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Polymorphisms in the *IFNL3/IL28B* gene and hepatitis C: From adults to children

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Abstract

The purpose of the present review is to summarise the current knowledge on the association between single nucleotide polymorphisms (SNPs) in the *interferon L3 (IFNL3)* gene and hepatitis C virus (HCV) infection in children. Many studies in adults have demonstrated that genetic variation in *IFNL3* is a strong predictor of the virological response in treatment-naive patients with HCV genotype 1 who were treated with Pegylated-IFN- α and ribavirin. Genetic variation in *IFNL3* is also associated with the spontaneous clearance of HCV. Thus far, few paediatric studies have explored the association between variations in the *IFNL3* gene and either spontaneous or treatment-induced clearance of HCV. The CC genotype of the rs12979860 SNP is associated with the spontaneous clearance of HCV in children independently of HCV genotype. Four paediatric studies have shown that both the CC genotype of the rs12979860 SNP and the TT genotype of the rs8099917 SNP are associated with the treatment-induced (IFN monotherapy and

Pegylated-IFN- α and ribavirin association) clearance of HCV, while the rs12980275 SNP did not affect the virological response. The possible role of *IFNL3* gene variation as a pre-treatment and on-treatment predictor of virological response in children is highly attractive but still undetermined. Further paediatric studies are needed to evaluate if testing for SNPs in *IFNL3*, either alone or together with other predictors of response to treatment, could be used to direct treatment strategies, including an avoidance of unnecessary protease inhibitor therapy and the duration of treatment.

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Key words: Hepatitis C virus; Children; Interferon L3; IL28B; Interferon- λ ; Treatment; Virological response

Core tip: Single nucleotide polymorphisms in the *interferon L3 (IFNL3)* gene have been associated with both spontaneous and treatment-induced clearance of hepatitis C virus in children. Data from adult studies suggest a role of *IFNL3* testing in the decision-making process of whether to treat a patient, the use of two or three drugs and whether the standard duration of treatment or a shorter duration should be proposed. These options are attractive if applicable to children. While waiting for the approval of new interferon-free regimens, paediatric collaborative studies to evaluate the possible role of genetic polymorphisms of *IFNL3* as pre-treatment and on-treatment predictors of response, alone or together with other predictors, are highly needed.

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INTRODUCTION

The major aims of the present review are (1) to provide paediatricians with a brief overview of the current knowledge on the association between single nucleotide polymorphisms (SNPs) in the *interferon L3* (*IFNL3*) gene and hepatitis C virus (HCV) infection in adults; and (2) to summarise the data available in children with regards to future possible research endeavours and the possible impact of these data on the management of chronic HCV infection in children.

NOMENCLATURE AND CORRECT DEFINITION OF THE *IFNL3/IL28B* GENE

Two major SNPs, rs12979860 and rs8099917, have been identified on chromosome 19q13.13 as variants that are associated with both spontaneous HCV clearance and response to treatment with Pegylated-IFN- α (Peg-IFN- α) combined with ribavirin^[1,2]. The rs12979860 SNP is located 3 kilobases upstream of the promoter region of the *IFNL3* gene as well as of the *IFNL1* and *IFNL2* genes. The rs8099917 SNP lies between *IFNL3* and *IFNL2*, about 8 kilobases downstream from *IFNL3* and about 16 kb upstream from *IFNL2*. *IFNL1*, *IFNL2* and *IFNL3* are three closely related genes (known as IFN- λ genes) that are located in close proximity to each other on chromosome 19. The *IFNL1*, *IFNL2* and *IFNL3* genes were formerly known as *IL29*, *IL28A* and *IL28B*, respectively, and encode for type-III IFNs (IFN- λ 1, IFN- λ 2 and IFN- λ 3 formerly *IL29*, *IL28A* and *IL28B*, respectively)^[3-6]. The nomenclature that was used to describe the IFN- λ family reflects its structural similarity to the IL-10 superfamily and its close functional correlation to type-I IFNs^[7]. Recently, Prokunina-Olsson *et al.*^[8] described a dinucleotide variant upstream of the *IFNL3* gene in ss469415590 (TT or HG) that is in strong linkage disequilibrium with rs12979860. In individuals of African ancestry, the *IFNL4*-generating ss469415590[Δ G] allele was shown to be superior to the rs12979860[T] allele in predicting poorer response to the treatment of chronic hepatitis C with Peg-IFN- α and ribavirin. This SNP results in a frame shift mutation that leads to a novel gene product designated as IFN- λ 4, which has a high (40.8%) amino acid sequence homology with IFN- λ 3^[8].

Although the majority of the articles published on this topic refer to the *IL28B* gene and *IL28B*, which are the accepted names, *IFNL3* gene and IFN- λ 3 will be used in this review.

BIOLOGY AND MECHANISM OF ACTION OF TYPE-III IFNS

IFNs have a direct antiviral activity on viral replication and an indirect antiviral activity that is mediated by the activation of host genes that regulate an immune response against the virus^[9-12]. The binding of type III IFNs to their receptor complexes activates Janus kinase (JAK) and

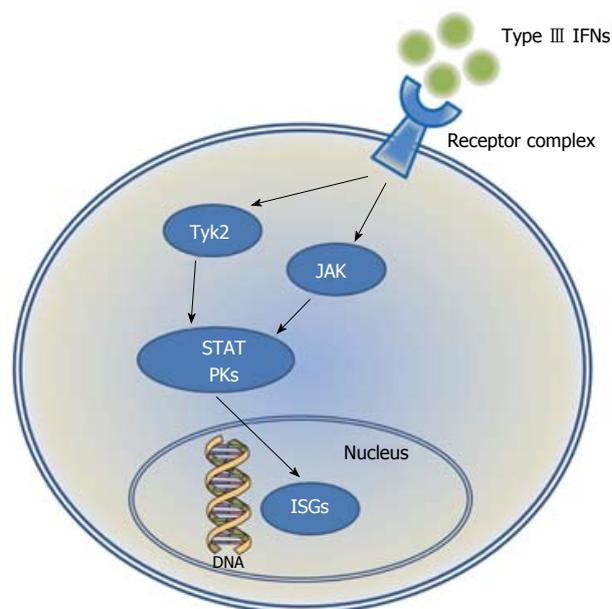


Figure 1 Type III interferons bind to their receptor complexes and activate Janus kinase and protein tyrosine kinase 2, which leads to activation of the signal transducer and activator of transcription protein kinases. Activation of the JAK-STAT pathway leads, in turn, to the induction ISGs, which have immunomodulatory functions and are responsible for the antiviral activity of IFN- λ s (see text for more details). IFNs: Interferons; JAK: Janus kinase; Tyk2: Tyrosine kinase 2; STAT PKs: Signal transducer and activator of transcription protein kinases; ISGs: IFN-stimulated genes.

protein tyrosine kinase 2, which leads to the activation of the signal transducer and activator of transcription (STAT) protein kinases^[13]. Activation of the JAK-STAT pathway leads, in turn, to the induction of genes with immunomodulatory functions, namely, IFN-stimulated genes that are responsible for the antiviral activity of IFN- λ s (Figure 1)^[13]. Although types I and III IFNs share the same second messengers (*i.e.*, JAK/STAT), the IFN- λ s are known to induce the expression of IFN-stimulated genes in a manner different from that of type I IFNs^[13]. The rs12979860 T/C polymorphism, with its particular location upstream of the promoter region for the *IFNL3* gene as well as its proximity to the *IFNL1* and *IFNL2* genes, can theoretically influence all three IFN- λ genes. Thus, the rs12979860 T/C polymorphism has been hypothesised and tested as a surrogate marker of altered promoter activity in this particular region. Although early studies failed to find altered mRNA expression of *IFNL3* associated with the rs12979860 SNP, the specificity of real-time PCR primers for *IFNL3* has increased (to distinguish between IFN- λ 3 and the closely related IFN- λ 2). It is now clear that SNPs in the *IFNL3* gene do affect the expression of IFN- λ 3 within the liver, peripheral blood mononuclear cells and whole blood, with the unfavourable T allele resulting in less IFN- λ 3 expression^[13].

SNPS IN THE *IFNL3* GENE AND HEPATITIS C IN ADULTS

The association between SNPs of the *IFNL3* gene and

the outcome of HCV infection was first described in September 2009 by Ge *et al*^[1] (Table 1). The authors performed a genome wide association study of more than 1600 adults with chronic infections of genotype 1 HCV who underwent combined treatment with Peg-IFN- α and ribavirin. A SNP on chromosome 19q13.13, rs12979860, was associated with a sustained virological response (SVR, defined as an undetectable level of HCV RNA 24 wk after the end of treatment). The authors found that the CC genotype of the rs12979860 SNP was associated with an improved response to treatment in all of the patients, independent of their ethnicities, when compared to the CT and the TT genotypes^[1]. The highest genome-wide significance was found in the European-American population sample (CC *vs* CT and TT odds ratio, OR = 7.3; 95%CI: 5.1-10.4; $P = 1.06 \times 10^{-25}$)^[1]. Then, Thomas *et al*^[2] determined the effect of rs12979860 variation on the outcome of HCV infection in a cohort of more than 1000 adults with either persistent infection or spontaneous clearance. The C allele and the CC genotype of the rs12979860 SNP were associated with spontaneous resolution of HCV infection among individuals of both European and African ancestry (CT *vs* CC, OR = 0.35; 95%CI: 0.25-0.48; $P = 4 \times 10^{-11}$; TT *vs* CC, OR = 0.29; 95%CI: 0.18-0.47; $P = 4 \times 10^{-7}$). Interestingly, in the same study, the geographic frequency of distribution of the different alleles was explored in 2371 individuals with unknown HCV status from 51 populations worldwide^[2]. The protective C allele was more frequent and fixed in East Asians (range 90%-100%), had an intermediate frequency in Europeans (range 52%-85%) and was the minor allele in Africans (range 23%-54%)^[2]. The pattern of distribution of the C allele closely reflected the heterogeneity in response to IFN-based treatments in different ethnic groups^[14-16], supporting the hypothesis that this genetic polymorphism explains much of the variation that exists within a population in response to treatment with Peg-IFN- α combined with ribavirin^[2]. Since October 2009, multiple studies have confirmed and reinforced the association between the C allele of the rs12979860 SNP and the spontaneous and treatment-induced clearance of HCV in adults (for a comprehensive review see Lange and Zeuzem^[3]).

At around the same time of the publication by Ge *et al*^[1], two other groups each led by Tanaka *et al*^[17] and Suppiah *et al*^[18], reported the results of genome wide association studies to determine the SVR of patients who were treated for HCV genotype 1 infection. Tanaka *et al*^[17] found that the rs12980275 and the rs8099917 SNPs in the *IFNL3* gene were associated with an SVR within a Japanese population (null virological response *vs* SVR for rs12980275, OR = 26.7; 95%CI: 9.3-76.5; $P = 7.41 \times 10^{-15}$ and for rs8099917, OR = 36.5; 95%CI: 11.6-114.6; $P = 5 \times 10^{-14}$). The role of the rs8099917 SNP was confirmed by Suppiah *et al*^[18] in an Australian cohort with HCV genotype 1 infection, where those who were homozygous for the T allele had a greater chance to eradicate the virus as a result of treatment with Peg-IFN- α

combined with ribavirin than patients carrying the G allele (OR = 1.98; 95%CI: 1.57-2.52; $P = 9.25 \times 10^{-9}$)^[18]. Subsequent studies confirmed the relationships between the rs8099917 SNP and HCV clearance, but fewer data are available on rs12980275^[3].

Although the initial observations that were described were found in patients who were infected and treated for HCV genotype 1 infection, different studies have since confirmed the major role of these SNPs on the outcome of treatment for genotype 4 infection and the minor role in the treatment outcomes of patients infected with HCV genotypes 2 and 3^[3].

SNPS IN THE *IFNL3* GENE AND VIRAL KINETICS OF RESPONSE TO TREATMENT

The data described above demonstrate that genetic variation of *IFNL3* is a strong predictor of a SVR in treatment-naïve patients who are infected with HCV genotype 1 who are treated with Peg-IFN- α and ribavirin. SNPs in the *IFNL3* gene together with race, gender, age, weight, serum glucose, hepatic steatosis, liver fibrosis stage and adherence to therapy are pre-treatment predictors of virological response^[19]. In addition to pre-treatment predictors, the likelihood of a SVR is associated with on-treatment predictors, particularly with the rate of virological decline during therapy, commonly referred to as "viral kinetics of response". Rapid virological response (RVR, an undetectable level of HCV RNA after 4 wk of treatment) and early virological response (undetectable level of HCV RNA acid after 12 wk of treatment) predict the likelihood of achieving an SVR^[19,20]. For patients who achieve an RVR, SVR rates are higher than 70%, and therapy can be shortened^[21,22]. There is evidence that the CC genotype of the rs12979860 SNP in the *IFNL3* gene is associated with significantly higher rates of viral clearance after 2, 4, 12 and 48 wk of treatment and a lower virological relapse rate^[23]. The correlation between RVR and the CC genotype of the *IFNL3* gene is so close that recently these two on-treatment predictors have been considered to drive one another to promote an SVR^[24]. It is worth noting that evaluation of the rs8099917 SNP is important for adults who do not achieve an RVR because although the CC genotype is predictive of an SVR in this group of patients, it is not associated with an SVR for those individuals who have achieved an RVR^[24]. These findings suggest that testing for *IFNL3* SNPs can be useful for making informed decisions about whether to continue therapy for patients who do not achieve an RVR.

SNPS OF THE *IFNL3* GENE AND HCV PROTEASE INHIBITORS IN ADULTS

Recently, two direct-acting antiviral agents, boceprevir^[20,25-27] and telaprevir^[20,27-29] have been approved for combined use with Peg-IFN- α and ribavirin in adults with chronic genotype 1 hepatitis C. Triple therapy has

Table 1 Selected studies exploring the association between single nucleotide polymorphisms in the *interferon L3* gene and spontaneous and treatment-induced clearance of hepatitis C virus in adults

Ref.	Number of patients enrolled	SNPs evaluated	Summary of the results
Ge <i>et al</i> ^[1]	1671	rs12979860	The CC genotype was associated with response to treatment with Peg-IFN- α and ribavirin independent of the ethnicity of the patient CC <i>vs</i> CT and TT, OR = 7.3; 95%CI: 5.1-10.4; $P = 1.06 \times 10^{-25}$
Thomas <i>et al</i> ^[2]	1008	rs12979860	The C allele and CC genotype were associated with spontaneous resolution of HCV infection among individuals of both European and African ancestry CT <i>vs</i> CC, OR = 0.35; 95%CI: 0.25-0.48; $P = 4 \times 10^{-11}$; TT <i>vs</i> CC, OR = 0.29; 95%CI: 0.18-0.47; $P = 4 \times 10^{-7}$
Tanaka <i>et al</i> ^[127]	314	rs12980275 rs8099917	The T allele of the rs8099917 SNP and the A allele of the rs12980275 SNP were associated with response to treatment with Peg-IFN- α and ribavirin Japanese patients null virological response <i>vs</i> SVR for rs12980275, OR = 26.7; 95%CI: 9.3-76.5; $P = 7.41 \times 10^{-13}$ and for rs8099917 OR = 36.5; 95%CI: 11.6-114.6; $P = 5 \times 10^{-14}$
Suppiah <i>et al</i> ^[18]	293	rs8099917	The T allele was associated with response to treatment with Peg-IFN- α and ribavirin in Australian patients OR = 1.98; 95%CI: 1.57-2.52; $P = 9.25 \times 10^{-9}$

SNPs: Single nucleotide polymorphisms; HCV: Hepatitis C virus; IFN: Interferon.

been proven to be more effective than combined dual treatment, but the role of SNPs in the *IFNL3* gene in the context of the increased SVR rates after triple therapy has been debated. Regardless, it has become increasingly evident that the response to triple therapy is also affected by polymorphisms in the *IFNL3* gene^[30,31]. Retrospective analyses from both of the boceprevir^[32] and the telaprevir^[33,34] registration trials showed that, although the presence of a direct-acting antiviral agent does attenuate the difference, treatment-naïve individuals with the rs12979860 CC genotype responded better in that they had higher SVR rates, better viral kinetics of response and a consequent lower risk of selection of resistance-associated HCV variants compared with individuals with the CT and TT genotypes^[32,34]. In addition, the major benefit of direct-acting antiviral agents is that they allow for a shorter treatment duration (24-28 wk) with response-guided therapy. Furthermore, it is evident that patients with the CT and TT genotypes are those who might benefit more from the addition of a third drug. In treatment-experienced patients who are scheduled to receive boceprevir/telaprevir therapy, there may be little utility for *IFNL3* genotyping once patients have been stratified based on a response to prior treatment^[32,34].

SNPS IN THE *IFNL3* GENE AND SPONTANEOUS CLEARANCE OF HCV IN CHILDREN

Thus far, three studies have been published on the association between spontaneous clearance of HCV in children and SNPs in the *IFNL3* gene (Table 2). Ruiz-Extremera *et al*^[35] explored the role of rs12979860 in 8 children with chronic infection and 7 with transient viremia. All of the children included in the study acquired the infection perinatally from their mothers and were infected with the HCV genotype 1. The CC genotype was present in 5/7 children with transient viremia (83%) and

in 1/8 (17%) with chronic infection ($P = 0.04$)^[35]. The same correlation between the rs12979860 SNP in the *IFNL3* gene and the spontaneous clearance of HCV in children was subsequently established for infection with HCV genotypes 2 and 3 in a cohort of 28 Italian children who were infected perinatally^[36]. Again, the CC genotype was found in 3/4 (75%) and in 4/20 (20%) of the children with spontaneous clearance and chronic infection, respectively (CC *vs* CT and TT, OR = 15; 90%CI: 1.2-376; $P = 0.04$)^[36]. These two studies demonstrated for the first time that the rs12979860 SNP in the *IFNL3* gene is associated with the spontaneous clearance of HCV independently of age and HCV genotype. These preliminary results have been confirmed in two recently closed cross-sectional multicentre collaborative studies^[37,38]. In one of these studies, 177 Italian children were enrolled^[38]. Thirty children with spontaneous clearance of HCV and 147 children with persistent infection were compared with a population sample of ethnically matched controls with unknown hepatitis C status obtained using data from the 1000 Genomes Project. The children with spontaneous clearance had greater frequencies of the C allele and the C/C genotype (76.7% and 56.7%, respectively) compared with both children with viral persistence (C allele 56.5%, $P 0.004$; C/C genotype 32.7%, $P = 0.02$) and to the ethnically matched individuals (C allele 59.7%, $P = 0.02$; C/C genotype 34.7%, $P = 0.03$). Children with the C/C genotype were 2 times more likely to show clearance of the hepatitis C virus relative to children with the C/T and T/T genotypes combined (OR = 2.7; 90%CI: 1.3-5.8)^[38].

SNPS IN THE *IFNL3* GENE AND TREATMENT-INDUCED CLEARANCE OF HCV IN CHILDREN

In 2011, at the Annual Meeting of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition, Hierro *et al*^[39] presented the result of a study

Table 2 Paediatric studies exploring the association between single nucleotide polymorphisms in the *interferon L3* gene and treatment-induced clearance of hepatitis C virus

Ref.	Number of children enrolled	SNPs evaluated	Summary of the results
Hierro <i>et al</i> ^[39]	69	rs12979860 rs8099917	The CC genotype of rs12979860 and the T/T genotype of rs8099917 were associated with treatment-induced (IFN monotherapy and Peg-IFN- α and ribavirin association) clearance of HCV (viral genotype data not provided)
Domagalski <i>et al</i> ^[40]	82	rs12979860 rs8099917 rs12980275	The CC genotype of rs12979860 and the T/T genotype of rs8099917 were associated with treatment-induced (Peg-IFN- α and ribavirin association) clearance of HCV (viral genotypes 1 and 4; OR = 6.81; 95%CI: 1.98-23.42; $P = 0.001$ and OR = 3.14; 95%CI: 1.26-7.85; $P = 0.013$, respectively) The rs12980275 SNP was not associated with virological response.
Komatsu <i>et al</i> ^[41]	63	rs8099917	The rs8099917 SNP was not associated with treatment-induced (response-guided IFN monotherapy and/or Peg-IFN- α and ribavirin association) clearance of HCV (viral genotypes 1, 2, 3 and 4)
Shaker <i>et al</i> ^[42]	34	rs12979860	The CC genotype of rs12979860 was associated with treatment-induced (Peg-IFN- α and ribavirin association) clearance of HCV (viral genotype 4) OR = 2.45; 95%CI not reported; $P = 0.02$

SNPs: Single nucleotide polymorphisms; HCV: Hepatitis C virus; IFN: Interferon.

that explored the rs12979860 and rs8099917 SNPs in the *IFNL3* gene in a cohort of 92 Spanish children with chronic hepatitis C. Both the CC genotype of the rs12979860 SNP and the TT genotype of the rs8099917 SNP were associated with a response to treatment in the 69 children who received treatment (7 with IFN and 62 with Peg-IFN- α and ribavirin; overall SVR 59% for CC *vs* 25% for non-CC, $P = 0.01$ and SVR 52% for TT *vs* 21% non-TT, $P = 0.009$)^[39].

Subsequently, 3 further studies (Table 2) were published that investigated the association between SNPs in the *IFNL3* gene and treatment outcomes for HCV infection in children^[40-42]. In 82 Polish children infected with HCV genotypes 1 and 4 and who were treated with Peg-IFN- α and ribavirin, the rs12979860 CC and the rs8099917 TT genotypes were associated with higher SVR rates (OR = 6.81; 95%CI: 1.98-23.42; $P = 0.001$ and OR = 3.14; 95%CI: 1.26-7.85; $P = 0.013$, respectively), while the rs12980275 SNP was not found to be significantly associated with a SVR^[40]. Interestingly, early virological response was associated with the rs12979860 CC genotype^[40]. This observation suggests that, as in adults, variations in the *IFNL3* gene influence early on-treatment viral kinetics in children.

The rs8099917 SNP in the *IFNL3* gene was evaluated in 63 Japanese children with mixed genotypes who were treated with response-guided Peg-IFN as a monotherapy or combined with ribavirin^[41]. In this study, the duration of the treatment was not the standard 48 wk for genotypes 1 and 4 and 24 wk for genotypes 2 and 3, but rather, it was determined based on when the levels of HCV RNA became undetectable in serum. No association was found between the rs8099917 SNP and SVR in the children who were treated^[41]. These results are in agreement with the observation that, in adults, different *IFNL3* SNPs appeared to have limited potential for response-guided treatment strategies^[43,44].

Finally, very recently, rs12979860 was found to be associated with a response to combined dual treatment in 34 Egyptian children infected with HCV genotype 4. Children with the CC genotype were found to be 2 times

more likely to achieve an SVR compared to those with CT and TT genotypes together (OR = 2.45; 95%CI not reported; $P = 0.02$)^[42].

IFN-BASED TREATMENT IN CHILDREN WITH CHRONIC HEPATITIS C AND SNPS IN THE *IFNL3* GENE: TO TREAT OR NOT TO TREAT?

Children who develop a chronic hepatitis C infection usually experience a mild disease^[45-47]. In the largest paediatric observational study that has been conducted thus far, end-stage liver disease was described in a small subgroup (3%) of children with chronic HCV infection^[45]. Although HCV can lead to advanced liver disease during childhood, the vast majority of children with chronic infection experience a slow, progressive disease. In the majority of these children, there is no clear indication for antiviral therapy^[48,49]. For this reason, whether to treat children is a complex decision that should be individualised for each child and based on the efficacy of the treatment and on rate and severity of treatment-related adverse events. In that context, the possible role of *IFNL3* gene variations as pre-treatment and on-treatment predictors of an SVR in children is highly attractive. For adults, as for children, the initial hope to improve the prediction of response to poorly tolerated IFN-based regimens using *IFNL3* gene testing was the same. Currently, it is clear that for adult patients, the positive predictive value of *IFNL3* association with response to treatment cannot be translated into a sufficiently sensitive or specific test that can be used independently to predict the outcomes for individual patients.

GENETIC VARIATION OF THE *IFNL3* GENE IN CHILDREN: POSSIBLE FUTURE RESEARCH SCENARIOS

The natural history of HCV infection in children is dif-

ferent compared to that in adults^[45]. Today, the majority of children infected by HCV acquire the infection perinatally from their mothers^[45,50-52]. Spontaneous clearance of HCV is an unpredictable event that occurs in the first 30 mo of life in less than 20% of the infected children^[45,47,53]. The association between genetic variation of *IFNL3* and spontaneous clearance of HCV in children supports the hypothesis that innate immunity plays an important role in children as in adults in the spontaneous elimination of the virus^[54]. Future research efforts should be oriented towards elucidating the role of innate immunity in the successful eradication of HCV infection as well as its ineffective control in the majority of children who develop a chronic infection.

With regards to treatment-induced clearance of HCV, *IFNL3* testing is not sufficiently sensitive to be used alone to predict the outcome of treatment for individual patients. To achieve this goal, a consideration of both multiple pre-treatment and on-treatment factors seems to be an appropriate research strategy to be developed further. The likelihood of achieving such treatment algorithms is unrealistic for adults in the context of a rapidly evolving scenario of new, highly effective IFN-free treatments. The time-lapse to new treatments in children will be longer; therefore, the determination of the role of *IFNL3* genotype variation is still possible. Additional paediatric studies are needed to evaluate whether *IFNL3* genotype testing alone or together with other predictors of response to treatment with Peg-IFN- α and ribavirin, with or without direct-acting antiviral agents, could provide useful information as to whether a patient should avoid treatment, avoid protease inhibitor therapy entirely or undergo a shorter duration of triple therapy.

REFERENCES

- 1 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]
- 2 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]
- 3 Lange CM, Zeuzem S. IL28B single nucleotide polymorphisms in the treatment of hepatitis C. *J Hepatol* 2011; **55**: 692-701 [PMID: 21440591 DOI: 10.1016/j.jhep.2011.03.006]
- 4 Urban T, Charlton MR, Goldstein DB. Introduction to the genetics and biology of interleukin-28B. *Hepatology* 2012; **56**: 361-366 [PMID: 22511448 DOI: 10.1002/hep.25794]
- 5 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]
- 6 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]
- 7 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]
- 8 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]
- 9 Ank N, West H, Paludan SR. IFN-lambda: novel antiviral cytokines. *J Interferon Cytokine Res* 2006; **26**: 373-379 [PMID: 16734557]
- 10 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]
- 11 Robek MD, Boyd BS, Chisari FV. Lambda interferon inhibits hepatitis B and C virus replication. *J Virol* 2005; **79**: 3851-3854 [PMID: 15731279]
- 12 Muir AJ, Shiffman ML, Zaman A, Yoffe B, de la Torre A, Flamm S, Gordon SC, Marotta P, Vierling JM, Lopez-Talavera JC, Byrnes-Blake K, Fontana D, Freeman J, Gray T, Hausman D, Hunder NN, Lawitz E. Phase 1b study of pegylated interferon lambda 1 with or without ribavirin in patients with chronic genotype 1 hepatitis C virus infection. *Hepatology* 2010; **52**: 822-832 [PMID: 20564352 DOI: 10.1002/hep.23743]
- 13 Langhans B, Kupfer B, Braunschweiger I, Arndt S, Schulte W, Nischalke HD, Nattermann J, Oldenburg J, Sauerbruch T, Spengler U. Interferon-lambda serum levels in hepatitis C. *J Hepatol* 2011; **54**: 859-865 [PMID: 21145813 DOI: 10.1016/j.jhep.2010.08.020]
- 14 Muir AJ, Bornstein JD, Killenberg PG. Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites. *N Engl J Med* 2004; **350**: 2265-2271 [PMID: 15163776]
- 15 Liu CH, Liu CJ, Lin CL, Liang CC, Hsu SJ, Yang SS, Hsu CS, Tseng TC, Wang CC, Lai MY, Chen JH, Chen PJ, Chen DS, Kao JH. Pegylated interferon-alpha-2a plus ribavirin for treatment-naive Asian patients with hepatitis C virus genotype 1 infection: a multicenter, randomized controlled trial. *Clin Infect Dis* 2008; **47**: 1260-1269 [PMID: 18834319 DOI: 10.1086/592579]
- 16 Yan KK, Guirgis M, Dinh T, George J, Dev A, Lee A, Zekry A. Treatment responses in Asians and Caucasians with chronic hepatitis C infection. *World J Gastroenterol* 2008; **14**: 3416-3420 [PMID: 18528940]
- 17 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]
- 18 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 associ-

- ated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet* 2009; **41**: 1100-1104 [PMID: 19749758 DOI: 10.1038/ng.447]
- 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 **Ghany MG,** Nelson DR, Strader DB, Thomas DL, Seeff LB. An update on treatment of genotype 1 chronic hepatitis C virus infection: 2011 practice guideline by the American Association for the Study of Liver Diseases. *Hepatology* 2011; **54**: 1433-1444 [PMID: 21898493 DOI: 10.1002/hep.24641]
 - 21 **Mangia A,** Minerva N, Bacca D, Cozzolongo R, Ricci GL, Carretta V, Vinelli F, Scotto G, Montalto G, Romano M, Cristofaro G, Mottola L, Spirito F, Andriulli A. Individualized treatment duration for hepatitis C genotype 1 patients: A randomized controlled trial. *Hepatology* 2008; **47**: 43-50 [PMID: 18069698]
 - 22 **Chen TM,** Huang PT, Lin CH, Tsai MH, Lin LF, Liu CC, Ho KS, Tung JN. Feasibility of individualized treatment for hepatitis C patients in the real world. *J Gastroenterol Hepatol* 2010; **25**: 61-69 [PMID: 19780879 DOI: 10.1111/j.1440-1746.2009.05946.x]
 - 23 **Thompson AJ,** Muir AJ, Sulkowski MS, Ge D, Fellay J, Shianna KV, Urban T, Afdhal NH, Jacobson IM, Esteban R, Poordad F, Lawitz EJ, McCone J, Shiffman ML, Galler GW, Lee WM, Reindollar R, King JW, Kwo PY, Ghalib RH, Freilich B, Nyberg LM, Zeuzem S, Poynard T, Vock DM, Pieper KS, Patel K, Tillmann HL, Noviello S, Koury K, Pedicone LD, Brass CA, Albrecht JK, Goldstein DB, McHutchison JG. Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. *Gastroenterology* 2010; **139**: 120-9.e18 [PMID: 20399780 DOI: 10.1053/j.gastro.2010.04.013]
 - 24 **Lai M,** Afdhal NH. Clinical utility of interleukin-28B testing in patients with genotype 1. *Hepatology* 2012; **56**: 367-372 [PMID: 22511388 DOI: 10.1002/hep.25793]
 - 25 **Poordad F,** McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195-1206 [PMID: 21449783 DOI: 10.1056/NEJMoa1010494]
 - 26 **Bacon BR,** Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1207-1217 [PMID: 21449784 DOI: 10.1056/NEJMoa1009482]
 - 27 **European Association for the Study of the Liver.** EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2014; **60**: 392-420 [PMID: 24331294 DOI: 10.1016/j.jhep.2013.11.003]
 - 28 **Jacobson IM,** McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kauffman RS, Zeuzem S. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; **364**: 2405-2416 [PMID: 21696307 DOI: 10.1056/NEJMoa1012912]
 - 29 **Zeuzem S,** Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, Younossi Z, Foster GR, Horban A, Ferenci P, Nevens F, Müllhaupt B, Pockros P, Terg R, Shouval D, van Hoek B, Weiland O, Van Heeswijk R, De Meyer S, Luo D, Boogaerts G, Polo R, Picchio G, Beumont M. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; **364**: 2417-2428 [PMID: 21696308 DOI: 10.1056/NEJMoa1013086]
 - 30 **Hofmann WP,** Zeuzem S. A new standard of care for the treatment of chronic HCV infection. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 257-264 [PMID: 21468124 DOI: 10.1038/nrgastro.2011.49]
 - 31 **Asselah T,** Marcellin P. New direct-acting antivirals' combination for the treatment of chronic hepatitis C. *Liver Int* 2011; **31** Suppl 1: 68-77 [PMID: 21205141 DOI: 10.1111/j.1478-3231.2010.02411.x]
 - 32 **Poordad F,** Bronowicki JP, Gordon SC, Zeuzem S, Jacobson IM, Sulkowski MS, Poynard T, Morgan TR, Molony C, Pedicone LD, Sings HL, Burroughs MH, Sniukiene V, Boparai N, Goteti VS, Brass CA, Albrecht JK, Bacon BR. Factors that predict response of patients with hepatitis C virus infection to boceprevir. *Gastroenterology* 2012; **143**: 608-18.e1-5 [PMID: 22626609 DOI: 10.1053/j.gastro.2012.05.011]
 - 33 **Jacobson IM,** Catlett I, Marcellin P. Telaprevir substantially improved SVR rates across all IL28B genotypes in the ADVANCE trial [Abstract 1369]. *J Hepatol* 2011; **54**: S542-S543
 - 34 **Pol S,** Aerssens J, Zeuzem S, Andreone P, Lawitz EJ, Roberts S, Younossi Z, Foster GR, Focaccia R, Horban A, Pockros PJ, Van Heeswijk RP, De Meyer S, Luo D, Botfield M, Beumont M, Picchio G. Limited impact of IL28B genotype on response rates in telaprevir-treated patients with prior treatment failure. *J Hepatol* 2013; **58**: 883-889 [PMID: 23321318 DOI: 10.1016/j.jhep.2012.12.023]
 - 35 **Ruiz-Extremera A,** Muñoz-Gómez JA, Salmerón-Ruiz MA, de Rueda PM, Quiles-Pérez R, Gila-Medina A, Casado J, Belén Martín A, Sanjuan-Nuñez L, Carazo A, Pavón EJ, Ocete-Hita E, León J, Salmerón J. Genetic variation in interleukin 28B with respect to vertical transmission of hepatitis C virus and spontaneous clearance in HCV-infected children. *Hepatology* 2011; **53**: 1830-1838 [PMID: 21413051 DOI: 10.1002/hep.24298]
 - 36 **Indolfi G,** Sambrotta M, Moriondo M, Azzari C, Resti M. Genetic variation in interleukin-28B locus is associated with spontaneous clearance of HCV in children with non-1 viral genotype infection. *Hepatology* 2011; **54**: 1490-1491 [PMID: 21674555 DOI: 10.1002/hep.24482]
 - 37 **Indolfi G,** Mangone G, Calvo PL, Bartolini E, Regoli M, Ser-ranti D, Calitri C, Tovo PA, de Martino M, Azzari C, Resti M. Interleukin 28B rs12979860 single-nucleotide polymorphism predicts spontaneous clearance of hepatitis C virus in children. *J Pediatr Gastroenterol Nutr* 2014; **58**: 666-668 [PMID: 24792632 DOI: 10.1097/MPG.0000000000000275]
 - 38 **Indolfi G,** Mangone G, Bartolini E, Nebbia G, Calvo PL, Moriondo M, Tovo PA, de Martino M, Azzari C, Resti M. Comparative analysis of rs12979860 SNP of the IFNL3 gene in children with hepatitis C and ethnic matched controls using 1000 Genomes Project data. *PLoS One* 2014; **9**: e85899 [PMID: 24465773 DOI: 10.1371/journal.pone.0085899]
 - 39 **Hierro L,** Alvarez L, Lledin MD, Andueza L, Gordo-Giralt R, Camarena C, de la Vega A, Munoz-Bartolo G, Frauca E, Diaz C, Jara P. IL28B gene polymorphisms in children with chronic hepatitis C. *J Ped Gastroenterol Nutr* 2011; **52**: E22
 - 40 **Domagalski K,** Pawłowska M, Tretyn A, Halota W, Pilarczyk M, Smukalska E, Linkowska K, Grzybowski T. Impact of IL-28B polymorphisms on pegylated interferon plus ribavirin treatment response in children and adolescents infected with HCV genotypes 1 and 4. *Eur J Clin Microbiol Infect Dis* 2013; **32**: 745-754 [PMID: 23314745 DOI: 10.1007/s10096-012-1799-z]
 - 41 **Komatsu H,** Inui A, Tsunoda T, Sogo T, Fujisawa T. Association between an IL-28B genetic polymorphism and the efficacy of the response-guided pegylated interferon therapy in children with chronic hepatic C infection. *Hepatol Res* 2013; **43**: 327-338 [PMID: 22970660 DOI: 10.1111/j.1872-034X.2012.01087.x]
 - 42 **Shaker OG,** Nassar YH, Nour ZA, El Raziky M. Single-nucleotide polymorphisms of IL-10 and IL-28B as predictors of the response of IFN therapy in HCV genotype 4-infected children. *J Pediatr Gastroenterol Nutr* 2013; **57**: 155-160 [PMID:

- 23880623 DOI: 10.1097/MPG.0b013e31828feb0]
- 43 **Mangia A**, Thompson AJ, Santoro R, Piazzolla V, Copetti M, Minerva N, Petruzzellis D, Mottola L, Bacca D, McHutchison JG. Limited use of interleukin 28B in the setting of response-guided treatment with detailed on-treatment virological monitoring. *Hepatology* 2011; **54**: 772-780 [PMID: 21626525 DOI: 10.1002/hep.24458]
- 44 **Liu CH**, Liang CC, Liu CJ, Tseng TC, Lin CL, Yang SS, Su TH, Lin JW, Chen JH, Chen PJ, Chen DS, Kao JH. Interleukin 28B genetic polymorphisms play a minor role in identifying optimal treatment duration in HCV genotype 1 slow responders to pegylated interferon plus ribavirin. *Antivir Ther* 2012; **17**: 1059-1067 [PMID: 22898703 DOI: 10.3851/IMP2322]
- 45 **Bortolotti F**, Verucchi G, Cammà C, Cabibbo G, Zancan L, Indolfi G, Giacchino R, Marcellini M, Marazzi MG, Barbera C, Maggiore G, Vajro P, Bartolacci S, Balli F, Maccabruni A, Guido M. Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. *Gastroenterology* 2008; **134**: 1900-1907 [PMID: 18439604 DOI: 10.1053/j.gastro.2008.02.082]
- 46 **European Paediatric Hepatitis C Virus Network**. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. *Clin Infect Dis* 2005; **41**: 45-51 [PMID: 15937762]
- 47 **Resti M**, Jara P, Hierro L, Azzari C, Giacchino R, Zuin G, Zancan L, Pedditzi S, Bortolotti F. Clinical features and progression of perinatally acquired hepatitis C virus infection. *J Med Virol* 2003; **70**: 373-377 [PMID: 12766999]
- 48 **Robinson JL**, Doucette K. The natural history of hepatitis C virus infection acquired during childhood. *Liver Int* 2012; **32**: 258-270 [PMID: 22098487 DOI: 10.1111/j.1478-3231.2011.02633.x]
- 49 **Wirth S**, Kelly D, Sokal E, Socha P, Mieli-Vergani G, Dhawan A, Lacaille F, Saint Raymond A, Olivier S, Taminiau J. Guidance for clinical trials for children and adolescents with chronic hepatitis C. *J Pediatr Gastroenterol Nutr* 2011; **52**: 233-237 [PMID: 21076340 DOI: 10.1097/MPG.0b013e3181f6f09c]
- 50 **Indolfi G**, Azzari C, Resti M. Perinatal transmission of hepatitis C virus. *J Pediatr* 2013; **163**: 1549-1552.e1 [PMID: 23919905 DOI: 10.1016/j.jpeds.2013.06.077]
- 51 **Indolfi G**, Resti M. Perinatal transmission of hepatitis C virus infection. *J Med Virol* 2009; **81**: 836-843 [PMID: 19319981 DOI: 10.1002/jmv.21437]
- 52 **Indolfi G**, Azzari C, Resti M. Hepatitis: Immunoregulation in pregnancy and perinatal transmission of HCV. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 6-7 [PMID: 24296582 DOI: 10.1038/nrgastro.2013.230]
- 53 **Indolfi G**, Bartolini E, Resti M. Spontaneous clearance of hepatitis C virus in vertically infected children: any clue for treatment? *Eur J Pediatr* 2011; **170**: 1621; author reply 1623 [PMID: 21932009 DOI: 10.1007/s00431-011-1582-7]
- 54 **Prendergast AJ**, Klenerman P, Goulder PJ. The impact of differential antiviral immunity in children and adults. *Nat Rev Immunol* 2012; **12**: 636-648 [PMID: 22918466 DOI: 10.1038/nri3277]

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