

## IL28B polymorphisms predict the virological response to standard therapy in patients with chronic hepatitis C virus genotype 4 infection

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### Abstract

**Background** Genome-wide association studies have recently revealed that several single-nucleotide polymorphisms (SNPs) in the interleukin (IL) 28B genes can predict the sustained virological response (SVR) to pegylated interferon- $\alpha$ 2a/b plus ribavirin in hepatitis C virus (HCV)-genotype 1 patients. However, data for patients infected with HCV genotype 4 (HCV-G4) are limited.

**Aim** We analyzed the association of IL28B SNPs (hematological, biochemical, virological, and pathological factors) with SVR in the HCV-G4 monoinfected cohort of patients.

**Patients and methods** One hundred twenty-nine treatment-naïve HCV-G4 patients undergoing treatment were recruited from three tertiary care centers in Saudi Arabia. Five IL28B SNPs (rs12979860, rs12980275, rs8105790, rs8099917, and rs72486680) were identified by polymerase

chain reaction and DNA sequencing. SVR was statistically correlated with various clinical, histopathological, virological, and genetic parameters.

**Results** SVR was significantly associated with the CC and AA alleles of rs12979860 ( $p = 0.008$ ) and rs12980275 ( $p = 0.004$ ), respectively. Moreover, albumin levels ( $p = 0.002$ ) and platelet count ( $p = 0.039$ ) showed significant differences in the SVR and No SVR groups. On multivariate analysis, the CC allele of rs12979860 (OR, 2.89; 95 % CI 1.6–6.2,  $p = 0.006$ ) and albumin levels (OR, 1.2; 95 % CI 1.1–1.4,  $p = 0.001$ ) independently predicted SVR.

**Conclusions** IL28B polymorphism (CC allele of rs12979860) predicts the sustained response to antiviral therapy in HCV-G4.

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## Introduction

The disease burden caused by hepatitis C virus (HCV) infection entails a serious public health problem, with a worldwide prevalence estimated at 3 % [1]. HCV genotypes 1, 2, and 3 are common throughout America and Europe, while genotype 4 is predominant in the Middle East and Africa, where it is responsible for more than 80 % of HCV infections [2]. In Saudi Arabia, the prevalence of HCV is estimated to be 1–3 % with a predominance of genotype 4 (G4, 64 %) followed by genotype 1 (G1, 23 %) [2].

Currently, pegylated interferon-alpha 2a/b (Peg-IFN- $\alpha$ 2a/b) in combination with ribavirin is used as the standard therapy for treating chronic HCV infection [3]. With this combination, sustained virological response (SVR) has been observed in 80 % of patients infected with HCV genotypes 2 and 3, as opposed to 40–60 % of patients infected with HCV G1 or G4 [4]. Because of this limited efficacy in G1 and G4 patients, as well as significant adverse effects, it is highly desirable to identify baseline factors that could predict the treatment outcome.

In recent years, host genetic factors in the form of single nucleotide polymorphisms (SNPs) have been reported to predict treatment outcomes in Peg-IFN and ribavirin combination therapy [5], wherein interleukin (IL) 28B gene polymorphisms have attracted immense attention. The IL28B gene encodes for the cytokine interferon-lambda 3 (IFN- $\lambda$ 3), which is located on chromosome 19 and is in

close proximity to IL-28A and IL-29 encoding for interferon-lambda 2 (IFN- $\lambda$ 2) and IFN- $\lambda$ 1, respectively. IFN- $\lambda$ s are similar to IFN- $\alpha$  and have both antiviral and immunomodulatory properties, but are predominantly expressed from fewer cell types [6, 7]. In 2009, three independent genome-wide association studies (GWAS) reported a significant association of SNPs in the IL28B region with SVR in HCV-G1 [8–10]. The most significant SNPs were rs12979860 [8], rs8099917 [9, 10], rs12980275, and rs7248668 [9]. Following these, another GWAS study by Rauch et al. [11] reported SNP rs8099917 and a novel SNP rs8105790 to be significantly associated with the response to Peg-IFN therapy. Subsequently, these results were confirmed in different ethnic populations including Japanese, Australians, Europeans, African-Americans, and Hispanics [11–13]. However, it was observed that different ethnic groups have marked differential distribution of IL28B polymorphisms. For instance, the favorable CC allele of rs12979860 is least frequent in African-Americans and most frequent in Asians [14]. Several groups also investigated the impact of IL28B variants on SVR in HCV genotype 2- or 3-infected patients and found that rs12979860 and rs8099917 have no impact on SVR [15, 16]. In contrast, there are scant data on the role of IL28B polymorphism in G4 infected patients.

In the present study, we examined the impact of five major IL28B SNPs (rs12980275, rs8105790, rs12979860, rs8099917, and rs72486680) in addition to clinical,

**Table 1** Univariate analysis of nongenetic factors affecting SVR in HCV-G4 patients

Variable	All ( <i>n</i> = 129)	No SVR ( <i>n</i> = 57)	SVR ( <i>n</i> = 72)	<i>p</i> value <sup>a</sup>
Age (years)	49 (18–68)	49 (20–68)	48 (18–68)	0.300
Male	66 (51.2)	27 (47.4)	39 (54.0)	0.443 <sup>b</sup>
WBC (10 <sup>9</sup> /l)	7 (2–17)	6 (4–11)	7 (2–17)	0.248
Hemoglobin (g/l)	142 (76–191)	136 (76–162)	144 (84–191)	0.131
Platelet (10 <sup>9</sup> /l)	226 (109–659)	186 (109–659)	237 (110–590)	0.039
Bilirubin ( $\mu$ mol/l)	10 (2–42)	10 (2–24)	10 (4–42)	0.852
ALT (U/l)	68 (12–350)	72 (12–188)	65 (17–350)	0.838
ALP (U/l)	49 (15–290)	46 (16–140)	49 (15–290)	0.699
GGT (U/l)	65 (15–1041)	74 (15–241)	56 (18–1041)	0.252
Albumin (g/l)	40 (26–51)	38 (26–48)	42 (33–51)	0.002
Creatinine ( $\mu$ mol/l)	68 (41–735)	63 (49–100)	71 (41–735)	0.058
HCV RNA Log <sub>10</sub>	5.9 (1.8–8.0)	6.1 (3.3–7.6)	5.9 (1.8–8.0)	0.278
Grade (A2–3) <sup>c</sup>	57 (68.7)	23 (65.7)	34 (70.8)	0.620 <sup>b</sup>
Stage (F2–4) <sup>c</sup>	61 (74.4)	27 (77.1)	35 (72.9)	0.661 <sup>b</sup>

Data are expressed as medians (ranges) or *n* (%) as appropriate. HCV RNA represents the pretreatment values

*n* number, SVR sustained virological response, HCV hepatitis C virus, WBC white blood cells, ALT alanine aminotransferase, ALP alkaline phosphatase, GGT gamma-glutamyl transpeptidase

<sup>a</sup> Mann-Whitney *U*-tests unless otherwise stated

<sup>b</sup> Fisher's exact test

<sup>c</sup> METAVIR score in 83 patients

hematological, biochemical, virological, and liver histological severity on SVR in Saudi patients chronically infected with HCV-G4.

## Patients and methods

### Patients

A total of 129 treatment-naïve patients with chronic HCV infection from three different hospitals (King Khalid University Hospital, King Faisal Specialist Hospital and Research Centre, and Riyadh Military Hospital) in Riyadh, Saudi Arabia, were included in this study. These hospitals serve as referral centers for population groups residing in different geographical regions of the country. The study protocol conformed to the 1975 Declaration of Helsinki and was approved by the institutional review boards of the three hospitals. All patients signed an informed consent prior to the enrollment in the study.

### Treatment regimen and definitions

Patients were treated either with Peg-IFN- $\alpha$ -2a and ribavirin at doses of 180  $\mu$ g/week and 1,000–1,200 mg/day, respectively, or Peg-IFN- $\alpha$ -2b and ribavirin at doses of 80–120  $\mu$ g/week and 800–1200 mg/day, respectively. The complete course of therapy was 48 weeks. SVR was defined as undetectable HCV RNA 24 weeks after the end of treatment (i.e., at week 72). Nonresponse was designated when HCV RNA did not reduce by  $>2 \log_{10}$  from the pretreatment values at 12 weeks of treatment. Relapse was designated when HCV RNA reappeared within 24 weeks after the end-of-treatment response. Both nonresponders and relapsers were grouped as the “No SVR” group in this present study.

### IL28B genotyping

Genomic DNA was extracted from blood samples using a QIAamp DNA Blood Mini Kit (Qiagen, Valencia, CA, USA) according to the recommended procedures. DNA was quantified using the NanoDrop<sup>TM</sup> 1000 Spectrophotometer (Thermo Scientific, Wilmington, DE, USA).

A total of five SNPs located around the IL28B gene that showed a significant association with SVR in previous studies were selected for this study (Fig. 1 in Supplementary Material available online). For SNPs rs12979860 and rs12980275, a sequencing reaction was set up using the BigDye Terminator Cycle Sequencing Kit according to the manufacturer’s instructions (BigDye<sup>®</sup> Terminator v3.1 Cycle Sequencing Kit; Applied Biosystems, Foster City, CA, USA). For rs8105790, rs8099917,

and rs7248668, the TaqMan 5’ nuclease SNP genotyping assays were used. All assay reagents including primers and probes were purchased from Applied Biosystems Inc. The discrimination between wild-type and mutant alleles was achieved based on labeling the probes with two different dyes, namely VIC for wild-type and FAM for mutant alleles.

### Statistical analyses

The Statistical Package for Social Sciences (SPSS, version 16.0; SPSS Inc., Chicago, IL, USA) was used. A  $p$  value of  $<0.05$  was considered statistically significant. Continuous variables were compared using Student’s unpaired  $t$  test or the Mann-Whitney  $U$ -test as appropriate. The chi-square or Fisher’s exact test was used to compare frequencies and proportions. Multivariate logistic regression analysis was performed to determine the role of genetic and biochemical variables as independent predictors of SVR.

## Results

### Patients’ characteristics

Patients’ baseline characteristics are presented in Table 1. The median (range) age was 49 (18–68) years; baseline liver biopsy was performed in 83 (64.3 %) of the patients. Of these, 57 (68.7 %) had a significant inflammation grade (Metavir, A2–3), and 61 (74.4 %) had a significant fibrosis stage (F2–4). Eighty-five percent of patients received Peg-IFN- $\alpha$ 2a. In terms of treatment response, 72 (55.8 %) patients achieved SVR, while 57 (44.2 %) did not [49 (38.0 %) nonresponders and 8 (6.2 %) relapsers]. There was no significant relationship of response type with age, gender, white blood cell (WBC) count, hemoglobin, total bilirubin, alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), creatinine levels, inflammation grade, or fibrosis stage. However, a significant difference was found in albumin levels ( $p = 0.002$ ) and platelet counts ( $p = 0.039$ ) between SVR and non-SVR groups (Table 1).

### Association of IL28 polymorphism with the treatment response

The frequency distribution of the five IL28B SNPs is given in Table 2. The relationship of IL28B SNPs with the response type was examined using univariate analysis. As shown in Table 2, the CC alleles of rs12979860 (OR, 1.5; 95 % CI 1.1–2.0,  $p = 0.008$ ) and AA Alleles of rs12980275 (OR, 1.6; 95 % CI 1.2–2.1,  $p = 0.004$ ) were significantly associated with SVR. In addition, the TT Alleles of rs8105790 showed a

**Table 2** Univariate analysis of IL28B polymorphism in relation to SVR in HCV-G4 patients

Variables	SNP	All ( <i>n</i> = 129)	No SVR ( <i>n</i> = 57)	SVR ( <i>n</i> = 72)	<i>p</i> value	OR (95 % CI)		
rs12979860	CC	48 (37.2)	14 (24.6)	34 (47.2)	0.018			
	CT	69 (53.5)	35 (61.4)	34 (47.2)				
	TT	12 (9.3)	8 (14.0)	04 (5.6)				
		CC	48 (37.2)	14 (24.6)	34 (47.2)	0.008	1.5 (1.1–2.0)	
		CT + TT	81 (62.8)	43 (75.4)	38 (52.8)			
		TT	12 (9.3)	8 (14.0)	4 (5.6)			
rs12980275	CT + CC	117 (90.7)	49 (86.0)	68 (94.4)	0.100	0.6 (0.8–9.7)		
	AA	47 (36.4)	13 (22.8)	34 (47.2)			0.016	
	AG	66 (51.2)	35 (61.4)	31 (43.0)				
	GG	16 (12.4)	9 (15.8)	7 (10.0)				
		AA	47 (36.4)	13 (22.8)	34 (47.2)	0.004	1.6 (1.2–2.1)	
		AG + GG	82 (63.6)	44 (77.2)	38 (52.8)			
GG		16 (12.4)	9 (15.8)	7 (10.0)				
rs8105790	AG + AA	113 (87.6)	48 (84.2)	65 (90.0)	0.291	1.8 (0.4–1.4)		
	CC	27 (21.0)	13 (22.8)	14 (19.4)			0.193	
	CT	77 (59.7)	37 (64.9)	40 (55.6)				
	TT	25 (19.4)	7 (21.4)	18 (25.0)				
		CC	27 (21.0)	13 (22.8)	14 (19.4)	0.641	0.9 (0.6–1.4)	
		CT + TT	102 (79.0)	44 (71.4)	58 (80.6)			
TT		25 (19.4)	7 (12.3)	18 (25.0)				
rs8099917	CT + CC	104 (80.6)	50 (87.7)	54 (75.0)	0.070	1.4 (1.0–1.9)		
	GG	14 (10.9)	9 (15.8)	5 (6.9)			0.228	
	GT	12 (9.3)	4 (9.2)	8 (11.1)				
	TT	103 (79.8)	38 (77.0)	59 (81.9)				
		GG	14 (10.9)	9 (15.8)	5 (6.9)	0.109	0.6 (0.3–1.3)	
		GT + TT	105 (89.1)	48 (84.2)	67 (93.1)			
TT		103 (79.8)	44 (77.2)	59 (81.9)				
rs7248668	GT + GG	26 (20.2)	13 (22.8)	13 (18.1)	0.502	1.1 (0.8–1.7)		
	AA	14 (10.9)	6 (11.5)	8 (11.1)			0.278	
	AG	32 (24.8)	16 (33.3)	14 (21.4)				
	GG	83 (64.3)	33 (57.9)	50 (71.8)				
		AA	14 (10.9)	6 (10.5)	8 (11.1)	0.922	1.0 (0.6–1.7)	
		AG + GG	115 (89.1)	51 (89.5)	64 (88.9)			
GG		83 (64.3)	33 (57.9)	50 (69.4)				
	AG + AA	46 (35.7)	24 (42.1)	22 (30.6)	0.170	1.3 (0.9–1.8)		

Data are expressed as *n* (%)

*n* number, SVR sustained virological response, HCV hepatitis C virus, OR odds ratio, CI confidence interval

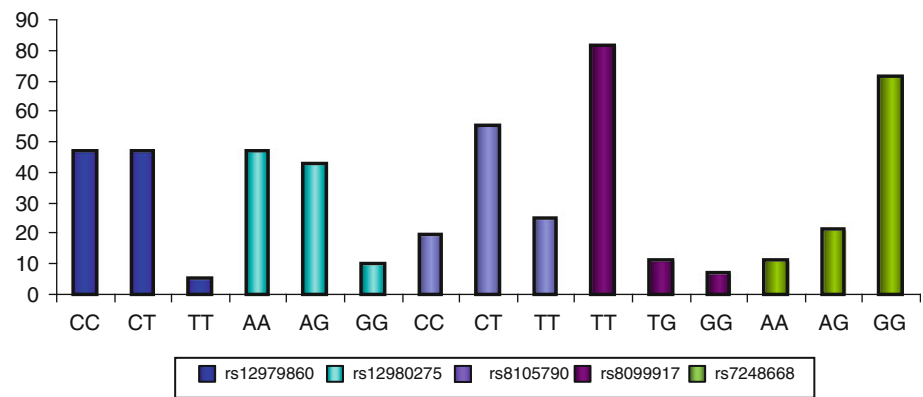
tendency to be associated with SVR, but did not reach statistical significance (OR, 1.4; 95 % CI 1.0–1.9, *p* = 0.070). Figure 1 presents the rate of SVR arranged according to IL28B genotypes. Patients receiving Peg-IFN- $\alpha$ -2a (85 %) were compared to patients receiving Peg-IFN- $\alpha$ -2b, and no significant differences were found in terms of response or genetic predictors of response.

Multivariate logistic regression analysis was performed using the three IL28B SNPs, i.e., rs12979860, 12980275, and rs8105790, as well as two biochemical variables, i.e., platelet count and albumin levels (which were significantly

associated with SVR in the univariate analyses). We found that the presence of the CC allele of rs12979860 (OR, 2.9; 95 % CI 1.6–6.2, *p* = 0.006) and albumin levels (OR, 1.2; 95 % CI 1.1–1.4, *p* = 0.001) independently predicted SVR (Table 3).

## Discussion

In the last few years, IL28B gene polymorphisms have been extensively studied in HCV genotype 1-infected

**Fig. 1** The association of SVR with IL28B SNPs**Table 3** Independent predictors of SVR in HCV-G4 patients

	OR	95 % CI	<i>p</i> value
CC (rs12979860)	2.89	1.35–6.20	0.006
Albumin	1.22	1.10–1.40	0.001

OR odds ratio, CI confidence interval, HCV hepatitis C virus

patients because of their predictive role in the treatment outcome and possible association with disease progression [5]. When studied in different ethnic populations, it has been shown that allele distributions of IL28B SNPs are different between races and ethnic backgrounds [14]. This is thought to partially explain the difference in response rates to current antiviral therapy between races and different HCV genotypes. Our analysis of IL28B allele frequencies in HCV-G4 patients of Arab ethnicity showed that the CC allele of rs12979860 and the AA allele of rs12980275 were associated with a significantly higher SVR.

To our knowledge, only three other groups have investigated the effect of a single IL28B SNP, rs12979860, on response to therapy in monoinfected HCV-G4 patients. In one study, Asselah et al. [17] investigated 82 HCV-G4 infected patients from three different ethnic groups: Egyptians, Europeans, and sub-Saharan Africans. The SVR rates were 81.8, 46.5, and 29.4 % for genotypes CC, CT, and TT, respectively. In another study from Austria, in which Egyptian HCV-G4 patients ( $n = 47$ ) were included, a retrospective evaluation of the impact of the same SNP rs12979860 on virological relapse was performed [18]. The study showed that individuals with a CC genotype were more likely to achieve SVR than those who carried the T allele. In addition, relapse was uncommon in HCV-G4 patients who achieved a rapid virological response. Although consistent with the results in individuals infected with HCV-G1, the low number of patients prevented authors from drawing firm conclusions in the G4 infected cohort [18]. This has also been confirmed in a recent study conducted on 103 HCV-G4 infected patients of European

and North African ethnicity again showing a strong predictive role of rs12979860 polymorphism on SVR [19].

Generally, the genetic polymorphisms near the IL28B gene are associated with the virological nonresponse (no relapse), indicating possible resistance to interferon. Although the number of relapsers in our study was very low (6.2 %), we reanalyzed the five IL28B SNPs in association with nonresponse (excluding relapse) and found that the results were not different from the data presented.

Our present study, on the other hand, has multiple strengths that build on the scarce body of knowledge in HCV-G4. First, it is comparatively the largest study in a HCV-G4 infected cohort, including 129 patients. Second, all patients belong to the same ethnic group, thereby helping to unify the independent effect of ethnicity on the response to therapy and allowing for a more clear examination of the role of the studied SNPs. It is worth noting that while previous studies in HCV-G4 patients were conducted in Egyptian patients, ours was a Saudi population (i.e., North African versus Arab ethnicity). Previous studies have shown that genotype distributions of SNP rs12979860 were different in different ethnic groups [14]. In line with this, Asselah et al. [17] also reported differential frequencies of the C allele of rs12979860 among the three ethnic groups in their study, i.e. 61.4, 54.7, and 31.0 %, for patients of Egyptian, European, and sub-Saharan African origin, respectively. In our present study population of Arab (Saudi) ethnicity, the C allele was observed in 64 %, being closer to what was reported in Egyptians previously. Nevertheless, a significant association between IL28B and SVR remained in each ethnic group, as reported by De Nicola et al. [19]. Finally, unlike other studies, we investigated the association of all five previously reported IL28B SNPs, albeit in other HCV genotypes, with the treatment response. With this approach we identified the association of two SNPs, rs12979860 and rs12980275 (Table 2), with a higher response in HCV-G4, of which the former has been confirmed in the multivariate analysis.

Despite these strengths, our present study has some limitations. Principally, we were unable to include the early viral kinetics in our present study because of a lack of complete data on rapid virological response in some patients. In addition, all patients underwent a 48-week treatment regimen and did not undergo the recently suggested extension of treatment duration to 72 weeks in slow virological responders. However, the vast majority of our patients were treated prior to the recommendations for modifying treatment duration were made.

In a recent expert panel recommendation on the management of HCV-G4, no sufficient evidence was available to make any solid recommendations regarding the use of IL28B testing in the management of patients infected with this genotype [4]. Based on our present study, as well as the study by Asselah et al. [17] and De Nicola et al. [19], it is clear that IL28B plays a major role in predicting the response to antiviral therapy in HCV-G4 patients, similar to other genotypes, arguing for a need to incorporate IL28B testing in guideline recommendations. Further studies are needed to elucidate how this important tool can now be used in clinical practice. Clearly, its use in selecting patients for treatment, determining the potential dose and duration of therapy, opting for two versus three medications, and many other relevant clinical questions remain to be studied.

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## References

- Hepatitis C. Fact Sheet No. 164. Revised October 2000, WHO 2000, 3 p. Available at <http://www.who.int/mediacentre/factsheets/fs164/en/>. Accessed 12 Dec 2011.
- Khattab MA, Ferenci P, Hadziyannis SJ, et al. Management of hepatitis C virus genotype 4: Recommendations of an international expert panel. *J Hepatol* 2011;54(6):1250–1262.
- Hadziyannis SJ, Sette H Jr, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004;140(5):346–355.
- Zeuzem S, Berg T, Moeller B, Hinrichsen H, et al. Expert opinion on the treatment of patients with chronic hepatitis C. *J Viral Hep* 2009;16(2):75–90.
- Lange CM, Zeuzem S. IL28B single nucleotide polymorphisms in the treatment of hepatitis C. *J Hepatol* 2011;55(3):692–701.
- Pagliaccetti NE, Robek MD. Interferon-lambda in the immune response to hepatitis B virus and hepatitis C virus. *J Interferon Cytokine Res* 2010;30(8):585–590.
- Hou W, Wang X, Ye L, et al. Lambda interferon inhibits human immunodeficiency virus type 1 infection of macrophages. *J Virol* 2009;83(8):3834–3842.
- Ge D, Fellay J, Thompson AJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009;461(7262):399–401.
- Tanaka Y, Nishida N, Sugiyama M, et al. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009;41(10):1105–1109.
- Suppiah V, Moldovan M, Ahlenstiel G, et al. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet* 2009;41(10):1100–1104.
- Rauch A, Kutalik Z, Descombes P et al. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. *Gastroenterology* 2010 138(4):1338–1345, 1345.e1–1345.e7.
- Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature* 2009;461(7265):798–801.
- McCarthy JJ, Li JH, Thompson A, et al. Replicated association between an IL28B gene variant and a sustained response to pegylated interferon and ribavirin. *Gastroenterology* 2010;138(7):2307–2314.
- Clark PJ, Thompson AJ, McHutchison JG. IL28B genomic-based treatment paradigms for patients with chronic hepatitis C infection: the future of personalized HCV therapies. *Am J Gastroenterol* 2011;106(1):38–45.
- Moghaddam A, Melum E, Reinton N, et al. IL28B genetic variation and treatment response in patients with hepatitis C virus genotype 3 infection. *Hepatology* 2011;53(3):746–754.
- Yu ML, Huang CF, Huang JF, et al. Role of interleukin-28B polymorphisms in the treatment of hepatitis C virus genotype 2 infection in Asian patients. *Hepatology* 2011;53(1):7–13.
- Asselah T, De Muynck S, Broet P, et al. (2012) IL28B polymorphism is associated with treatment response in patients with genotype 4 chronic hepatitis C. *J Hepatol* 2012;56(3):527–532.
- Scherzer TM, Stattermayer AF, Strasser M, et al. Impact of IL28B on treatment outcome in hepatitis C virus G1/4 patients receiving response-guided therapy with peginterferon alpha-2a (40KD)/ribavirin. *Hepatology* 2011;54(5):1518–1526.
- De Nicola S, Aghemo A, Rumi MG, et al. Interleukin 28B polymorphism predicts pegylated interferon plus ribavirin treatment outcome in chronic hepatitis C genotype 4. *Hepatology* 2012;55(2):336–342.