% with no deficiency, 17% with mild, 33% with moderate ($P = NS$) |

CHC: Chronic hepatitis C; Hb: Hemoglobin; RBV: Ribavirin; Peg-IFN: Peg-Interferon; SNP: Single nucleotide polymorphism; NS: Not significant.

**Table 3  Studies on the role of the polymorphisms influencing the vitamin D metabolism in hepatitis C virus chronic infection**

| Ref. | No. of patients | Country | Type of study | Liver disease | Polymorphism | Outcome | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Cirrhosis | SVR | HCC |
| Baur *et al*[142] | 155 | Switzerland | Cross-sectional | Chronic hepatitis | rs7975232 | | OR = 2.67 (95%CI: 1.24-5.70)[1,4] | |
| | | | | | rs731236 | | OR = 6.05 (95%CI: 1.71-21.43)[2,4] | |
| | | | | | rs1544410 | | No association (*P* = 0.085) | |
| | | | | | CC/CC/AA[3] | | OR = 2.50 (95%CI: 1.07-5.87)[4] | |
| Baur *et al*[143] | 223 | Switzerland | Cross-sectional | 185 chronic hepatitis | rs7975232 | 2.67 (95%CI: 1.29-5.51)[1] | | |
| | | | | 38 cirrhosis | rs731236 | No association | | |
| | | | | | rs1544410 | No association | | |
| | | | | | CC/CC/AA[3] | 2.54 (95%CI: 1.07-6.01) | | |
| Falleti *et al*[141] | 206 | Italy | Cross-sectional | Chronic liver disease | rs7041 rs4588 | | OR = 0.164 (95%CI: 0.056-0.482)[5] | |
| Falleti *et al*[140] | 206 | Italy | Cross-sectional | Chronic liver disease | rs10741657 | | 1.778 (95%CI: 1.135-2.788)[6] | |
| | | | | | rs7041 | | No association (*P* = 0.679) | |
| | | | | | rs4588 | | No association(*P* = 0.458) | |
| | | | | | rs10877012 | | No association (*P* = 0.422) | |
| | | | | | VDPFA[7] | | OR = 2.30 (95%CI: 1.02-5.22)[8] | |
| García-Martín *et al*[144] | 238 | Spain | Cross-sectional | 169 chronic hepatitis | rs2228570 | | 0.438 (95%CI: 0.204-0.882)[4,9] | |
| | | | | 33 cirrhosis 36 not assessed | CC/CC/AA3 | | 2.743 (95%CI: 1.313-5.731)[4] | |
| Lange *et al*[139] | 110 | Germany | Case-control | Chronic liver disease | rs10877012 | | 10/13 AA *vs* 27/41 AC and 24/56 CC (*P* < 0.05) | |
| Lange *et al*[162] | 5604 | Germany, Switzerland, Japan | Case-control/retrospective cohort | 1279 HCC | rs2282679 | | | OR = 1.56 (95%CI: 1.12-2.15)[10] |
| | | | | 4325 chronic liver disease | rs7944926 | | | OR = 1.56 (95%CI: 1.13-1.78)[11] |
| | | | | | rs1993116 | | | No association (*P* = 0.07)[12] |
| | | | | | | | | HR = 1.81 (95%CI: 1.03-3.13)[13] |

[1]CC *vs* CA + AA; [2]AA + AG *vs* GG; [3]CCA haplotype comprises rs1544410 (BsmI) C, rs7975232 (ApaI) C and rs731236 (TaqI) A alleles of *VDR* gene; [4]OR for non-SVR; [5]OR for non-SVR in WT *vs* non-WT; WT were patients carrying ≥ 3 major alleles (GG/CC, GT/CC and GG/CA); [6]GG + GC *vs* CC; [7]VDPFA (Vitamin D Pathway Functional Alleles) was constructed giving a value of 1 to the functional allele of each gene and a value of 0 to the other alleles. Thus, for each patient a VDPFA value ranging from 0 to 8 was obtained; [8]VPDFA > 5 *vs* ≤ 5; [9]TT + TC *vs* CC; [10]TT + TG *vs* GG, 2534 patients; [11]TT *vs* TC + CC, 2420 patients; [12]5591 patients; [13]GG *vs* GA + AA, 1657 patients. SVR: Sustained viral response; HCC: Hepatocellular carcinoma.

flammation[153] and fibrosis[154]. In addition, spontaneous and treatment-induced HCV viral clearance have been found to be associated with the rs2069707 G allele of the *IFN-γ* gene[155] and with KIR2DL3 and HLAC1 haplotypes[156,157].

More recently, an association between the polymorphism at codon 63 of the cannabinoid receptor 2 gene (*CB2*) and HCV infection was suggested[158,159]. This polymorphism leads to the substitution of glutamine, Gln (Q), with arginine, Arg (R), causing a different polarization state of the protein. The CB2 variants have been demonstrated to affect differently the ability of the CB2 receptor to exert its inhibitory function[160]. Specifically, *in-vitro* T lymphocytes from CB2-63 RR homozygotes showed an approximately two-fold reduction in the endocannabinoid-induced inhibition of proliferation compared to cells from CB2-63 QQ homozygotes[161]. In a cohort of 169 biopsy-proven CHC patients, the CB2-63 QQ variant was found to be independently associated with more extensive neuroinflammation[160], whereas in 253 patients with HCV chronic infection this variant was found to be independently associated with a persistently normal aminotransferase status identified by the Authors as the end-stage of the necroinflammatory activity[159]. Further investigations are needed to better define the role of the CB2 variants.

## DISCUSSION

Several genetic polymorphisms seem to influence the outcome of CHC and the response to antiviral treatment, which allows individualized strategies to be devised for monitoring the course of the disease and for the choice of treatment. The recent introduction of second and third generation DAAs in Peg-IFN-based and IFN-free treatments have certainly reduced the clinical importance of these predictors, which, however, may still be useful with difficult-to-treat patients and in developing countries

**Table 4  Role of other single nucleotide polymorphisms in hepatitis C virus infection**

| Ref. | Gene | SNPs/haplotypes | Important results |
|---|---|---|---|
| | CRS (7 genes): | | |
| Huang *et al*[145] | *AZIN1* | rs62522600 | The Cirrhosis Risk Score was evaluated both in retrospective and prospective studies |
| Marcolongo *et al*[146] | *TLR4* | rs4986791 | and appeared to be a useful predictor of fibrosis progression in patients with mild |
| Trépo *et al*[148] | *TRMP5* | rs886277 | chronic hepatitis C, even in special populations (*i.e.*, liver transplant recipients or HIV- |
| Curto *et al*[147] | *AP3S2* | rs2290351 | HCV coinfected patients) |
| do O *et al*[150] | *B008027* | rs4290029 | |
| Fernández-Rodríguez *et al*[149] | *AQP2* | rs2878771 | |
| | *STXBP5* | rs17740066 | |
| Nattermann *et al*[152] | *IL-6* | rs1800795 | The CC genotype was associated with lower plasma levels of IL-6 and seemed to |
| Yee *et al*[151] | | | correlate with higher SVR rate and lower grading and staging, although the data |
| Falleti *et al*[153] | | | from the literature are discordant, probably due to the heterogeneity of the study |
| Cussigh *et al*[154] | | | populations (*i.e.*, different virological and clinical characteristics, HIV-coinfection, *etc.*) |
| Khakoo *et al*[156] | *KIR-HLA* | KIR2DL3/HLAC1 | The association between KIR2DL3 and HLAC1 appeared to be related to both a |
| Knapp *et al*[157] | | | spontaneous and treatment-induced resolution of HCV infection |
| Huang *et al*[145] | *IFNγ* | rs2069707 | The C764G polymorphism seemed to be associated with a higher SVR rate and a more |
| | | | frequent spontaneous viral clearance |
| Hellier *et al*[163] | *CCR5* | CCR5Δ32 | The CCR5Δ32 deletion, which was associated with resistance to HIV infection, seemed |
| Nattermann *et al*[164] | | | to correlate with lower spontaneous clearance of HCV and milder inflammation and |
| Goulding *et al*[165] | | | fibrosis, although the data from the literature are discordant |
| Coppola *et al*[158] | *CNR2* | rs35761398 | The CB2-65 QQ genotype was associated with the PNALT status in chronic HCV |
| Coppola *et al*[159] | | | infection, but also with a higher HAI |

PNALT: Persistently normal alanine-amino-transferase; HAI: Histological activity index; SVR: Sustained viral response; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; IL- 6: Interleukin-6; SNPs: Single nucleotide polymorphisms.

where the cost of the new DAAs is at present a serious obstacle to their use.

## COMMENTS

### Background
Chronic hepatitis C (CHC) is a life-threatening disease since nearly a quarter of patients progress to liver cirrhosis and nearly 3% of hepatitis C virus (HCV) cirrhotic patients per year develop hepatocellular carcinoma.

### Research frontiers
Genome-wide association studies have recently shown that some nucleotide polymorphisms may influence the clinical course and the response to antiviral treatment in patients with chronic hepatitis C.

### Innovations and breakthroughs
Several studies associated the polymorphisms in the interleukin 28B (*IL28B*) gene on chromosome 19 (19q13.13) with a spontaneous viral clearance in acute hepatitis C and with the response to the pegylated interferon (Peg-IFN)-based treatments in CHC patients. The achievement of sustained virological response in CHC patients treated with Peg-IFN-based antiviral therapy has been also associated with the vitamin D-associated polymorphisms in some preliminary investigations. Other studies demonstrated that inosine triphosphate pyrophosphatase (ITPA) genetic variants protect HCV-genotype-1 CHC patients from ribavirin-induced anemia. Evidence of an association between a polymorphism in the patatin-like phospholipase domain (PNPLA3) with hepatic steatosis in CHC patients has been also given in recent studies. Several other polymorphisms have been investigated to assess their possible impact on the natural history and response to treatment in patients with CHC, but the results are preliminary and further confirmation is needed.

### Applications
In this review article the authors focus on old and new host genetic factors influencing the outcome of CHC and the response to antiviral treatment to offer some guidance for individualized follow up and therapy in clinical practice.

### Terminology
The *IL28B* gene region encodes for an endogenous antiviral cytokine interferon-λ3 involved in both the early stage of the host innate immune response to HCV infection and, by binding to a cellular class Ⅱ cytokine receptor complex, in the activation of interferon stimulating genes through the JAK-STAT pathway. The *PNPLA3* gene encodes for a 481 amino acid protein called adiponutrin, which belongs to the patatin-like phospholipase family and is mainly expressed in both human adipocytes and hepatocytes. The protein presents a sequence similar to that of adipose tissue triglyceride lipase, and has both triglyceride lipase and transcylase activity. In patients with reduced ITPA activity, inosine triphosphate accumulates in erythrocytes, replacing the GTP activity and producing adenosine monophosphate, thus avoiding the inhibition of the ATP-dependent oxidative metabolism and erythrocyte hemolysis by ribavirin. An anti-inflammatory and anti-fibrotic role of vitamin D in chronic liver diseases has been hypothesized only recently.

### Peer-review
Good work, which comprehensive summary of genetic polymorphisms that effect on the CHC.

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