**Name of journal: World Journal of Clinical Cases**

**ESPS Manuscript NO: 12820**

**Columns: Systematic Reviews**

**Role of genetic polymorphisms in hepatitis C virus chronic infection**

Coppola N *et al*. Genetic polymorphisms in chronic hepatitis C

Nicola Coppola, Mariantonietta Pisaturo, Caterina Sagnelli, Lorenzo Onorato, Evangelista Sagnelli

**Nicola Coppola, Mariantonietta Pisaturo, Lorenzo Onorato, Evangelista Sagnelli,** Department of Mental Health and Public Medicine, Section of Infectious Diseases, Second University of Naples, 80131 Naples, Italy

**Sagnelli Caterina**, Department of Clinical and Experimental Medicine and Surgery “F. Magrassi e A. Lanzara”, Second University of Naples, 80131 Naples, Italy

**Author contributions:** All the authors equally contributed to this work.

**Conflict-of-interest:** All the authors of the manuscript declare that they have no conflict of interest in connection with this paper.

**Data sharing:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to: Dr. Nicola Coppola,** Department of Public Medicine, Section of Infectious Diseases, Second University of Naples, Via: L. Armanni 5, 80131 Naples, Italy. [nicola.coppola@unina2.it](mailto:nicola.coppola@unina2.it)

**Telephone:** +39-81-5666719

**Fax:** +39-81-5666013

**Received:** July 27, 2014

**Peer-review started:** July 27, 2014

**First decision:** November 27, 2014

**Revised:** December 9, 2014

**Accepted:** June 4, 2015

**Article in press:**

**Published online:**

**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 *IL28B* 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.

**DISCUSSION**: 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.

**Kew words**: Single nucleotide polymorphism; Hepatitis C virus infection; Interleukin 28-B; Inosine triphosphate pyrophosphatase; Patatin-like phospholipase domain-containing protein 3

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**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 28-B, 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.

Coppola N, Pisaturo M, Sagnelli C, Onorato L, Sagnelli E. Role of genetic polymorphisms in hepatitis C virus chronic infection. *World J Clin Cases* 2015; In press

**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 (*IL-28B*) 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.

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.

**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 acute hepatitis C***

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 months 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 rs8099917 TT genotype was found to be associated with more severe liver necroinflammation 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 rs8099917 TT (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 PegIFN plus RBV treatment[84].

The SNPs rs12979860 CC and rs8099917 TT 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 weeks, 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 kineticsin 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 IL28 B 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 rs12979860 CC or rs8099917 TT genotypes[89,90]. It has also been reported that the recipients with rs12979860 TT 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 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 inosine triphosphate pyrophosphatase (ITPA) activity, however, inosine triphosphate (ITP) accumulates in erythrocytes[117-120],replacing the GTP activity and producing adenosine monophosphate (AMP)[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 (Hb) 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[116,128-132] (Table 2).

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-dihydroxyvitamin 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[139] (Table 3). Falleti *et al*[140] found a significantly higher likelihood of response to antiviral treatment in patients with a higher “vitamin D pathway functional score” (VDPFS), 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 vitamin D receptor 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, 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 necroinflammation[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 necroinflammation[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.

**CONCLUSION**

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 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 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 *IL28B* gene on chromosome 19 (19q13.13) with a spontaneous viral clearance in AHC and with the response to the 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 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 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 (ITP) accumulates in erythrocytes,replacing the GTP activity and producing adenosine monophosphate (AMP), 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***

The authors here performed a review of the current evidence on the role of some SNP in the outcome of CHC and in the response to antiviral treatment**.**

**REFERENCES**

1 **Chuang WL**, Yu ML. Host factors determining the efficacy of hepatitis C treatment. *J Gastroenterol* 2013; **48**: 22-30 [PMID: 23104468 DOI: 10.1007/s00535-012-0669-x]

2 **Burra P**. Hepatitis C. *Semin Liver Dis* 2009; **29**: 53-65 [PMID: 19235659 DOI: 10.1055/s-0029-1192055]

3 **Sagnelli E**, Santantonio T, Coppola N, Fasano M, Pisaturo M, Sagnelli C. Acute hepatitis C: clinical and laboratory diagnosis, course of the disease, treatment. *Infection* 2014; **42**: 601-610 [PMID: 24619833 DOI: 10.1007/s15010-014-0608-2]

4 **Sagnelli E**, Tonziello G, Pisaturo M, Sagnelli C, Coppola N. Clinical applications of antibody avidity and immunoglobulin M testing in acute HCV infection. *Antivir Ther* 2012; **17**: 1453-1458 [PMID: 23322703 DOI: 10.3851/IMP2471]

5 **Sagnelli E**, Coppola N, Marrocco C, Coviello G, Rossi G, Battaglia M, Sagnelli C, Messina V, Tonziello A, Scolastico C, Filippini P. Diagnosis of HCV related acute hepatitis by serial determination of IgM to HCV: a preliminary observation. *J Biol Regul Homeost Agents* 2003; **17**: 207-210 [PMID: 14518726]

6 **Sagnelli E**, Coppola N, Marrocco C, Coviello G, Battaglia M, Messina V, Rossi G, Sagnelli C, Scolastico C, Filippini P. Diagnosis of hepatitis C virus related acute hepatitis by serial determination of IgM anti-HCV titres. *J Hepatol* 2005; **42**: 646-651 [PMID: 15826712 DOI: 10.1016/j.jhep.2004.12.027]

7 **Coppola N**, Pisapia R, Marrocco C, Martini S, Vatiero LM, Messina V, Tonziello G, Sagnelli C, Filippini P, Piccinino F, Sagnelli E. Anti-HCV IgG avidity index in acute hepatitis C. *J Clin Virol* 2007; **40**: 110-115 [PMID: 17720621 DOI: 10.1016/j.jcv.2007.07.005]

8 **Coppola N**, Vatiero LM, Sagnelli E. HCV genotype 2 as a risk factor for reactivation of chronic HCV infection. *Gut* 2005; **54**: 1207 [PMID: 16009701 DOI: 10.1136/gut.2005.070649]

9 **Sagnelli E**, Pisaturo M, Stanzione M, Messina V, Alessio L, Sagnelli C, Starace M, Pasquale G, Coppola N. Clinical presentation, outcome, and response to therapy among patients with acute exacerbation of chronic hepatitis C. *Clin Gastroenterol Hepatol* 2013; **11**: 1174-1180.e11 [PMID: 23591280 DOI: 10.1016/j.cgh.2013.03.025]

10 **Seeff LB**. Natural history of chronic hepatitis C. *Hepatology* 2002; **36**: S35-S46 [PMID: 12407575 DOI: 10.1002/hep.1840360706]

11 **Aghemo A**, Colombo M. Hepatocellular carcinoma in chronic hepatitis C: from bench to bedside. *Semin Immunopathol* 2013; **35**: 111-120 [PMID: 23010890 DOI: 10.1007/s00281-012-0330-z]

12 **Dohmen K**, Kawano A, Takahashi K, Shigematsu H, Tanaka H, Haruno M, Yanagita K, Ichiki Y, Mori T, Hayashida K, Shimoda S, Ishibashi H, Nomura H. The incidence and risk factors for the development of hepatocellular carcinoma after peginterferon plus ribavirin therapy for chronic hepatitis C. *Hepatogastroenterology* 2013; **60**: 2034-2038 [PMID: 24719946]

13 **Harada N**, Hiramatsu N, Oze T, Morishita N, Yamada R, Hikita H, Miyazaki M, Yakushijin T, Miyagi T, Yoshida Y, Tatsumi T, Kanto T, Kasahara A, Oshita M, Mita E, Hagiwara H, Inui Y, Katayama K, Tamura S, Yoshihara H, Imai Y, Inoue A, Hayashi N, Takehara T. Risk factors for hepatocellular carcinoma in hepatitis C patients with normal alanine aminotransferase treated with pegylated interferon and ribavirin. *J Viral Hepat* 2014; **21**: 357-365 [PMID: 24716638 DOI: 10.1111/jvh.12151]

14 **Ishikawa T**. Strategy for improving survival and reducing recurrence of HCV-related hepatocellular carcinoma. *World J Gastroenterol* 2013; **19**: 6127-6130 [PMID: 24115808 DOI: 10.3748/wjg.v19.i37.6127]

15 **Kim MN**, Kim BK, Han KH. Hepatocellular carcinoma in patients with chronic hepatitis C virus infection in the Asia-Pacific region. *J Gastroenterol* 2013; **48**: 681-688 [PMID: 23463401 DOI: 10.1007/s00535-013-0770-9]

16 **Asia-Pacific Working Party on Prevention of Hepatocellular Carcino.** Prevention of hepatocellular carcinoma in the Asia-Pacific region: consensus statements. *J Gastroenterol Hepatol* 2010; **25**: 657-663 [PMID: 20492323 DOI: 10.1111/j.1440-1746.2009.06167.x]

17 **Kanda T**, Yokosuka O, Omata M. Hepatitis C virus and hepatocellular carcinoma. *Biology* (Basel) 2013; **2**: 304-316 [PMID: 24832662 DOI: 10.3390/biology2010304]

18 **Tomoda T**, Nouso K, Sakai A, Ouchida M, Kobayashi S, Miyahara K, Onishi H, Nakamura S, Yamamoto K, Shimizu K. Genetic risk of hepatocellular carcinoma in patients with hepatitis C virus: a case control study. *J Gastroenterol Hepatol* 2012; **27**: 797-804 [PMID: 22004425 DOI: 10.1111/j.1440-1746.2011.06948.x]

19 **European Association for the Study of the Liver.** EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2011; **55**: 245-264 [PMID: 21371579 DOI: 10.1016/j.jhep.2011.02.023]

20 **Coppola N**, Pisaturo M, Tonziello G, Sagnelli C, Sagnelli E, Angelillo IF. Efficacy of Pegylated interferon α-2a and α-2b in patients with genotype 1 chronic hepatitis C: a meta-analysis. *BMC Infect Dis* 2012; **12**: 357 [PMID: 23245594 DOI: 10.1186/1471-2334-12-357]

21 **Ghany MG**, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009; **49**: 1335-1374 [PMID: 19330875 DOI: 10.1002/hep.22759]

22 **Italian Association for the Study of the Liver;** Italian Society of Infectious, Tropical Diseases; Italian Society for the Study of Sexually Transmitted Diseases. Practice guidelines for the treatment of hepatitis C: recommendations from an AISF/SIMIT/SIMAST Expert Opinion Meeting. *Dig Liver Dis* 2010; **42**: 81-91 [PMID: 19748329 DOI: 10.1016/j.dld.2009.08.001]

23 **European Association of the Study of the Liver.** 2011 European Association of the Study of the Liver hepatitis C virus clinical practice guidelines. *Liver Int* 2012; **32** Suppl 1: 2-8 [PMID: 22212565 DOI: 10.1111/j.1478-3231.2011.02703.x]

24 **Sagnelli E**, Pisaturo M, Martini S, Sagnelli C, Filippini P, Coppola N. Advances in the treatment of hepatitis B virus/hepatitis C virus coinfection. *Expert Opin Pharmacother* 2014; **15**: 1337-1349 [PMID: 24773464 DOI: 10.1517/14656566.2014.913571]

25 **Thomas DL**, Thio CL, Martin MP, Qi Y, Ge D, O'Huigin C, Kidd J, Kidd K, Khakoo SI, Alexander G, Goedert JJ, Kirk GD, Donfield SM, Rosen HR, Tobler LH, Busch MP, McHutchison JG, Goldstein DB, Carrington M. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature* 2009; **461**: 798-801 [PMID: 19759533 DOI: 10.1038/nature08463]

26 **Ge D**, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, Heinzen EL, Qiu P, Bertelsen AH, Muir AJ, Sulkowski M, McHutchison JG, Goldstein DB. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; **461**: 399-401 [PMID: 19684573 DOI: 10.1038/nature08309]

27 **Suppiah V**, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, Bassendine M, Spengler U, Dore GJ, Powell E, Riordan S, Sheridan D, Smedile A, Fragomeli V, Müller T, Bahlo M, Stewart GJ, Booth DR, George J. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet* 2009; **41**: 1100-1104 [PMID: 19749758 DOI: 10.1038/ng.447]

28 **Rauch A**, Kutalik Z, Descombes P, Cai T, Di Iulio J, Mueller T, Bochud M, Battegay M, Bernasconi E, Borovicka J, Colombo S, Cerny A, Dufour JF, Furrer H, Günthard HF, Heim M, Hirschel B, Malinverni R, Moradpour D, Müllhaupt B, Witteck A, Beckmann JS, Berg T, Bergmann S, Negro F, Telenti A, Bochud PY; Swiss Hepatitis C Cohort Study; Swiss HIV Cohort Study. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. *Gastroenterology* 2010; **138**: 1338-1345, 1345.e1-7 [PMID: 20060832 DOI: 10.1053/j.gastro.2009.12.056]

29 **Fellay J**, Thompson AJ, Ge D, Gumbs CE, Urban TJ, Shianna KV, Little LD, Qiu P, Bertelsen AH, Watson M, Warner A, Muir AJ, Brass C, Albrecht J, Sulkowski M, McHutchison JG, Goldstein DB. ITPA gene variants protect against anaemia in patients treated for chronic hepatitis C. *Nature* 2010; **464**: 405-408 [PMID: 20173735 DOI: 10.1038/nature08825]

30 **Thompson AJ**, Fellay J, Patel K, Tillmann HL, Naggie S, Ge D, Urban TJ, Shianna KV, Muir AJ, Fried MW, Afdhal NH, Goldstein DB, McHutchison JG. Variants in the ITPA gene protect against ribavirin-induced hemolytic anemia and decrease the need for ribavirin dose reduction. *Gastroenterology* 2010; **139**: 1181-1189 [PMID: 20547162 DOI: 10.1053/j.gastro.2010.06.016]

31 **Ochi H**, Maekawa T, Abe H, Hayashida Y, Nakano R, Kubo M, Tsunoda T, Hayes CN, Kumada H, Nakamura Y, Chayama K. ITPA polymorphism affects ribavirin-induced anemia and outcomes of therapy--a genome-wide study of Japanese HCV virus patients. *Gastroenterology* 2010; **139**: 1190-1197 [PMID: 20637204 DOI: 10.1053/j.gastro.2010.06.071]

32 **Romeo S,** Kozlitina J, Xing C, Pertsemlidis A, Cox D, Pennacchio LA, Boerwinkle E, Cohen JC, Hobbs HH. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. *Nat Genet* 2008; **40**: 1461-1465 [PMID: 188206474 DOI: 10.1038/ng.257]

33 **Yuan X**, Waterworth D, Perry JR, Lim N, Song K, Chambers JC, Zhang W, Vollenweider P, Stirnadel H, Johnson T, Bergmann S, Beckmann ND, Li Y, Ferrucci L, Melzer D, Hernandez D, Singleton A, Scott J, Elliott P, Waeber G, Cardon L, Frayling TM, Kooner JS, Mooser V. Population-based genome-wide association studies reveal six loci influencing plasma levels of liver enzymes. *Am J Hum Genet* 2008; **83**: 520-528 [PMID: 18940312 DOI: 10.1016/j.ajhg.2008.09.012]

34 **Coppola N**, Pisaturo M, Sagnelli C, Sagnelli E, Angelillo IF. Peg-interferon plus ribavirin with or without boceprevir or telaprevir for HCV genotype 1: a meta-analysis on the role of response predictors. *PLoS One* 2014; **9**: e94542 [PMID: 24728219 DOI: 10.1371/journal.pone.0094542]

35 **Pearlman BL**. Protease inhibitors for the treatment of chronic hepatitis C genotype-1 infection: the new standard of care. *Lancet Infect Dis* 2012; **12**: 717-728 [PMID: 22647717 DOI: 10.1016/S1473-3099(12)70060-9]

36 **Welsch C**, Jesudian A, Zeuzem S, Jacobson I. New direct-acting antiviral agents for the treatment of hepatitis C virus infection and perspectives. *Gut* 2012; **61** Suppl 1: i36-i46 [PMID: 22504918 DOI: 10.1136/gutjnl-2012-302144]

37 **Butt AA**, Kanwal F. Boceprevir and telaprevir in the management of hepatitis C virus-infected patients. *Clin Infect Dis* 2012; **54**: 96-104 [PMID: 22156853 DOI: 10.1093/cid/cir774]

38 **Aghemo A**, Degasperi E, Colombo M. Directly acting antivirals for the treatment of chronic hepatitis C: unresolved topics from registration trials. *Dig Liver Dis* 2013; **45**: 1-7 [PMID: 22695478 DOI: 10.1016/j.dld.2012.05.002]

39 **Feeney ER**, Chung RT. Antiviral treatment of hepatitis C. *BMJ* 2014; **348**: g3308 [PMID: 25002352 DOI: 10.1136/bmj.g3308]

40 **Lam B**, Henry L, Younossi Z. Sofosbuvir (Sovaldi) for the treatment of hepatitis C. *Expert Rev Clin Pharmacol* 2014; **7**: 555-566 [PMID: 24918162]

41 **Degasperi E**, Aghemo A. Sofosbuvir for the treatment of chronic hepatitis C: between current evidence and future perspectives. *Hepat Med* 2014; **6**: 25-33 [PMID: 24822024 DOI: 10.2147/HMER.S44375]

42 **Lawitz E**, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, Symonds WT, McHutchison JG, Membreno FE. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. *Lancet* 2014; **383**: 515-523 [PMID: 24209977 DOI: 10.1016/S0140-6736(13)62121-2]

43 **Kowdley KV**, Lawitz E, Crespo I, Hassanein T, Davis MN, DeMicco M, Bernstein DE, Afdhal N, Vierling JM, Gordon SC, Anderson JK, Hyland RH, Dvory-Sobol H, An D, Hindes RG, Albanis E, Symonds WT, Berrey MM, Nelson DR, Jacobson IM. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. *Lancet* 2013; **381**: 2100-2107 [PMID: 23499440 DOI: 10.1016/S0140-6736(13)60247-0]

44 **Kotenko SV**, Gallagher G, Baurin VV, Lewis-Antes A, Shen M, Shah NK, Langer JA, Sheikh F, Dickensheets H, Donnelly RP. IFN-lambdas mediate antiviral protection through a distinct class II cytokine receptor complex. *Nat Immunol* 2003; **4**: 69-77 [PMID: 12483210]

45 **Marcello T**, Grakoui A, Barba-Spaeth G, Machlin ES, Kotenko SV, MacDonald MR, Rice CM. Interferons alpha and lambda inhibit hepatitis C virus replication with distinct signal transduction and gene regulation kinetics. *Gastroenterology* 2006; **131**: 1887-1898 [PMID: 17087946]

46 **Tanaka Y**, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, Nakagawa M, Korenaga M, Hino K, Hige S, Ito Y, Mita E, Tanaka E, Mochida S, Murawaki Y, Honda M, Sakai A, Hiasa Y, Nishiguchi S, Koike A, Sakaida I, Imamura M, Ito K, Yano K, Masaki N, Sugauchi F, Izumi N, Tokunaga K, Mizokami M. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009; **41**: 1105-1109 [PMID: 19749757 DOI: 10.1038/ng.449]

47 **Spada E**, Mele A, Berton A, Ruggeri L, Ferrigno L, Garbuglia AR, Perrone MP, Girelli G, Del Porto P, Piccolella E, Mondelli MU, Amoroso P, Cortese R, Nicosia A, Vitelli A, Folgori A. Multispecific T cell response and negative HCV RNA tests during acute HCV infection are early prognostic factors of spontaneous clearance. *Gut* 2004; **53**: 1673-1681 [PMID: 15479691]

48 **Folgori A**, Spada E, Pezzanera M, Ruggeri L, Mele A, Garbuglia AR, Perrone MP, Del Porto P, Piccolella E, Cortese R, Nicosia A, Vitelli A. Early impairment of hepatitis C virus specific T cell proliferation during acute infection leads to failure of viral clearance. *Gut* 2006; **55**: 1012-1019 [PMID: 16484505]

49 **Ray SC**, Wang YM, Laeyendecker O, Ticehurst JR, Villano SA, Thomas DL. Acute hepatitis C virus structural gene sequences as predictors of persistent viremia: hypervariable region 1 as a decoy. *J Virol* 1999; **73**: 2938-2946 [PMID: 10074143]

50 **Farci P**, Shimoda A, Coiana A, Diaz G, Peddis G, Melpolder JC, Strazzera A, Chien DY, Munoz SJ, Balestrieri A, Purcell RH, Alter HJ. The outcome of acute hepatitis C predicted by the evolution of the viral quasispecies. *Science* 2000; **288**: 339-344 [PMID: 10764648]

51 **Harris HE**, Eldridge KP, Harbour S, Alexander G, Teo CG, Ramsay ME. Does the clinical outcome of hepatitis C infection vary with the infecting hepatitis C virus type? *J Viral Hepat* 2007; **14**: 213-220 [PMID: 17305887 DOI: 10.1111/j.1365-2893.2006.00795.x]

52 **Ciccozzi M**, Lo Presti A, Ciccaglione AR, Zehender G, Ciotti M. Phylogeny and phylodinamic of Hepatitis C in Italy. *BMC Infect Dis* 2012; **12** Suppl 2: S5 [PMID: 23173700 DOI: 10.1186/1471-2334-12-S2-S5]

53 **Petrov V**, Stevenaert A, Collignon J. [Post-traumatic arteriovenious fistula of the posterior fossa (author's transl)]. *Neurochirurgie* 1978; **24**: 429-432 [PMID: 752817 DOI: 10.1007/BF01739909]

54 **Micallef JM**, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat* 2006; **13**: 34-41 [PMID: 16364080 DOI: 10.1111/j.1365-2893.2005.00651.x]

55 **Wang CC**, Krantz E, Klarquist J, Krows M, McBride L, Scott EP, Shaw-Stiffel T, Weston SJ, Thiede H, Wald A, Rosen HR. Acute hepatitis C in a contemporary US cohort: modes of acquisition and factors influencing viral clearance. *J Infect Dis* 2007; **196**: 1474-1482 [PMID: 18008226 DOI: 10.1086/522608]

56 **Rehermann B**. Hepatitis C virus versus innate and adaptive immune responses: a tale of coevolution and coexistence. *J Clin Invest* 2009; **119**: 1745-1754 [PMID: 19587449 DOI: 10.1172/JCI39133]

57 **Post J**, Ratnarajah S, Lloyd AR. Immunological determinants of the outcomes from primary hepatitis C infection. *Cell Mol Life Sci* 2009; **66**: 733-756 [PMID: 19011759 DOI: 10.1007/s00018-008-8270-4]

58 **Tillmann HL**, Thompson AJ, Patel K, Wiese M, Tenckhoff H, Nischalke HD, Lokhnygina Y, Kullig U, Göbel U, Capka E, Wiegand J, Schiefke I, Güthoff W, Grüngreiff K, König I, Spengler U, McCarthy J, Shianna KV, Goldstein DB, McHutchison JG, Timm J, Nattermann J. A polymorphism near IL28B is associated with spontaneous clearance of acute hepatitis C virus and jaundice. *Gastroenterology* 2010; **139**: 1586-1592, 1592.e1 [PMID: 20637200 DOI: 10.1053/j.gastro.2010.07.005]

59 **Grebely J**, Petoumenos K, Hellard M, Matthews GV, Suppiah V, Applegate T, Yeung B, Marks P, Rawlinson W, Lloyd AR, Booth D, Kaldor JM, George J, Dore GJ. Potential role for interleukin-28B genotype in treatment decision-making in recent hepatitis C virus infection. *Hepatology* 2010; **52**: 1216-1224 [PMID: 20803561 DOI: 10.1002/hep.23850]

60 **Zheng MH**, Li Y, Xiao DD, Shi KQ, Fan YC, Chen LL, Liu WY, Luo YW, Chen YP. Interleukin-28B rs12979860C/T and rs8099917T/G contribute to spontaneous clearance of hepatitis C virus in Caucasians. *Gene* 2013; **518**: 479-482 [PMID: 23266640 DOI: 10.1016/j.gene.2012.12.067]

61 **Calleri G**, Cariti G, Gaiottino F, De Rosa FG, Bargiacchi O, Audagnotto S, Quaglia S, De Blasi T, Romano P, Traverso A, Leo G, Carbone R, Del Mastro B, Tinelli M, Caramello P, Di Perri G. A short course of pegylated interferon-alpha in acute HCV hepatitis. *J Viral Hepat* 2007; **14**: 116-121 [PMID: 17244251 DOI: 10.1111/j.1365-2893.2006.00802.x]

62 **Kamal SM**, Moustafa KN, Chen J, Fehr J, Abdel Moneim A, Khalifa KE, El Gohary LA, Ramy AH, Madwar MA, Rasenack J, Afdhal NH. Duration of peginterferon therapy in acute hepatitis C: a randomized trial. *Hepatology* 2006; **43**: 923-931 [PMID: 16628640 DOI: 10.1002/hep.21197]

63 **De Rosa FG**, Bargiacchi O, Audagnotto S, Garazzino S, Cariti G, Calleri G, Lesioba O, Belloro S, Raiteri R, Di Perri G. Twelve-week treatment of acute hepatitis C virus with pegylated interferon- alpha -2b in injection drug users. *Clin Infect Dis* 2007; **45**: 583-588 [PMID: 17682992 DOI: 10.1086/520660]

64 **Santantonio T**, Fasano M, Sagnelli E, Tundo P, Babudieri S, Fabris P, Toti M, Di Perri G, Marino N, Pizzigallo E, Angarano G. Acute hepatitis C: a 24-week course of pegylated interferon α-2b versus a 12-week course of pegylated interferon α-2b alone or with ribavirin. *Hepatology* 2014; **59**: 2101-2109 [PMID: 24442928 DOI: 10.1002/hep.26991]

65 **Deterding K**, Grüner N, Buggisch P, Wiegand J, Galle PR, Spengler U, Hinrichsen H, Berg T, Potthoff A, Malek N, Großhennig A, Koch A, Diepolder H, Lüth S, Feyerabend S, Jung MC, Rogalska-Taranta M, Schlaphoff V, Cornberg M, Manns MP, Wedemeyer H. Delayed versus immediate treatment for patients with acute hepatitis C: a randomised controlled non-inferiority trial. *Lancet Infect Dis* 2013; **13**: 497-506 [PMID: 23523674 DOI: 10.1016/S1473-3099(13)70059-8]

66 **Grebely J**, Page K, Sacks-Davis R, van der Loeff MS, Rice TM, Bruneau J, Morris MD, Hajarizadeh B, Amin J, Cox AL, Kim AY, McGovern BH, Schinkel J, George J, Shoukry NH, Lauer GM, Maher L, Lloyd AR, Hellard M, Dore GJ, Prins M. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. *Hepatology* 2014; **59**: 109-120 [PMID: 23908124 DOI: 10.1002/hep.26639]

67 **Abe H**, Ochi H, Maekawa T, Hayes CN, Tsuge M, Miki D, Mitsui F, Hiraga N, Imamura M, Takahashi S, Ohishi W, Arihiro K, Kubo M, Nakamura Y, Chayama K. Common variation of IL28 affects gamma-GTP levels and inflammation of the liver in chronically infected hepatitis C virus patients. *J Hepatol* 2010; **53**: 439-443 [PMID: 20576307 DOI: 10.1016/j.jhep.2010.03.022]

68 **Marabita F**, Aghemo A, De Nicola S, Rumi MG, Cheroni C, Scavelli R, Crimi M, Soffredini R, Abrignani S, De Francesco R, Colombo M. Genetic variation in the interleukin-28B gene is not associated with fibrosis progression in patients with chronic hepatitis C and known date of infection. *Hepatology* 2011; **54**: 1127-1134 [PMID: 21721028 DOI: 10.1002/hep.24503]

69 **Fabris C**, Falleti E, Cussigh A, Bitetto D, Fontanini E, Bignulin S, Cmet S, Fornasiere E, Fumolo E, Fangazio S, Cerutti A, Minisini R, Pirisi M, Toniutto P. IL-28B rs12979860 C/T allele distribution in patients with liver cirrhosis: role in the course of chronic viral hepatitis and the development of HCC. *J Hepatol* 2011; **54**: 716-722 [PMID: 21146242 DOI: 10.1016/j.jhep.2010.07.019]

70 **Joshita S**, Umemura T, Katsuyama Y, Ichikawa Y, Kimura T, Morita S, Kamijo A, Komatsu M, Ichijo T, Matsumoto A, Yoshizawa K, Kamijo N, Ota M, Tanaka E. Association of IL28B gene polymorphism with development of hepatocellular carcinoma in Japanese patients with chronic hepatitis C virus infection. *Hum Immunol* 2012; **73**: 298-300 [PMID: 22245236 DOI: 10.1016/j.humimm.2011.12.021]

71 **Chayama K**, Hayes CN, Abe H, Miki D, Ochi H, Karino Y, Toyota J, Nakamura Y, Kamatani N, Sezaki H, Kobayashi M, Akuta N, Suzuki F, Kumada H. IL28B but not ITPA polymorphism is predictive of response to pegylated interferon, ribavirin, and telaprevir triple therapy in patients with genotype 1 hepatitis C. *J Infect Dis* 2011; **204**: 84-93 [PMID: 21628662 DOI: 10.1093/infdis/jir210]

72 **Thompson AJ**, McHutchison JG. Will IL28B polymorphism remain relevant in the era of direct-acting antiviral agents for hepatitis C virus? *Hepatology* 2012; **56**: 373-381 [PMID: 22511355 DOI: 10.1002/hep.25792]

73 **Liu S**, Cipriano LE, Holodniy M, Owens DK, Goldhaber-Fiebert JD. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. *Ann Intern Med* 2012; **156**: 279-290 [PMID: 22351713 DOI: 10.7326/0003-4819-156-4-201202210-00005]

74 **Gane EJ**, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, Berrey MM. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013; **368**: 34-44 [PMID: 23281974 DOI: 10.1056/NEJMoa1208953]

75 **Poordad F**, Lawitz E, Kowdley KV, Cohen DE, Podsadecki T, Siggelkow S, Heckaman M, Larsen L, Menon R, Koev G, Tripathi R, Pilot-Matias T, Bernstein B. Exploratory study of oral combination antiviral therapy for hepatitis C. *N Engl J Med* 2013; **368**: 45-53 [PMID: 23281975 DOI: 10.1056/NEJMoa1208809]

76 **Koff RS**. Review article: the efficacy and safety of sofosbuvir, a novel, oral nucleotide NS5B polymerase inhibitor, in the treatment of chronic hepatitis C virus infection. *Aliment Pharmacol Ther* 2014; **39**: 478-487 [PMID: 24387618 DOI: 10.1111/apt.12601]

77 **Sulkowski MS**, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Schwartz H, Nelson DR, Everson GT, Eley T, Wind-Rotolo M, Huang SP, Gao M, Hernandez D, McPhee F, Sherman D, Hindes R, Symonds W, Pasquinelli C, Grasela DM. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014; **370**: 211-221 [PMID: 24428467 DOI: 10.1056/NEJMoa1306218]

78 **Li S**, Hu P, Zhang QQ, Liu YH, Hu HD, Zhang DZ, Ren H. Single nucleotide polymorphisms of the IL28B and sustained virologic response of patients with chronic hepatitis C to PEG-interferon/ribavirin therapy: A meta-analysis: Meta-analysis of IL28B. *Hepat Mon* 2011; **11**: 163-172 [PMID: 22087138]

79 **Rangnekar AS**, Fontana RJ. Meta-analysis: IL-28B genotype and sustained viral clearance in HCV genotype 1 patients. *Aliment Pharmacol Ther* 2012; **36**: 104-114 [PMID: 22612303 DOI: 10.1111/j.1365-2036.2012.05145.x]

80 **Chen Y**, Xu HX, Wang LJ, Liu XX, Mahato RI, Zhao YR. Meta-analysis: IL28B polymorphisms predict sustained viral response in HCV patients treated with pegylated interferon-α and ribavirin. *Aliment Pharmacol Ther* 2012; **36**: 91-103 [PMID: 22591106 DOI: 10.1111/j.1365-2036.2012.05131.x]

81 **Jiménez-Sousa MA**, Fernández-Rodríguez A, Guzmán-Fulgencio M, García-Álvarez M, Resino S. Meta-analysis: implications of interleukin-28B polymorphisms in spontaneous and treatment-related clearance for patients with hepatitis C. *BMC Med* 2013; **11**: 6 [PMID: 23298311 DOI: 10.1186/1741-7015-11-6]

82 **Eslam M**, Leung R, Romero-Gomez M, Mangia A, Irving WL, Sheridan D, Spengler U, Mollison L, Cheng W, Bugianesi E, McLeod D, Zaitoun AM, Attino V, Goeltz D, Nattermann J, Douglas M, Booth DR, George J, Ahlenstiel G. IFNL3 polymorphisms predict response to therapy in chronic hepatitis C genotype 2/3 infection. *J Hepatol* 2014; **61**: 235-241 [PMID: 24768758 DOI: 10.1016/j.jhep.2014.03.039]

83 **Sarrazin C**, Susser S, Doehring A, Lange CM, Müller T, Schlecker C, Herrmann E, Lötsch J, Berg T. Importance of IL28B gene polymorphisms in hepatitis C virus genotype 2 and 3 infected patients. *J Hepatol* 2011; **54**: 415-421 [PMID: 21112657 DOI: 10.1016/j.jhep.2010.07.041]

84 **Hayashi K**, Katano Y, Ishizu Y, Kuzuya T, Honda T, Ishigami M, Itoh A, Hirooka Y, Ishikawa T, Nakano I, Yoshioka K, Toyoda H, Kumada T, Goto H. Association of interleukin 28B polymorphism and mutations in the NS5A region of hepatitis C virus genotype 2 with interferon responsiveness. *J Gastroenterol Hepatol* 2015; **30**: 178-183 [PMID: 24995561 DOI: 10.1111/jgh.12673]

85 **Firdaus R**, Biswas A, Saha K, Mukherjee A, Chaudhuri S, Chandra A, Konar A, Sadhukhan PC. Impact of host IL28B rs12979860, rs8099917 in interferon responsiveness and advanced liver disease in chronic genotype 3 hepatitis C patients. *PLoS One* 2014; **9**: e99126 [PMID: 24914551 DOI: 10.1371/journal.pone.0099126]

86 **Boglione L**, Cusato J, De Nicolò A, Cariti G, Allegra S, Ghisetti V, Di Perri G, D'Avolio A. Identification of naïve HVC-4 patients who may be treated with pegylated-interferon and ribavirin according to IL28B polymorphisms. *Antiviral Res* 2014; **106**: 105-110 [PMID: 24726902 DOI: 10.1016/j.antiviral.2014.03.016]

87 **Youssef SS**, Abbas EA, Abd el Aal AM, Omran MH, Barakat A, Seif SM. IL28B rs 12979860 predicts response to treatment in Egyptian hepatitis C virus genotype 4 patients and alpha fetoprotein increases its predictive strength. *J Interferon Cytokine Res* 2014; **34**: 505-509 [PMID: 24660823 DOI: 10.1089/jir.2013.0115]

88 **Guedj J**, Pang PS, Denning J, Rodriguez-Torres M, Lawitz E, Symonds W, Perelson AS. Analysis of hepatitis C viral kinetics during administration of two nucleotide analogues: sofosbuvir (GS-7977) and GS-0938. *Antivir Ther* 2014; **19**: 211-220 [PMID: 24464551 DOI: 10.3851/IMP2733]

89 **Charlton MR**, Thompson A, Veldt BJ, Watt K, Tillmann H, Poterucha JJ, Heimbach JK, Goldstein D, McHutchison J. Interleukin-28B polymorphisms are associated with histological recurrence and treatment response following liver transplantation in patients with hepatitis C virus infection. *Hepatology* 2011; **53**: 317-324 [PMID: 21254179 DOI: 10.1002/hep.24074]

90 **Fukuhara T**, Taketomi A, Motomura T, Okano S, Ninomiya A, Abe T, Uchiyama H, Soejima Y, Shirabe K, Matsuura Y, Maehara Y. Variants in IL28B in liver recipients and donors correlate with response to peg-interferon and ribavirin therapy for recurrent hepatitis C. *Gastroenterology* 2010; **139**: 1577-1585, 1585.e1-3 [PMID: 20708617 DOI: 10.1053/j.gastro.2010.07.058]

91 **Rydel TJ**, Williams JM, Krieger E, Moshiri F, Stallings WC, Brown SM, Pershing JC, Purcell JP, Alibhai MF. The crystal structure, mutagenesis, and activity studies reveal that patatin is a lipid acyl hydrolase with a Ser-Asp catalytic dyad. *Biochemistry* 2003; **42**: 6696-6708 [PMID: 12779324 DOI: 10.1021/bi027156r]

92 **He S,** McPhaul C, Li JZ, Garuti R, Kinch L, Grishin NV, Cohen JC, Hobbs H. A sequence variation (I148M) in PNPLA3 associated with nonalcoholic fatty liver disease disrupts triglyceride hydrolysis. *J Biol Chem* 2010; **285**: 6706-6715 [ PMID: 20034933 DOI: 10.1074/jbc.M109.064501]

93 **Westin J**, Nordlinder H, Lagging M, Norkrans G, Wejstål R. Steatosis accelerates fibrosis development over time in hepatitis C virus genotype 3 infected patients. *J Hepatol* 2002; **37**: 837-842 [PMID: 12445426 DOI: 10.1016/S0168-8278(02)00299-4]

94 **Adinolfi LE**, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001; **33**: 1358-1364 [PMID: 11391523 DOI: 10.1053/jhep.2001.24432]

95 **Akuta N**, Suzuki F, Tsubota A, Suzuki Y, Someya T, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Kumada H. Efficacy of interferon monotherapy to 394 consecutive naive cases infected with hepatitis C virus genotype 2a in Japan: therapy efficacy as consequence of tripartite interaction of viral, host and interferon treatment-related factors. *J Hepatol* 2002; **37**: 831-836 [PMID: 12445425 DOI: 10.1016/S0168-8278(02)00301-X]

96 **Trépo E**, Pradat P, Potthoff A, Momozawa Y, Quertinmont E, Gustot T, Lemmers A, Berthillon P, Amininejad L, Chevallier M, Schlué J, Kreipe H, Devière J, Manns M, Trépo C, Sninsky J, Wedemeyer H, Franchimont D, Moreno C. Impact of patatin-like phospholipase-3 (rs738409 C& gt; G) polymorphism on fibrosis progression and steatosis in chronic hepatitis C. *Hepatology* 2011; **54**: 60-69 [PMID: 21488075 DOI: 10.1002/hep.24350]

97 **Valenti L**, Rumi M, Galmozzi E, Aghemo A, Del Menico B, De Nicola S, Dongiovanni P, Maggioni M, Fracanzani AL, Rametta R, Colombo M, Fargion S. Patatin-like phospholipase domain-containing 3 I148M polymorphism, steatosis, and liver damage in chronic hepatitis C. *Hepatology* 2011; **53**: 791-799 [PMID: 21319195 DOI: 10.1002/hep.24123]

98 **Cai T**, Dufour JF, Muellhaupt B, Gerlach T, Heim M, Moradpour D, Cerny A, Malinverni R, Kaddai V, Bochud M, Negro F, Bochud PY. Viral genotype-specific role of PNPLA3, PPARG, MTTP, and IL28B in hepatitis C virus-associated steatosis. *J Hepatol* 2011; **55**: 529-535 [PMID: 21236304 DOI: 10.1016/j.jhep.2010.12.020]

99 **Zampino R**, Coppola N, Cirillo G, Boemio A, Pisaturo M, Marrone A, Macera M, Sagnelli E, Perrone L, Adinolfi LE, Miraglia del Giudice E. Abdominal fat interacts with PNPLA3 I148M, but not with the APOC3 variant in the pathogenesis of liver steatosis in chronic hepatitis C. *J Viral Hepat* 2013; **20**: 517-523 [PMID: 23808989 DOI: 10.1111/jvh.12053]

100 **Zampino R**, Florio A, Coppola N, Cirillo G, Macera M, Marrone A, Adinolfi LE, Del Giudice EM. PNPLA3 I148M variant as a risk factor for carotid atherosclerosis in chronic hepatitis C. *Int J Cardiol* 2014; **172**: 291-292 [PMID: 24461483 DOI: 10.1016/j.ijcard.2013.12.231]

101 **Clark PJ**, Thompson AJ, Zhu Q, Vock DM, Zhu M, Patel K, Harrison SA, Naggie S, Ge D, Tillmann HL, Urban TJ, Shianna K, Fellay J, Goodman Z, Noviello S, Pedicone LD, Afdhal N, Sulkowski M, Albrecht JK, Goldstein DB, McHutchison JG, Muir AJ. The association of genetic variants with hepatic steatosis in patients with genotype 1 chronic hepatitis C infection. *Dig Dis Sci* 2012; **57**: 2213-2221 [PMID: 22543885 DOI: 10.1007/s10620-012-2171-y]

102 **Nakamura M**, Kanda T, Nakamoto S, Miyamura T, Jiang X, Wu S, Yokosuka O. No correlation between PNPLA3 rs738409 genotype and fatty liver and hepatic cirrhosis in Japanese patients with HCV. *PLoS One* 2013; **8**: e81312 [PMID: 24349054 DOI: 10.1371/journal.pone.0081312]

103 **Dunn W**, O'Neil M, Zhao J, Wu CH, Roberts B, Chakraborty S, Sherman C, Weaver B, Taylor R, Olson J, Olyaee M, Gilroy R, Schmitt T, Wan YJ, Weinman SA. Donor PNPLA3 rs738409 genotype affects fibrosis progression in liver transplantation for hepatitis C. *Hepatology* 2014; **59**: 453-460 [PMID: 24123231 DOI: 10.1002/hep.26758]

104 **Nischalke HD**, Berger C, Luda C, Berg T, Müller T, Grünhage F, Lammert F, Coenen M, Krämer B, Körner C, Vidovic N, Oldenburg J, Nattermann J, Sauerbruch T, Spengler U. The PNPLA3 rs738409 148M/M genotype is a risk factor for liver cancer in alcoholic cirrhosis but shows no or weak association in hepatitis C cirrhosis. *PLoS One* 2011; **6**: e27087 [PMID: 22087248 DOI: 10.1371/journal.pone.0027087]

105 **Guyot E**, Sutton A, Rufat P, Laguillier C, Mansouri A, Moreau R, Ganne-Carrié N, Beaugrand M, Charnaux N, Trinchet JC, Nahon P. PNPLA3 rs738409, hepatocellular carcinoma occurrence and risk model prediction in patients with cirrhosis. *J Hepatol* 2013; **58**: 312-318 [PMID: 23069476 DOI: 10.1016/j.jhep.2012.09.036]

106 **Trépo E**, Nahon P, Bontempi G, Valenti L, Falleti E, Nischalke HD, Hamza S, Corradini SG, Burza MA, Guyot E, Donati B, Spengler U, Hillon P, Toniutto P, Henrion J, Franchimont D, Devière J, Mathurin P, Moreno C, Romeo S, Deltenre P. Association between the PNPLA3 (rs738409 C& gt; G) variant and hepatocellular carcinoma: Evidence from a meta-analysis of individual participant data. *Hepatology* 2014; **59**: 2170-2177 [PMID: 24114809 DOI: 10.1002/hep.26767]

107 **Lai MY**, Kao JH, Yang PM, Wang JT, Chen PJ, Chan KW, Chu JS, Chen DS. Long-term efficacy of ribavirin plus interferon alfa in the treatment of chronic hepatitis C. *Gastroenterology* 1996; **111**: 1307-1312 [PMID: 8898645 DOI: 10.1053/gast.1996.v111.pm8898645]

108 **Hézode C**, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, Bronowicki JP, Bourlière M, Gharakhanian S, Bengtsson L, McNair L, George S, Kieffer T, Kwong A, Kauffman RS, Alam J, Pawlotsky JM, Zeuzem S. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med* 2009; **360**: 1839-1850 [PMID: 19403903 DOI: 10.1056/NEJMoa0807650]

109 **Fried MW**. Side effects of therapy of hepatitis C and their management. *Hepatology* 2002; **36**: S237-S244 [PMID: 12407599 DOI: 10.1002/hep.1840360730]

110 **Hadziyannis SJ**, Sette H, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; **140**: 346-355 [PMID: 14996676 DOI: 10.7326/0003-4819-140-5-200403020-00010]

111 **McHutchison JG**, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, Dienstag J, Lee WM, Mak C, Garaud JJ, Albrecht JK. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology* 2002; **123**: 1061-1069 [PMID: 12360468 DOI: 10.1053/gast.2002.35950]

112 **Reddy KR**, Shiffman ML, Morgan TR, Zeuzem S, Hadziyannis S, Hamzeh FM, Wright TL, Fried M. Impact of ribavirin dose reductions in hepatitis C virus genotype 1 patients completing peginterferon alfa-2a/ribavirin treatment. *Clin Gastroenterol Hepatol* 2007; **5**: 124-129 [PMID: 17196435 DOI: 10.1016/j.cgh.2006.10.008]

113 **Kwo PY**, Lawitz EJ, McCone J, Schiff ER, Vierling JM, Pound D, Davis MN, Galati JS, Gordon SC, Ravendhran N, Rossaro L, Anderson FH, Jacobson IM, Rubin R, Koury K, Pedicone LD, Brass CA, Chaudhri E, Albrecht JK. Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naive patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet* 2010; **376**: 705-716 [PMID: 20692693 DOI: 10.1016/S0140-6736(10)60934-8]

114 **Stickel F**, Helbling B, Heim M, Geier A, Hirschi C, Terziroli B, Wehr K, De Gottardi A, Negro F, Gerlach T. Critical review of the use of erythropoietin in the treatment of anaemia during therapy for chronic hepatitis C. *J Viral Hepat* 2012; **19**: 77-87 [PMID: 22239497 DOI: 10.1111/j.1365-2893.2011.01527.x]

115 **De Franceschi L**, Fattovich G, Turrini F, Ayi K, Brugnara C, Manzato F, Noventa F, Stanzial AM, Solero P, Corrocher R. Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C virus infection: role of membrane oxidative damage. *Hepatology* 2000; **31**: 997-1004 [PMID: 10733558 DOI: 10.1053/he.2000.5789]

116 **Thompson AJ**, Santoro R, Piazzolla V, Clark PJ, Naggie S, Tillmann HL, Patel K, Muir AJ, Shianna KV, Mottola L, Petruzzellis D, Romano M, Sogari F, Facciorusso D, Goldstein DB, McHutchison JG, Mangia A. Inosine triphosphatase genetic variants are protective against anemia during antiviral therapy for HCV2/3 but do not decrease dose reductions of RBV or increase SVR. *Hepatology* 2011; **53**: 389-395 [PMID: 21274861 DOI: 10.1002/hep.24068]

117 **Sumi S**, Marinaki AM, Arenas M, Fairbanks L, Shobowale-Bakre M, Rees DC, Thein SL, Ansari A, Sanderson J, De Abreu RA, Simmonds HA, Duley JA. Genetic basis of inosine triphosphate pyrophosphohydrolase deficiency. *Hum Genet* 2002; **111**: 360-367 [PMID: 12384777 DOI: 10.1007/s00439-002-0798-z]

118 **Cao H**, Hegele RA. DNA polymorphisms in ITPA including basis of inosine triphosphatase deficiency. *J Hum Genet* 2002; **47**: 620-622 [PMID: 12436200 DOI: 10.1007/s100380200095]

119 **Arenas M**, Duley J, Sumi S, Sanderson J, Marinaki A. The ITPA c.94C& gt; A and g.IVS2+21A& gt; C sequence variants contribute to missplicing of the ITPA gene. *Biochim Biophys Acta* 2007; **1772**: 96-102 [PMID: 17113761]

120 **Stepchenkova EI**, Tarakhovskaya ER, Spitler K, Frahm C, Menezes MR, Simone PD, Kolar C, Marky LA, Borgstahl GE, Pavlov YI. Functional study of the P32T ITPA variant associated with drug sensitivity in humans. *J Mol Biol* 2009; **392**: 602-613 [PMID: 19631656 DOI: 10.1016/j.jmb.2009.07.051]

121 **Hitomi Y**, Cirulli ET, Fellay J, McHutchison JG, Thompson AJ, Gumbs CE, Shianna KV, Urban TJ, Goldstein DB. Inosine triphosphate protects against ribavirin-induced adenosine triphosphate loss by adenylosuccinate synthase function. *Gastroenterology* 2011; **140**: 1314-1321 [PMID: 21199653 DOI: 10.1053/j.gastro.2010.12.038]

122 **Hai H**, Tamori A, Enomoto M, Morikawa H, Uchida-Kobayashi S, Fujii H, Hagihara A, Kawamura E, Thuy le TT, Tanaka Y, Kawada N. Relationship between inosine triphosphate genotype and outcome of extended therapy in hepatitis C virus patients with a late viral response to pegylated-interferon and ribavirin. *J Gastroenterol Hepatol* 2014; **29**: 201-207 [PMID: 23980585 DOI: 10.1111/jgh.12376]

123 **Ahmed WH**, Furusyo N, Zaky S, Eldin AS, Aboalam H, Ogawa E, Murata M, Hayashi J. Pre-treatment role of inosine triphosphate pyrophosphatase polymorphism for predicting anemia in Egyptian hepatitis C virus patients. *World J Gastroenterol* 2013; **19**: 1387-1395 [PMID: 23538996 DOI: 10.3748/wjg.v19.i9.1387]

124 **Azakami T**, Hayes CN, Sezaki H, Kobayashi M, Akuta N, Suzuki F, Kumada H, Abe H, Miki D, Tsuge M, Imamura M, Kawakami Y, Takahashi S, Ochi H, Nakamura Y, Kamatani N, Chayama K. Common genetic polymorphism of ITPA gene affects ribavirin-induced anemia and effect of peg-interferon plus ribavirin therapy. *J Med Virol* 2011; **83**: 1048-1057 [PMID: 21503919 DOI: 10.1002/jmv.22069]

125 **Kurosaki M**, Tanaka Y, Nishida N, Sakamoto N, Enomoto N, Matsuura K, Asahina Y, Nakagawa M, Watanabe M, Sakamoto M, Maekawa S, Tokunaga K, Mizokami M, Izumi N. Model incorporating the ITPA genotype identifies patients at high risk of anemia and treatment failure with pegylated-interferon plus ribavirin therapy for chronic hepatitis C. *J Med Virol* 2013; **85**: 449-458 [PMID: 23297176 DOI: 10.1002/jmv.23497]

126 **Matsuura K**, Tanaka Y, Watanabe T, Fujiwara K, Orito E, Kurosaki M, Izumi N, Sakamoto N, Enomoto N, Yatsuhashi H, Kusakabe A, Shinkai N, Nojiri S, Joh T, Mizokami M. ITPA genetic variants influence efficacy of PEG-IFN/RBV therapy in older patients infected with HCV genotype 1 and favourable IL28B type. *J Viral Hepat* 2014; **21**: 466-474 [PMID: 24750345 DOI: 10.1111/jvh.12171]

127 **DʼAvolio A**, Ciancio A, Siccardi M, Smedile A, Baietto L, Simiele M, Marucco DA, Cariti G, Calcagno A, de Requena DG, Sciandra M, Cusato J, Troshina G, Bonora S, Rizzetto M, Di Perri G. Inosine triphosphatase polymorphisms and ribavirin pharmacokinetics as determinants of ribavirin-associate anemia in patients receiving standard anti-HCV treatment. *Ther Drug Monit* 2012; **34**: 165-170 [PMID: 22406654 DOI: 10.1097/FTD.0b013e31824bf778]

128 **Eskesen AN**, Melum E, Moghaddam A, Bjøro K, Verbaan H, Ring-Larsen H, Dalgard O. Genetic variants at the ITPA locus protect against ribavirin-induced hemolytic anemia and dose reduction in an HCV G2/G3 cohort. *Eur J Gastroenterol Hepatol* 2012; **24**: 890-896 [PMID: 22584257 DOI: 10.1097/MEG.0b013e3283546efd]

129 **Seto WK**, Tsang OT, Liu K, Chan JM, Wong DK, Fung J, Lai CL, Yuen MF. Role of IL28B and inosine triphosphatase polymorphisms in the treatment of chronic hepatitis C virus genotype 6 infection. *J Viral Hepat* 2013; **20**: 470-477 [PMID: 23730840 DOI: 10.1111/jvh.12047]

130 **Rau M**, Stickel F, Russmann S, Manser CN, Becker PP, Weisskopf M, Schmitt J, Dill MT, Dufour JF, Moradpour D, Semela D, Müllhaupt B, Geier A. Impact of genetic SLC28 transporter and ITPA variants on ribavirin serum level, hemoglobin drop and therapeutic response in patients with HCV infection. *J Hepatol* 2013; **58**: 669-675 [PMID: 23195617 DOI: 10.1016/j.jhep.2012.11.027]

131 **Clark PJ**, Aghemo A, Degasperi E, Galmozzi E, Urban TJ, Vock DM, Patel K, Thompson AJ, Rumi MG, D'Ambrosio R, Muir AJ, Colombo M. Inosine triphosphatase deficiency helps predict anaemia, anaemia management and response in chronic hepatitis C therapy. *J Viral Hepat* 2013; **20**: 858-866 [PMID: 24304455 DOI: 10.1111/jvh.12113]

132 **Rembeck K**, Waldenström J, Hellstrand K, Nilsson S, Nyström K, Martner A, Lindh M, Norkrans G, Westin J, Pedersen C, Färkkilä M, Langeland N, Buhl MR, Mørch K, Christensen PB, Lagging M. Variants of the inosine triphosphate pyrophosphatase gene are associated with reduced relapse risk following treatment for HCV genotype 2/3. *Hepatology* 2014; **59**: 2131-2139 [PMID: 24519039 DOI: 10.1002/hep.27009]

133 **Suzuki F**, Suzuki Y, Akuta N, Sezaki H, Hirakawa M, Kawamura Y, Hosaka T, Kobayashi M, Saito S, Arase Y, Ikeda K, Kobayashi M, Chayama K, Kamatani N, Nakamura Y, Miyakawa Y, Kumada H. Influence of ITPA polymorphisms on decreases of hemoglobin during treatment with pegylated interferon, ribavirin, and telaprevir. *Hepatology* 2011; **53**: 415-421 [PMID: 21246582 DOI: 10.1002/hep.24058]

134 **Ogawa E**, Furusyo N, Nakamuta M, Kajiwara E, Nomura H, Dohmen K, Takahashi K, Satoh T, Azuma K, Kawano A, Tanabe Y, Kotoh K, Shimoda S, Hayashi J. Clinical milestones for the prediction of severe anemia by chronic hepatitis C patients receiving telaprevir-based triple therapy. *J Hepatol* 2013; **59**: 667-674 [PMID: 23707372 DOI: 10.1016/j.jhep.2013.05.017]

135 **Aghemo A**, Grassi E, Rumi MG, D'Ambrosio R, Galmozzi E, Degasperi E, Castaldi D, Soffredini R, Colombo M. Limited utility of ITPA deficiency to predict early anemia in HCV patients with advanced fibrosis receiving Telaprevir. *PLoS One* 2014; **9**: e95881 [PMID: 24760000 DOI: 10.1371/journal.pone.0095881]

136 **Arteh J**, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. *Dig Dis Sci* 2010; **55**: 2624-2628 [PMID: 19960254 DOI: 10.1007/s10620-009-1069-9]

137 **Petta S**, Cammà C, Scazzone C, Tripodo C, Di Marco V, Bono A, Cabibi D, Licata G, Porcasi R, Marchesini G, Craxí A. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. *Hepatology* 2010; **51**: 1158-1167 [PMID: 20162613 DOI: 10.1002/hep.23489]

138 **Bitetto D**, Fattovich G, Fabris C, Ceriani E, Falleti E, Fornasiere E, Pasino M, Ieluzzi D, Cussigh A, Cmet S, Pirisi M, Toniutto P. Complementary role of vitamin D deficiency and the interleukin-28B rs12979860 C/T polymorphism in predicting antiviral response in chronic hepatitis C. *Hepatology* 2011; **53**: 1118-1126 [PMID: 21480318 DOI: 10.1002/hep.24201]

139 **Lange CM**, Bojunga J, Ramos-Lopez E, von Wagner M, Hassler A, Vermehren J, Herrmann E, Badenhoop K, Zeuzem S, Sarrazin C. Vitamin D deficiency and a CYP27B1-1260 promoter polymorphism are associated with chronic hepatitis C and poor response to interferon-alfa based therapy. *J Hepatol* 2011; **54**: 887-893 [PMID: 21145801 DOI: 10.1016/j.jhep.2010.08.036]

140 **Falleti E**, Cmet S, Fabris C, Fattovich G, Cussigh A, Bitetto D, Ceriani E, Lenisa I, Dissegna D, Ieluzzi D, Rostello A, Pirisi M, Toniutto P. Genetic polymorphisms of vitamin D pathway predict antiviral treatment outcome in slow responder naïve patients with chronic hepatitis C. *PLoS One* 2013; **8**: e80764 [PMID: 24244713 DOI: 10.1371/journal.pone.0080764]

141 **Falleti E**, Bitetto D, Fabris C, Fattovich G, Cussigh A, Cmet S, Ceriani E, Fornasiere E, Pasino M, Ieluzzi D, Pirisi M, Toniutto P. Vitamin D binding protein gene polymorphisms and baseline vitamin D levels as predictors of antiviral response in chronic hepatitis C. *Hepatology* 2012; **56**: 1641-1650 [PMID: 22610885 DOI: 10.1002/hep.25848]

142 **Baur K**, Mertens JC, Schmitt J, Iwata R, Stieger B, Frei P, Seifert B, Bischoff Ferrari HA, von Eckardstein A, Müllhaupt B, Geier A. The vitamin D receptor gene bAt (CCA) haplotype impairs the response to pegylated-interferon/ribavirin-based therapy in chronic hepatitis C patients. *Antivir Ther* 2012; **17**: 541-547 [PMID: 22300961 DOI: 10.3851/IMP2018]

143 **Baur K**, Mertens JC, Schmitt J, Iwata R, Stieger B, Eloranta JJ, Frei P, Stickel F, Dill MT, Seifert B, Ferrari HA, von Eckardstein A, Bochud PY, Müllhaupt B, Geier A. Combined effect of 25-OH vitamin D plasma levels and genetic vitamin D receptor (NR 1I1) variants on fibrosis progression rate in HCV patients. *Liver Int* 2012; **32**: 635-643 [PMID: 22151003 DOI: 10.1111/j.1478-3231.2011.02674.x]

144 **García-Martín E**, Agúndez JA, Maestro ML, Suárez A, Vidaurreta M, Martínez C, Fernández-Pérez C, Ortega L, Ladero JM. Influence of vitamin D-related gene polymorphisms (CYP27B and VDR) on the response to interferon/ribavirin therapy in chronic hepatitis C. *PLoS One* 2013; **8**: e74764 [PMID: 24073221 DOI: 10.1371/journal.pone.0074764]

145 **Huang H**, Shiffman ML, Friedman S, Venkatesh R, Bzowej N, Abar OT, Rowland CM, Catanese JJ, Leong DU, Sninsky JJ, Layden TJ, Wright TL, White T, Cheung RC. A 7 gene signature identifies the risk of developing cirrhosis in patients with chronic hepatitis C. *Hepatology* 2007; **46**: 297-306 [PMID: 17461418]

146 **Marcolongo M**, Young B, Dal Pero F, Fattovich G, Peraro L, Guido M, Sebastiani G, Palù G, Alberti A. A seven-gene signature (cirrhosis risk score) predicts liver fibrosis progression in patients with initially mild chronic hepatitis C. *Hepatology* 2009; **50**: 1038-1044 [PMID: 19676127 DOI: 10.1002/hep.23111]

147 **Curto TM**, Lagier RJ, Lok AS, Everhart JE, Rowland CM, Sninsky JJ. Predicting cirrhosis and clinical outcomes in patients with advanced chronic hepatitis C with a panel of genetic markers (CRS7). *Pharmacogenet Genomics* 2011; **21**: 851-860 [PMID: 21946897 DOI: 10.1097/FPC.0b013e32834c3e74]

148 **Trépo E**, Potthoff A, Pradat P, Bakshi R, Young B, Lagier R, Moreno C, Verset L, Cross R, Degré D, Lemmers A, Gustot T, Berthillon P, Rosenberg W, Trépo C, Sninsky J, Adler M, Wedemeyer H. Role of a cirrhosis risk score for the early prediction of fibrosis progression in hepatitis C patients with minimal liver disease. *J Hepatol* 2011; **55**: 38-44 [PMID: 21145859 DOI: 10.1016/j.jhep.2010.10.018]

149 **Fernández-Rodríguez A**, Berenguer J, Jiménez-Sousa MA, Guzmán-Fulgencio M, Micheloud D, Miralles P, López JC, Bellón JM, Aldamiz-Echevarria T, García-Broncano P, Carrero A, Alvarez E, Resino S. Prediction of hepatic fibrosis in patients coinfected with HIV and hepatitis C virus based on genetic markers. *J Acquir Immune Defic Syndr* 2013; **64**: 434-442 [PMID: 23797694 DOI: 10.1097/QAI.0b013e3182a06eb6]

150 **do O NT**, Eurich D, Schmitz P, Schmeding M, Heidenhain C, Bahra M, Trautwein C, Neuhaus P, Neumann UP, Wasmuth HE. A 7-gene signature of the recipient predicts the progression of fibrosis after liver transplantation for hepatitis C virus infection. *Liver Transpl* 2012; **18**: 298-304 [PMID: 22139994 DOI: 10.1002/lt.22475]

151 **Yee LJ**, Im K, Borg B, Yang H, Liang TJ. Interleukin-6 haplotypes and the response to therapy of chronic hepatitis C virus infection. *Genes Immun* 2009; **10**: 365-372 [PMID: 19387461 DOI: 10.1038/gene.2009.26]

152 **Nattermann J**, Vogel M, Berg T, Danta M, Axel B, Mayr C, Bruno R, Tural C, Klausen G, Clotet B, Lutz T, Grünhage F, Rausch M, Nischalke HD, Schewe K, Bienek B, Haerter G, Sauerbruch T, Rockstroh JK, Spengler U. Effect of the interleukin-6 C174G gene polymorphism on treatment of acute and chronic hepatitis C in human immunodeficiency virus coinfected patients. *Hepatology* 2007; **46**: 1016-1025 [PMID: 17668881]

153 **Falleti E**, Fabris C, Vandelli C, Colletta C, Cussigh A, Smirne C, Fontanini E, Cmet S, Minisini R, Bitetto D, Toniutto P, Pirisi M. Genetic polymorphisms of interleukin-6 modulate fibrosis progression in mild chronic hepatitis C. *Hum Immunol* 2010; **71**: 999-1004 [PMID: 20655350 DOI: 10.1016/j.humimm.2010.06.006]

154 **Cussigh A**, Falleti E, Fabris C, Bitetto D, Cmet S, Fontanini E, Bignulin S, Fornasiere E, Fumolo E, Minisini R, Pirisi M, Toniutto P. Interleukin 6 promoter polymorphisms influence the outcome of chronic hepatitis C. *Immunogenetics* 2011; **63**: 33-41 [PMID: 21072509 DOI: 10.1007/s00251-010-0491-7]

155 **Huang Y**, Yang H, Borg BB, Su X, Rhodes SL, Yang K, Tong X, Tang G, Howell CD, Rosen HR, Thio CL, Thomas DL, Alter HJ, Sapp RK, Liang TJ. A functional SNP of interferon-gamma gene is important for interferon-alpha-induced and spontaneous recovery from hepatitis C virus infection. *Proc Natl Acad Sci U S A* 2007; **104**: 985-990 [PMID: 17215375]

156 **Khakoo SI**, Thio CL, Martin MP, Brooks CR, Gao X, Astemborski J, Cheng J, Goedert JJ, Vlahov D, Hilgartner M, Cox S, Little AM, Alexander GJ, Cramp ME, O'Brien SJ, Rosenberg WM, Thomas DL, Carrington M. HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. *Science* 2004; **305**: 872-874 [PMID: 15297676]

157 **Knapp S**, Warshow U, Hegazy D, Brackenbury L, Guha IN, Fowell A, Little AM, Alexander GJ, Rosenberg WM, Cramp ME, Khakoo SI. Consistent beneficial effects of killer cell immunoglobulin-like receptor 2DL3 and group 1 human leukocyte antigen-C following exposure to hepatitis C virus. *Hepatology* 2010; **51**: 1168-1175 [PMID: 20077564 DOI: 10.1002/hep.23477]

158 **Coppola N**, Zampino R, Bellini G, Macera M, Marrone A, Pisaturo M, Boemio A, Nobili B, Pasquale G, Maione S, Adinolfi LE, Perrone L, Sagnelli E, Miraglia Del Giudice E, Rossi F. Association between a polymorphism in cannabinoid receptor 2 and severe necroinflammation in patients with chronic hepatitis C. *Clin Gastroenterol Hepatol* 2014; **12**: 334-340 [PMID: 23707465 DOI: 10.1016/j.cgh.2013.05.008]

159 **Coppola N**, Zampino R, Sagnelli C, Bellini G, Marrone A, Stanzione M, Capoluongo N, Boemio A, Minichini C, Adinolfi LE, Maione S, Del Giudice EM, Sagnelli E, Rossi F. Cannabinoid receptor 2-63 QQ variant is associated with persistently normal aminotransferase serum levels in chronic hepatitis C. *PLoS One* 2014; **9**: e99450 [PMID: 24940753 DOI: 10.1371/journal.pone.0099450]

160 **Carrasquer A**, Nebane NM, Williams WM, Song ZH. Functional consequences of nonsynonymous single nucleotide polymorphisms in the CB2 cannabinoid receptor. *Pharmacogenet Genomics* 2010; **20**: 157-166 [PMID: 20124950 DOI: 10.1097/FPC.0b013e3283367c6b]

161 **Sipe JC**, Arbour N, Gerber A, Beutler E. Reduced endocannabinoid immune modulation by a common cannabinoid 2 (CB2) receptor gene polymorphism: possible risk for autoimmune disorders. *J Leukoc Biol* 2005; **78**: 231-238 [PMID: 15845647]

162 **Lange CM**, Miki D, Ochi H, Nischalke HD, Bojunga J, Bibert S, Morikawa K, Gouttenoire J, Cerny A, Dufour JF, Gorgievski-Hrisoho M, Heim MH, Malinverni R, Müllhaupt B, Negro F, Semela D, Kutalik Z, Müller T, Spengler U, Berg T, Chayama K, Moradpour D, Bochud PY. Genetic analyses reveal a role for vitamin D insufficiency in HCV-associated hepatocellular carcinoma development. *PLoS One* 2013; **8**: e64053 [PMID: 23734184 DOI: 10.1371/journal.pone.0064053]

163 **Hellier S**, Frodsham AJ, Hennig BJ, Klenerman P, Knapp S, Ramaley P, Satsangi J, Wright M, Zhang L, Thomas HC, Thursz M, Hill AV. Association of genetic variants of the chemokine receptor CCR5 and its ligands, RANTES and MCP-2, with outcome of HCV infection. *Hepatology* 2003; **38**: 1468-1476 [PMID: 14647058]

164 **Nattermann J**, Timm J, Nischalke HD, Olbrich A, Michalk M, Tillmann HL, Berg T, Wedemeyer H, Tenckhoff H, Wiese M, Kullig U, Göbel U, Capka E, Schiefke I, Güthof W, Grüngreiff K, König I, Roggendorf M, Sauerbruch T, Spengler U. The predictive value of IL28B gene polymorphism for spontaneous clearance in a single source outbreak cohort is limited in patients carrying the CCR5Δ32 mutation. *J Hepatol* 2011; **55**: 1201-1206 [PMID: 21703201 DOI: 10.1016/j.jhep.2011.03.011]

165 **Goulding C**, McManus R, Murphy A, MacDonald G, Barrett S, Crowe J, Hegarty J, McKiernan S, Kelleher D. The CCR5-delta32 mutation: impact on disease outcome in individuals with hepatitis C infection from a single source. *Gut* 2005; **54**: 1157-1161 [PMID: 15863470]

**P-Reviewer:** Sirin G, Yokoyama Y **S-Editor:** Tian YL

**L-Editor: E-Editor:**

**Table 1** **Studies on the role of the rs738409PNPLA3 polymorphisms in HCV 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) |
| Trepo *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 (CI 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 |  |  |  |  |

1GG + GC *vs* CC non-genotype 3; 2Steatosis > 5%; 3Rs2896019 GG + GT *vs* TT genotype 1; 4Steatosis > 32%; 5GG + GC *vs* CC donors; 6Occurrence of Ishak staging ≥ 3, acute cellular rejection, chronic rejection or fibrosing cholestatic hepatitis during a 620-d (IQR 317-975) follow-up; 7226 pts; 8GG+GC *vs* CC, US diagnosis of steatosis and cirrhosis; 9F3 or F4; 10470 pts; 11325 pts.

**Table 2** **Studies on the role of ITPA polymorphisms in HCV chronic infection**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **No. of**  **patients** | **Country** | **Type of Study** | **SNPs** | **Liver disease/**  **HCV genotype** | **Therapy** | **Outcome** |
| Thompson *et al*[30] | 304 | USA | 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 × 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 | USA | 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 wks (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 × 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, ≥ 3g/dL reduction or < 10g/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 ITPase 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 × 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 *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 m2 (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 versus 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 HCV 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  rs731236  rs1544410  CC/CC/AA3 |  | OR = 2.67 (95%CI: 1.24-5.70)1,4  OR = 6.05 (95%CI: 1.71-21.43)2,4  No association (*P* = 0.085)  OR = 2.50 (95%CI: 1.07-5.87)4 |  |
| Baur *et al*[143] | 223 | Switzerland | Cross-sectional | 185 Chronic hepatitis  38 Cirrhosis | rs7975232  rs731236  rs1544410  CC/CC/AA3 | 2.67 (95%CI: 1.29-5.51)1  No association  No association  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  rs7041  rs4588  rs10877012  VDPFA7 |  | 1.778 (95%CI: 1.135-2.788)6  No association (*P* = 0.679)  No association(*P* = 0.458  No association (*P* = 0.422)  OR = 2.30 (95%CI: 1.02-5.22)8 |  |
| Garcia-Martin *et al*[144] | 238 | Spain | Cross-sectional | 169 Chronic hepatitis  33 Cirrhosis  36 Not assessed | rs2228570  CC/CC/AA3 |  | 0.438 (95%CI: 0.204-0.882)4,9  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 a* [162] | 5604 | Germany, Switzerland, Japan | Case-control/ retrospective cohort | 1279 HCC  4325 Chronic liver disease | rs2282679rs7944926rs1993116 |  |  | OR = 1.56 (95%CI: 1.12-2.15)10 OR = 1.56 (95%CI: 1.13-1.78)11 No association (*P* = 0.07)12 HR = 1.81 (95%CI: 1.03-3.13)13 |

1CC *vs* CA + AA; 2AA + AG *vs* GG; 3CCA haplotype comprises rs1544410 (BsmI) C, rs7975232 (ApaI) C and rs731236 (TaqI) A alleles of *VDR* gene; 4OR for non-SVR; 5OR for non-SVR in WT *vs* non-WT; WT were patients carrying ≥ 3 major alleles (GG/CC, GT/CC and GG/CA); 6GG + GC *vs* CC; 7VDPFA (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; 8VPDFA > 5 *vs* ≤ 5; 9TT + TC *vs* CC; 10TT + TG *vs* GG, 2534 pts; 11TT *vs* TC + CC, 2420 pts; 125591 pts; 13GG *vs* GA + AA, 1657 pts.

**Table 4** **Role of other SNPs in HCV infection**

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

PNALT: Persistently normal alanine-amino-transferase; HAI: Histological activity index; CHC: Chronic hepatitis C.