**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 4853**

**Columns:** Minireviews

**Interaction of IFNL3 with insulin resistance, steatosis and lipid metabolism in chronic** hepatitis C virus  **infection**

Eslam M *et al.* IFNL3 and metabolic profiles in HCV infection

Mohammed Eslam, David R Booth, Jacob George, Golo Ahlenstiel



**Mohammed Eslam, Jacob George and Golo Ahlenstiel,** Storr Liver Unit, Westmead Millennium Institute and Westmead Hospital, University of Sydney, Sydney, NSW 2145, Australia

**David R Booth,** Institute for Immunology and Allergy Research, Westmead Millennium Institute, University of Sydney, Sydney, NSW 2145, Australia

**Author Contributions:** Mohammed Eslam and Golo Ahlenstiel designed and wrote the manuscript and created the tables; David R Booth and Jacob George contributed to the writing and revised the manuscript.

**Supported by** a National Health and Medical Research Council Project grant (APP1006759) and the Robert W. Storr bequest to the Sydney Medical Foundation of the University of Sydney (Ahlenstiel G and George J); an International Postgraduate Research Scholarships and an Australian Postgraduate Award of the University of Sydney (Eslam M)

**Corresponding to: Dr. Golo Ahlenstiel,** Storr Liver Unit, Department of Gastroenterology and Hepatology, Westmead Hospital, Hawkesbury Road, Westmead, Sydney, NSW 2145, Australia. golo.ahlenstiel@sydney.edu.au

**Telephone:** +61-2- 98457705 **Fax:** +61- 2-9635 7582

**Received:** July 27, 2013  **Revised:** September 14, 2013

**Accepted:** September 29, 2013

**Published online:**

**Abstract**

Metabolic changes are inextricably linked to chronic hepatitis C (CHC). Recently polymorphisms in the IFNL3 (IL28B) region have been shown to be strongly associated with spontaneous and treatment induced recovery from hepatitis C virus (HCV) infection. Further, circumstantial evidence suggests a link between IFNL3 SNPs and lipid metabolism, steatosis and insulin resistance in CHC. The emerging picture suggests that the responder genotypes of IFNL3 polymorphisms are associated with a higher serum lipid profile, and less frequent steatosis and insulin resistance. This review analyzes the current data regarding this interaction and its meaning for HCV pathogenesis and disease progression.

© 2013 Baishideng. All rights reserved.

**Key words:** IFNL3; Chronic hepatitis C; Insulin resistance; Lipids

**Core tip:** Metabolic changes are inextricably linked to chronic hepatitis C (CHC). Recently polymorphisms in the IFNL3 region have been shown to be strongly associated with spontaneous and treatment induced recovery from hepatitis C virus (HCV) infection. Further, circumstantial evidence suggests a link between IFNL3 SNPs and lipid metabolism, steatosis and insulin resistance in CHC. The emerging picture suggests that the responder genotypes of IFNL3 polymorphisms are associated with a higher serum lipid profile, and less frequent steatosis and insulin resistance. This review analyzes the current data regarding this interaction and its meaning for HCV pathogenesis and disease progression.

Eslam M, Booth DR, George J, Ahlenstiel G. Interaction of IFNL3 with insulin resistance, steatosis and lipid metabolism in chronic hepatitis C virus infection.

**Available from:**

**DOI:**

**INTRODUCTION**

Hepatitis C virus (HCV) infection affects about 170 million people worldwide. It leads to slow but progressive hepatic inflammation and fibrosis in as many as 70% of infected individuals. Over time, 20% will develop cirrhosis and its related complications, and about 1%-2% of subjects may develop hepatocellular carcinoma after 2-3 decades of infection[1]. The natural history of HCV infection in terms of chronicity and disease progression seems to be largely determined by the host immune response to virus-infected hepatocytes. The interplay between many viral, host, genetic and environmental factors modifies the course of HCV infection and the degree of hepatic inflammation. In this context, the discovery of the association between IFNL3 polymorphisms and spontaneous or treatment induced clearance of HCV presented a major milestone in the study of chronic hepatitis C (CHC)[2-5].

Metabolic syndrome is a constellation of problems that includes obesity, dyslipidemia, diabetes, and insulin resistance[6]. The prevalence of metabolic syndrome is increasing, paralleling the obesity epidemic worldwide and in the United States and European countries especially[7]. Multiple levels of interaction between HCV, metabolic syndrome and genetics have been recently postulated, including a molecular interaction between IFNL3 polymorphisms and HCV associated glucose and lipid metabolism. In this review we summarize the current clinical evidence for an interaction between IFNL3 polymorphisms and metabolic syndrome, and its clinical implications.

**IFNS LAMBDA AND HEPATITIS C VIRUS**

The type III interferon (IFN) or IFN-λ (IFNL) family consists of three members: IFN-λ1, IFN-λ2 and IFN-λ3 (formerly known as IL-29, IL-28A and IL-28B), which were discovered in 2003 by computational prediction and are genetically distinct from type I IFNs[8,9], and a fourth, IFN-λ4, recently described from primary human hepatocytes[10]. Another recent study identified a novel TT/-G polymorphism in the CpG region upstream of IL28B, which is a better predictor of HCV clearance than rs12979860[11]. Whereas IFN-α binds to the constitutively expressed type I IFN receptor in almost all nucleated cells, IFN‑λ cytokines bind to a heterodimer of part of the IL-10 receptor and the IFNL receptor (IL10RA and IL28R, respectively)[12], the latter of which is only expressed in restricted cell types, including epithelial cells, plasmacytoid dendritic cells and hepatocytes[13]. IFNL stimulation results in the upregulation of interferon stimulated genes (ISGs) via the Jak–STAT (Janus kinase–signal transducer and activator of transcription) pathway similar to type I IFNs[12,14].

In an attempt to identify host genetic markers for IFN responsiveness to predict treatment outcome in CHC, genome-wide association studies identified SNPs in the IFNL3 (IL28B) region to be strongly associated not only with response to treatment with pegylated IFN-α (Peg-IFN-α) with ribavirin (RBV) in HCV genotype 1 infection[2-5], but also spontaneous recovery[15] (Table 1). This association has been validated in different ethnic populations and for various HCV genotypes[16,17]. In a recent meta-analysis, IFNL3 polymorphisms seem to be clinically useful even in the era of new direct acting antiviral drugs[18]. Moreover, the responder genotypes of the IFNL3 polymorphisms have been reported to be associated with increased hepatic inflammation in CHC patients[19,20].

**HCV-ASSOCIATED METABOLIC CHANGES**

CHC can be considered not only a viral disease, but also a metabolic disease. HCV interacts with lipid metabolism leading to steatosis, it impairs glucose metabolism leading to insulin resistance (IR) and diabetes mellitus type II and is associated with an increased risk of carotid atherosclerosis[21,22].

The prevalence of steatosis in patients with CHC is reported to be between 40 and 80% depending on the features of the population studied in terms of alcohol consumption, prevalence of overweight/obesity, diabetes and other risk factors for fatty liver[23,24]. However, when all common contributing factors to steatosis have been excluded, the prevalence of steatosis in CHC still remains about 40%. This figure represents an approximately 2-fold increase compared to the prevalence of steatosis in other common chronic liver diseases such as chronic hepatitis B virus infection (20%)[25].

Various studies have shown that both host and viral factors may contribute to the development of steatosis, with the relative importance of each varying with HCV genotype. In particular, in patients infected with HCV genotype 3, steatosis seems to be mostly virus-induced and often severe[20,26]. In contrast, in patients infected with non-genotype 3, steatosis seems to be mainly associated with host metabolic factors and correlates with body mass index (BMI) and central adiposity[3,27,28].

Steatosis is known to have deleterious clinical consequences in CHC, as it is associated with accelerated progression of liver fibrosis[29] and probably HCC[30]. It has also been shown in large clinical trials that steatosis impairs the response to antiviral therapy[31]. However, the effect is more prominent in patients with non-3a genotype[31], likely due to IR as the underlying mechanism affecting the response to standard dual therapy with Peg-IFN-α/ RBV, and suggesting that the viral steatosis does not impair response to treatment[26]. Increasing levels of IR are associated with reduced rates of rapid virological response (RVR) as well as SVR in patients with HCV genotype 1, 2, 3 and 4 infections when treated with dual therapy comprising Peg-IFN-α and RBV[32-34]. This observation has been confirmed in two meta-analyses[35,36]. A direct correlation between lipid profiles and the virologic response to Peg-IFN-α and RBV was also reported in some recent studies[37,38].

**IFNL3 POLYMORPHISM AND LIPID METABOLISM**

Since the discovery of the correlation of IFNL3 polymorphisms with HCV clearance, there is an accumulating body of evidence about an association between these polymorphisms and metabolic changes in CHC.

The IFNL3 responder genotype is associated with less pronounced disturbances of lipid metabolism in CHC, as reflected by higher serum cholesterol and lipoprotein levels: CHC genotype 1 individuals with IFNL3 rs12979860 CC genotype have significantly higher apolipoprotein B and LDL cholesterol (LDL-C) levels[39], and lower serum apolipoprotein E levels[40], compared to those with the non-responder CT and TT genotypes. In accordance with these findings, another study from Japan showed that the responder genotype of rs8099917 TT was associated with high LDL-C levels and high SVR[41]. This association may result from suppression of hepatic lipase and lipoprotein lipase by endogenous interferon, which in turn decreases serum LDL-C, implying a stronger endogenous interferon response to HCV in those subjects[37].

In a small cohort (55 patients), Sheridan *et al*[40] showed that although HCV RNA was significantly higher in those with rs12979860 CC genotype, this difference was mainly accounted for by a higher non-lipoviral particles (LVP) fraction. It is known that LVPs are low-density HCV particles that have high infectivity[42]. This may partially explain the paradox that the IFNL3 responder genotypes have higher HCVRNA total viral load, despite high viral load being a negative predictor of SVR[43]. However, further confirmation of this data in larger cohorts is required before any final conclusion can be extracted.

Chiba-Falek *et al*[44] investigated the genetic basis for the variance of LDL-C and apolipoprotein B levels in CHC patients and their potential interaction with IFNL3 genotype: Their data show that two of the APOE genomic region polymorphisms, rs7412 and rs429358 (which defines the ε4 isoform), appear to be associated with serum lipoprotein levels in HCV patients. Polymorphisms in ε4, however, were not associated with apolipoprotein E levels in HCV-infected Caucasians patients (in contrast to a healthy control cohort), and the overall amount of variance in serum apolipoprotein E levels explained by APOE genotype was much lower in the HCV cohort (7% *vs* 20 %). A recent genome-wide association studies in non-HCV-infected cohorts suggested associations of polymorphisms at the TOMM40-APOE genomic region with multiple lipid traits (LDL-C, triglycerides)[45]. In particular, two nonsynonymous single nucleotide polymorphisms in exon 4 of the APOE gene, rs429358 and rs7412 have been associated with lipid levels[45]. Further this study also refers to a potential interaction between TOMM40-APOE and IFNL3 polymorphisms, as rs429358 was associated with apolipoprotein B levels in a IFNL3 genotype dependent manner, i.e. the effect was more profound in patients carrying rs12979860 CC, than those carrying rs12979860 CT/TT. These results together suggest that HCV-associated dyslipidemia may not be controlled to the same extent by the same genes that affect lipids/lipoproteins in healthy (non-HCV infected) cohorts[44].

There is increasing evidence that the life cycle of HCV is directly linked to host lipoproteins: (1) HCV circulates in plasma with lipoprotein as an infectious complex; (2) Hepatocyte lipoprotein receptors are involved in HCV entry; (3) Replication of HCV RNA in hepatic cells is inhibited by inhibitors of lipid metabolism; (4) HCV particles released from hepatocytes are attached to lipoproteins; and (5) Serum lipid profiles (LDL-C, HDL-C and triglycerides) are associated with higher rates of spontaneous or treatment-induced HCV clearance[46]. At least, the latter is also affected by IFNL3 polymorphisms, opening up the possibility of interaction in mediating this effect. Thus, better understanding of the interaction between lipids, IFNL3 polymorphisms and the HCV life cycle will improve our understanding of HCV pathogenesis and open new avenues in treating HCV infection.

**IFNL3 POLYMORPHISM AND STEATOSIS**

The relationship between steatosis and IFNL3 genotype is still subject to debate, as the current literature demonstrates conflicting results. A retrospective analysis of 1604 patients enrolled in the IDEAL trial (Individualized Dosing Efficacy Versus Flat Dosing to Assess Optimal Pegylated Interferon Therapy) of HCV genotype 1 patients showed that the IFNL3 rs12979860 CC responder genotype was significantly associated with higher pretreatment LDL-C levels and less frequent hepatic steatosis[47]. In keeping with this, other recent studies show the same association between the IFNL3 rs12979860 CC genotype and less frequent steatosis in CHC genotype 1[48-50]. This observation also extends to two other IFNL3 polymorphisms, rs8099917[51] and rs12980275, which were associated with steatosis in genotypes non-3[52]. In contrast, a study from Japan failed to find a significant association between rs8099917 and hepatic steatosis in 122 Japanese Mongolian patients infected with HCV genotype 1b[53], and another study from Spain failed to confirm an association between rs12979860 and steatosis in 445 Caucasian patients[54]. These conflicting results may be owing to the relatively small sample size of these cohorts, differences in ethnicity, population characteristics and local other risk factors for steatosis, different IFNL3 SNPs being investigated, which may exhibit different features, and the respective assessments of individual pathologists.

In the setting of liver transplantation for CHC, a recent abstract presented at the European Association for the Study of the Liver (EASL) meeting 2013 suggested that IFNL3 rs12979860 TT nonresponder genotypes had an increased incidence of graft steatosis over time, while recipient IFNL3 was not associated with steatosis[55].

In an attempt to better understand the interaction of IFNL3 polymorphisms with other polymorphisms in influencing steatosis, a recent study investigated the interaction between IFNL3 rs12979860 and the Patatin-like phospholipase domain-containing 3 (PNPLA3) rs738409 polymorphism, a strong determinant of hepatic fat accumulation and steatohepatitis[56]. Albeit, the association between rs12979860 genotype and steatosis was independent of PNPLA3 GG genotype, the rs12979860 CC genotype protected from steatosis only in patients positive for the PNPLA3 G variant, a genetic risk factor for severe steatosis[57]. In another study, the PNPLA3 G variant showed a close association with steatosis in patients with rs12979860 CT/TT, but not rs12979860 CC genotype[54]. These findings suggest a potential interaction between IFNL3 and PNPLA3 polymorphisms on the risk for steatosis in non-genotype 3 CHC patients, though further analysis is required to better understand the nature of this interaction.

Finally, an interaction between IFNL3 genotype and an amino acid substitution at residue 70 (aa70) of the HCV core region has been suggested[53]. Although these authors failed to find a direct association between rs8099917 and hepatic steatosis, they found significant associations between rs8099917 and aa70 and between aa70 and hepatic steatosis[53]. This suggests that the amino acid at residue 70 of the HCV core region should be considered as a parameter for adjustment in any future studies of the correlation between IFNL3 genotype and steatosis.

**IFNL3 POLYMORPHISM AND INSULIN RESISTANCE**

The relationship between IR measured by HOMA and IFNL3 genotype is still subject to debate. Two recent reports showed that the responder IFNL3 rs12979860 CC genotype was associated with reduced IR in HCV genotype 1 patients[49-50], while other reports failed to find this association[58-60] with either rs8099917[58] or rs12979860[58-60]. Interestingly, a recent study from Spain shows that IR can predict SVR in CHC patients independently of the IFNL3 rs12979860 polymorphism[60]. This is quite intriguing as it sheds new light on the clinical observations linking higher LDL, less steatosis and lower insulin resistance with SVR.

**CONCLUSION**

In conclusion, the discovery of IFNL3 polymorphisms and their impact on CHC presents a major breakthrough in HCV research. The association of IFNL3 responder genotypes with higher LDL, less steatosis, less insulin resistance and SVR suggests a mechanistic link between IFNL3 and the metabolic syndrome in CHC. This sheds new light on the pathogenesis of CHC and opens exciting avenues to explore. Further work is needed to better understand the mechanistic explanation of these interrelated associations, and its potential implications in improving the current management of CHC patients.

**REFERENCES**

1 **Lee UE**, Friedman SL. Mechanisms of hepatic fibrogenesis. *Best Pract Res Clin Gastroenterol* 2011; **25**: 195-206 [PMID: 21497738 DOI: 10.1016/j.bpg.2011.02.005]

2 **Bochud PY**, Bibert S, Kutalik Z, Patin E, Guergnon J, Nalpas B, Goossens N, Kuske L, Müllhaupt B, Gerlach T, Heim MH, Moradpour D, Cerny A, Malinverni R, Regenass S, Dollenmaier G, Hirsch H, Martinetti G, Gorgiewski M, Bourlière M, Poynard T, Theodorou I, Abel L, Pol S, Dufour JF, Negro F. IL28B alleles associated with poor hepatitis C virus (HCV) clearance protect against inflammation and fibrosis in patients infected with non-1 HCV genotypes. *Hepatology* 2012; **55**: 384-394 [PMID: 22180014 DOI: 10.1002/hep.24678]

3 **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]

4 **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]

5 **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. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. *Gastroenterology* 2010; **138**: 1338-145, 1338-145, [PMID: 20060832 DOI: 10.1053/j.gastro.2009.12.056]

6 **Farrell GC**, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; **43**: S99-S112 [PMID: 16447287]

7 **Ford ES**, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among u.s. Adults. *Diabetes Care* 2004; **27**: 2444-2449 [PMID: 15451914]

8 **Gad HH**, Dellgren C, Hamming OJ, Vends S, Paludan SR, Hartmann R. Interferon-lambda is functionally an interferon but structurally related to the interleukin-10 family. *J Biol Chem* 2009; **284**: 20869-20875 [PMID: 19457860 DOI: 10.1074/jbc.M109.002923]

9 **Sheppard P**, Kindsvogel W, Xu W, Henderson K, Schlutsmeyer S, Whitmore TE, Kuestner R, Garrigues U, Birks C, Roraback J, Ostrander C, Dong D, Shin J, Presnell S, Fox B, Haldeman B, Cooper E, Taft D, Gilbert T, Grant FJ, Tackett M, Krivan W, McKnight G, Clegg C, Foster D, Klucher KM. IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nat Immunol* 2003; **4**: 63-68 [PMID: 12469119]

10 **Prokunina-Olsson L**, Muchmore B, Tang W, Pfeiffer RM, Park H, Dickensheets H, Hergott D, Porter-Gill P, Mumy A, Kohaar I, Chen S, Brand N, Tarway M, Liu L, Sheikh F, Astemborski J, Bonkovsky HL, Edlin BR, Howell CD, Morgan TR, Thomas DL, Rehermann B, Donnelly RP, O'Brien TR. A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. *Nat Genet* 2013; **45**: 164-171 [PMID: 23291588 DOI: 10.1038/ng.2521]

11 **Bibert S**, Roger T, Calandra T, Bochud M, Cerny A, Semmo N, Duong FH, Gerlach T, Malinverni R, Moradpour D, Negro F, Müllhaupt B, Bochud PY. IL28B expression depends on a novel TT/-G polymorphism which improves HCV clearance prediction. *J Exp Med* 2013; **210**: 1109-1116 [PMID: 23712427 DOI: 10.1084/jem.20130012]

12 **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]

13 **Sommereyns C**, Paul S, Staeheli P, Michiels T. IFN-lambda (IFN-lambda) is expressed in a tissue-dependent fashion and primarily acts on epithelial cells in vivo. *PLoS Pathog* 2008; **4**: e1000017 [PMID: 18369468 DOI: 10.1371/journal.ppat.1000017]

14 **Zhang L**, Jilg N, Shao RX, Lin W, Fusco DN, Zhao H, Goto K, Peng LF, Chen WC, Chung RT. IL28B inhibits hepatitis C virus replication through the JAK-STAT pathway. *J Hepatol* 2011; **55**: 289-298 [PMID: 21147189 DOI: 10.1016/j.jhep.2010.11.019]

15 **Grebely J**, Feld JJ, Applegate T, Matthews GV, Hellard M, Sherker A, Petoumenos K, Zang G, Shaw I, Yeung B, George J, Teutsch S, Kaldor JM, Cherepanov V, Bruneau J, Shoukry NH, Lloyd AR, Dore GJ. Plasma interferon-gamma-inducible protein-10 (IP-10) levels during acute hepatitis C virus infection. *Hepatology* 2013; **57**: 2124-2134 [PMID: 23325615 DOI: 10.1002/hep.26263]

16 **Mangia A**, Thompson AJ, Santoro R, Piazzolla V, Tillmann HL, Patel K, Shianna KV, Mottola L, Petruzzellis D, Bacca D, Carretta V, Minerva N, Goldstein DB, McHutchison JG. An IL28B polymorphism determines treatment response of hepatitis C virus genotype 2 or 3 patients who do not achieve a rapid virologic response. *Gastroenterology* 2010; **139**: 821-87 [PMID: 20621700 DOI: 10.1053/j.gastro.2010.05.079]

17 **De Nicola S**, Aghemo A, Rumi MG, Galmozzi E, Valenti L, Soffredini R, De Francesco R, Prati GM, D'Ambrosio R, Cheroni C, Donato MF, Colombo M. Interleukin 28B polymorphism predicts pegylated interferon plus ribavirin treatment outcome in chronic hepatitis C genotype 4. *Hepatology* 2012; **55**: 336-342 [PMID: 21932415 DOI: 10.1002/hep.24683]

18 **Bota S**, Sporea I, Şirli R, Neghină AM, Popescu A, Străin M. Role of interleukin-28B polymorphism as a predictor of sustained virological response in patients with chronic hepatitis C treated with triple therapy: a systematic review and meta-analysis. *Clin Drug Investig* 2013; **33**: 325-331 [PMID: 23532802 DOI: 10.1007/s40261-013-0074-0]

19 **Noureddin M,** Wright EC, Alter H, Clark S, Thomas E, Chen R, Zhao X, Conry-Cantilena C, Kleiner D, Liang TJ, Ghany MG. Association of IL28B genotype with fibrosis progression and clinical outcomes in patients with chronic hepatitis C: A longitudinal analysis. *Hepatology* 2013; [PMID: 23703931 DOI: 10.1002/hep.26506] [Epub ahead of print]

20 **Bochud PY**, Bibert S, Kutalik Z, Patin E, Guergnon J, Nalpas B, Goossens N, Kuske L, Müllhaupt B, Gerlach T, Heim MH, Moradpour D, Cerny A, Malinverni R, Regenass S, Dollenmaier G, Hirsch H, Martinetti G, Gorgiewski M, Bourlière M, Poynard T, Theodorou I, Abel L, Pol S, Dufour JF, Negro F. IL28B alleles associated with poor hepatitis C virus (HCV) clearance protect against inflammation and fibrosis in patients infected with non-1 HCV genotypes. *Hepatology* 2012; **55**: 384-394 [PMID: 22180014 DOI: 10.1002/hep.24678]

21 **Eslam M**, Khattab MA, Harrison SA. Insulin resistance and hepatitis C: an evolving story. *Gut* 2011; **60**: 1139-1151 [PMID: 21252203 DOI: 10.1136/gut.2010.228262]

22 **Hui JM**, Sud A, Farrell GC, Bandara P, Byth K, Kench JG, McCaughan GW, George J. Insulin resistance is associated with chronic hepatitis C virus infection and fibrosis progression corrected. *Gastroenterology* 2003; **125**: 1695-1704 [PMID: 14724822]

23 **Asselah T**, Rubbia-Brandt L, Marcellin P, Negro F. Steatosis in chronic hepatitis C: why does it really matter? *Gut* 2006; **55**: 123-130 [PMID: 16344578]

24 **Thomopoulos KC**, Arvaniti V, Tsamantas AC, Dimitropoulou D, Gogos CA, Siagris D, Theocharis GJ, Labropoulou-Karatza C. Prevalence of liver steatosis in patients with chronic hepatitis B: a study of associated factors and of relationship with fibrosis. *Eur J Gastroenterol Hepatol* 2006; **18**: 233-237 [PMID: 16462535]

25 **Rubbia-Brandt L**, Quadri R, Abid K, Giostra E, Malé PJ, Mentha G, Spahr L, Zarski JP, Borisch B, Hadengue A, Negro F. Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3. *J Hepatol* 2000; **33**: 106-115 [PMID: 10905593]

26 **Kumar D**, Farrell GC, Fung C, George J. Hepatitis C virus genotype 3 is cytopathic to hepatocytes: Reversal of hepatic steatosis after sustained therapeutic response. *Hepatology* 2002; **36**: 1266-1272 [PMID: 12395339]

27 **Khattab MA**, Abdel-fattah ME, Eslam M, Abdelaleem A, Abdelaleem RA, Shatat M, Ali A, Hamdy L, Tawfek H. Hepatic steatosis in genotype 4 chronic hepatitis C patients: implication for therapy. *J Clin Gastroenterol* 2010; **44**: 707-712 [PMID: 20195166 DOI: 10.1097/MCG.0b013e3181d2ef1a]

28 **Del Campo JA**, Romero-Gómez M. Steatosis and insulin resistance in hepatitis C: a way out for the virus? *World J Gastroenterol* 2009; **15**: 5014-5019 [PMID: 19859993 DOI: 10.3748/wjg.15.5014]

29 **Leandro G**, Mangia A, Hui J, Fabris P, Rubbia-Brandt L, Colloredo G, Adinolfi LE, Asselah T, Jonsson JR, Smedile A, Terrault N, Pazienza V, Giordani MT, Giostra E, Sonzogni A, Ruggiero G, Marcellin P, Powell EE, George J, Negro F. Relationship between steatosis, inflammation, and fibrosis in chronic hepatitis C: a meta-analysis of individual patient data. *Gastroenterology* 2006; **130**: 1636-1642 [PMID: 16697727]

30 **Ohata K**, Hamasaki K, Toriyama K, Matsumoto K, Saeki A, Yanagi K, Abiru S, Nakagawa Y, Shigeno M, Miyazoe S, Ichikawa T, Ishikawa H, Nakao K, Eguchi K. Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. *Cancer* 2003; **97**: 3036-3043 [PMID: 12784339]

31 **Poynard T**, Ratziu V, McHutchison J, Manns M, Goodman Z, Zeuzem S, Younossi Z, Albrecht J. Effect of treatment with peginterferon or interferon alfa-2b and ribavirin on steatosis in patients infected with hepatitis C. *Hepatology* 2003; **38**: 75-85 [PMID: 12829989]

32 **Romero-Gómez M**, Del Mar Viloria M, Andrade RJ, Salmerón J, Diago M, Fernández-Rodríguez CM, Corpas R, Cruz M, Grande L, Vázquez L, Muñoz-De-Rueda P, López-Serrano P, Gila A, Gutiérrez ML, Pérez C, Ruiz-Extremera A, Suárez E, Castillo J. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology* 2005; **128**: 636-641 [PMID: 15765399]

33 **Poustchi H**, Negro F, Hui J, Cua IH, Brandt LR, Kench JG, George J. Insulin resistance and response to therapy in patients infected with chronic hepatitis C virus genotypes 2 and 3. *J Hepatol* 2008; **48**: 28-34 [PMID: 17977612]

34 **Khattab M**, Eslam M, Sharwae MA, Shatat M, Ali A, Hamdy L. Insulin resistance predicts rapid virologic response to peginterferon/ribavirin combination therapy in hepatitis C genotype 4 patients. *Am J Gastroenterol* 2010; **105**: 1970-1977 [PMID: 20234345 DOI: 10.1038/ajg.2010.110]

35 **Deltenre P**, Louvet A, Lemoine M, Mourad A, Fartoux L, Moreno C, Henrion J, Mathurin P, Serfaty L. Impact of insulin resistance on sustained response in HCV patients treated with pegylated interferon and ribavirin: a meta-analysis. *J Hepatol* 2011; **55**: 1187-1194 [PMID: 21703195 DOI: 10.1016/j.jhep.2011.03.010]

36 **Eslam M**, Aparcero R, Kawaguchi T, Del Campo JA, Sata M, Khattab MA, Romero-Gomez M. Meta-analysis: insulin resistance and sustained virological response in hepatitis C. *Aliment Pharmacol Ther* 2011; **34**: 297-305 [PMID: 21623851 DOI: 10.1111/j.1365-2036.2011.04716.x]

37 **Lange CM**, von Wagner M, Bojunga J, Berg T, Farnik H, Hassler A, Sarrazin C, Herrmann E, Zeuzem S. Serum lipids in European chronic HCV genotype 1 patients during and after treatment with pegylated interferon-α-2a and ribavirin. *Eur J Gastroenterol Hepatol* 2010; **22**: 1303-1307 [PMID: 20729742 DOI: 10.1097/MEG.0b013e32833de92c]

38 **Ramcharran D**, Wahed AS, Conjeevaram HS, Evans RW, Wang T, Belle SH, Yee LJ. Associations between serum lipids and hepatitis C antiviral treatment efficacy. *Hepatology* 2010; **52**: 854-863 [PMID: 20690192 DOI: 10.1002/hep.23796]

39 **Li JH**, Lao XQ, Tillmann HL, Rowell J, Patel K, Thompson A, Suchindran S, Muir AJ, Guyton JR, Gardner SD, McHutchison JG, McCarthy JJ. Interferon-lambda genotype and low serum low-density lipoprotein cholesterol levels in patients with chronic hepatitis C infection. *Hepatology* 2010; **51**: 1904-1911 [PMID: 20235331 DOI: 10.1002/hep.23592]

40 **Sheridan DA**, Bridge SH, Felmlee DJ, Crossey MM, Thomas HC, Taylor-Robinson SD, Toms GL, Neely RD, Bassendine MF. Apolipoprotein-E and hepatitis C lipoviral particles in genotype 1 infection: evidence for an association with interferon sensitivity. *J Hepatol* 2012; **57**: 32-38 [PMID: 22414761 DOI: 10.1016/j.jhep.2012.02.017]

41 **Saito H,** Ito K, Aoki Y, Higami K, Sugiyama M, Mukaide M, Sato Y, Imamura M, Murata K, Masaki N, Mizokami M. IL28B polymorphism is associated with the level of LDL cholesterol and the important predictor for the PEG-IFN/RBV treatment with chronic hepatitis. *Hepatology* 2010; **52:** 732A

42 **Miyanari Y**, Atsuzawa K, Usuda N, Watashi K, Hishiki T, Zayas M, Bartenschlager R, Wakita T, Hijikata M, Shimotohno K. The lipid droplet is an important organelle for hepatitis C virus production. *Nat Cell Biol* 2007; **9**: 1089-1097 [PMID: 17721513]

43 **Chiba-Falek O**, Linnertz C, Guyton J, Gardner SD, Roses AD, McCarthy JJ, Patel K. Pleiotropy and allelic heterogeneity in the TOMM40-APOE genomic region related to clinical and metabolic features of hepatitis C infection. *Hum Genet* 2012; **131**: 1911-1920 [PMID: 22898894 DOI: 10.1007/s00439-012-1220-0]

44 **Chiba-Falek O**, Linnertz C, Guyton J, Gardner SD, Roses AD, McCarthy JJ, Patel K. Pleiotropy and allelic heterogeneity in the TOMM40-APOE genomic region related to clinical and metabolic features of hepatitis C infection. *Hum Genet* 2012; **131:** 1911-20

45 **Hindorff LA,** Junkins HA, Hall PN, Mehta JP, Manolio TA. A Catalog of PublishedGenome-Wide Association Studies, 2011. Available at: http: //www.genome.gov/gwastudies. Accessed July 9 2013

46 **Negro F**. Abnormalities of lipid metabolism in hepatitis C virus infection. *Gut* 2010; **59**: 1279-1287 [PMID: 20660700 DOI: 10.1136/gut.2009.192732]

47 **Clark PJ**, Thompson AJ, Zhu M, Vock DM, Zhu Q, Ge D, Patel K, Harrison SA, Urban TJ, Naggie S, Fellay J, Tillmann HL, Shianna K, Noviello S, Pedicone LD, Esteban R, Kwo P, Sulkowski MS, Afdhal N, Albrecht JK, Goldstein DB, McHutchison JG, Muir AJ. Interleukin 28B polymorphisms are the only common genetic variants associated with low-density lipoprotein cholesterol (LDL-C) in genotype-1 chronic hepatitis C and determine the association between LDL-C and treatment response. *J Viral Hepat* 2012; **19**: 332-340 [PMID: 22497812 DOI: 10.1111/j.1365-2893.2011.01553.x]

48 **Tillmann HL**, Patel K, Muir AJ, Guy CD, Li JH, Lao XQ, Thompson A, Clark PJ, Gardner SD, McHutchison JG, McCarthy JJ. Beneficial IL28B genotype associated with lower frequency of hepatic steatosis in patients with chronic hepatitis C. *J Hepatol* 2011; **55**: 1195-1200 [PMID: 21703198 DOI: 10.1016/j.jhep.2011.03.015]

49 **Petta S**, Rosso C, Leung R, Abate ML, Booth D, Salomone F, Gambino R, Rizzetto M, Caviglia P, Smedile A, Grimaudo S, Cammà C, Craxì A, George J, Bugianesi E. Effects of IL28B rs12979860 CC genotype on metabolic profile and sustained virologic response in patients with genotype 1 chronic hepatitis C. *Clin Gastroenterol Hepatol* 2013; **11**: 311-7.e1 [PMID: 23220171 DOI: 10.1016/j.cgh.2012.11.022]

50 **Stättermayer AF**, Rutter K, Beinhardt S, Scherzer TM, Stadlmayr A, Hofer H, Wrba F, Steindl-Munda P, Krebs M, Datz C, Trauner M, Ferenci P. Association of the IL28B genotype with insulin resistance in patients with chronic hepatitis C. *J Hepatol* 2012; **57**: 492-498 [PMID: 22634340 DOI: 10.1016/j.jhep.2012.04.036]

51 **Ohnishi M**, Tsuge M, Kohno T, Zhang Y, Abe H, Hyogo H, Kimura Y, Miki D, Hiraga N, Imamura M, Takahashi S, Ochi H, Hayes CN, Tanaka S, Arihiro K, Chayama K. IL28B polymorphism is associated with fatty change in the liver of chronic hepatitis C patients. *J Gastroenterol* 2012; **47**: 834-844 [PMID: 22350701 DOI: 10.1007/s00535-012-0550-y]

52 **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]

53 **Toyoda H**, Kumada T. Favorable association between genetic polymorphisms near the IL28B gene and hepatic steatosis: direct or indirect? *J Hepatol* 2012; **56**: 738-79; author reply 739 [PMID: 22340673 DOI: 10.1016/j.jhep.2011.07.030]

54 **Ampuero J,** Rojas L, Calle R, Ortíz-Fernández L, García-Lozano JR, Solá R, Forns X, Andrade R, Diago M, Pons JA, Navarro JM, Mill Án R, González-Escribano M, Romero-Gómez. M I148M PNPLA3 variant promotes steatosis according to viral and IL28B genotype but does not affect sustained viral response in patients with hepatitis C. *J Hepatol* 2013; **58** Suppl 1: S180A

55 **Veldt BJ,** Duarte-Rojo A, Thompson AJ, Heimbach JK, Janssen HLA, Tillmann HL, Goldstein DD, McHutchison JG, Charlton MR. Donor IL28B TT-polymorphism is associated with increased incidence of hepatic steatosis in liver transplant patients with chronic hepatitis C. *J Hepatol* 2013; **58** suppl 1: S207-S208

56 **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: 18820647 DOI: 10.1038/ng.257]

57 **Valenti L**, Aghemo A, Stättermayer AF. Interaction between IL28B and PNPLA3 genotypes in the pathogenesis of steatosis in chronic hepatitis C non genotype-3 patients. *J Hepatol* 2012; **56**: 1209-110; author reply 1209-110 [PMID: 22230871 DOI: 10.1016/j.jhep.2011.10.024]

58 **Ogawa E**, Furusyo N, Murata M, Ikezaki H, Ihara T, Hayashi T, Toyoda K, Taniai H, Okada K, Kainuma M, Hayashi J. Insulin resistance undermines the advantages of IL28B polymorphism in the pegylated interferon alpha-2b and ribavirin treatment of chronic hepatitis C patients with genotype 1. *J Hepatol* 2012; **57**: 534-540 [PMID: 22613000 DOI: 10.1016/j.jhep.2012.04.027]

59 **Huang JF**, Yu ML, Huang CF, Juo SH, Dai CY, Hsieh MY, Hou NJ, Yeh ML, Hsieh MH, Yang JF, Lin ZY, Chen SC, Shin SJ, Chuang WL. The outcomes of glucose abnormalities in pre-diabetic chronic hepatitis C patients receiving peginterferon plus ribavirin therapy. *Liver Int* 2012; **32**: 962-969 [PMID: 22356575 DOI: 10.1111/j.1478-3231.2012.02771.x]

60 **Del Campo JA**, Ampuero J, Rojas L, Conde M, Rojas A, Maraver M, Millán R, García-Valdecasas M, García-Lozano JR, González-Escribano MF, Romero-Gómez M. Insulin resistance predicts sustained virological response to treatment of chronic hepatitis C independently of the IL28b rs12979860 polymorphism. *Aliment Pharmacol Ther* 2013; **37**: 74-80 [PMID: 23121166 DOI: 10.1111/apt.12113]

**P-Reviewers** Germanidis G, Ozlem Y **S-Editor** Qi Y **L-Edito E-Editor**

**Table 1 Summary of the *IFNL3* polymorphisms identified by genome-wide association studies**

|  |  |  |  |
| --- | --- | --- | --- |
| **GWAS** | **Total**  **population** | ***IFNL3* SNP** | **Wild (responder) type/ non-responder allele** |
| Gad *et al*[8] | 1137 | *rs129798601* | C/T |
| Suppiah *et al*[9] | 848 | *rs80999172* | T/G |
| Tanaka *et al*[4] | 314 | *rs8099917*  *rs12980275* | T/G  A/G |
| Rauch *et al*[5] | 914 | *rs8099917* | T/G |

*rs12979860*1 and *rs8099917*2SNPs are strongly associated with clearance and commonly used in clinical practice. GWAS: genome-wide association studies.

**Table 2 *IFNL3* polymorphisms and steatosis in chronic hepatitis C**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **No. of patients** | **Study design** | **HCV genotype** | ***IFNL3* SNP** | **Results** | **Ethnicity** | **Ref.** |
| 1604 | Retrospective | HCV-1 | *rs12979860* | *CC* genotype associated with higher pretreatment LDL-C levels and less frequent hepatic steatosis | Caucasians | 46 |
| 145  180 | Retrospective analysis of two Independent cohorts:  1) (antifibrotic) Study cohort  2) *Duke cohort* | HCV-1 | *rs12979860* | *CC* genotype associated with less hepatic steatosis | 122 (84.1%) Caucasians  130 (72.2%) Caucasians | 47 |
| 434 | multi-center, Retrospective | HCV-1 | *rs12979860* | *CC* genotype associated with less frequent hepatic steatosis | Caucasians | 48 |
| 202 | Prospective | HCV-1: 181 (89.6%)  HCV-4: 21 (10.4%) | *rs12979860* | *CC* genotype associated with less frequent hepatic steatosis | Caucasians | 49 |
| 153 | Retrospective | HCV-1b | *rs8099917* | *TT* genotype associated with less hepatic steatosis (vesicular and clear cell changes) | Japanese | 50 |
| 626 | Retrospective analysis of the *Swiss Hepatitis C Cohort Study* | Non-HCV-3 | *rs12980275* | *G* associated with less hepatic steatosis only in non-HCV-3 | Caucasians | 51 |
| 122 | Retrospective | HCV-1b | *rs8099917* | No association with hepatic steatosis | Japanese Mongolian | 52 |
| 445 | Retrospective | HCV-1: 303 (68.1%)  HCV-2: 13 (2.9%)  HCV-3: 82 (18.4%) HCV-4: 47 (10.6%) | *rs12979860* | No association with hepatic steatosis | Caucasian | 53 |

HCV: Hepatitis C virus.

**Table 3 *IFNL3* polymorphisms and insulin resistance in chronic hepatitis C**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cohorts size** | **Study design** | **HCV genotype** | ***IFNL3* SNP** | **% IR** | **HOMA-IR** | **Results** | **Ethnicity** | **Ref.** |
| 434 | Multi-center, retrospective | HCV-1 (*n* = 434) | *rs12979860* | 50% | > 3 | *CC* genotype associated with reduced IR | Caucasians | 48 |
| 202 | Prospective | HCV-1 (*n* = 181)  HCV-4 (*n* = 21) | *rs12979860* | 32.2%  (65/202) | ≥ 3 | *CC* genotype associated with reduced IR | Caucasians | 49 |
| 328 | Retrospective | HCV-1 (*n* = 328) | *rs8099917* | 50% (84/168)  in *TT* genotype  vs  69.7% (53/76)  in *TG/GG* genotype | ≥ 2.45 in *TT* genotype  *vs*  ≥ 1.55 in *TG/GG* genotype | No differences in *IFNL3*  genotype distribution according to HOMA-IR | Japanese | 57 |
| 240 | Retrospective | HCV-1 (*n* = 188)  HCV-2 (*n* = 3)  HCV- (*n* = 30) HCV-4 (*n* = 19) | *rs12979860* | 46% (89/193) | ≥ 2 | No differences in HOMA-IR levels according to *IFNL3 genotypes* | Caucasians | 59 |

HCV: Hepatitis C virus.