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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

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Summary

Low-density lipoprotein cholesterol (LDL-C) levels and interleukin 28B (*IL28B*) polymorphism are associated with sustained viral response (SVR) to peginterferon/ribavirin (pegIFN/RBV) for chronic hepatitis C (CHC) infection. *IL28B* has been linked with LDL-C levels using a candidate gene approach, but it is not known whether other genetic variants are associated with LDL-C, nor how these factors definitively affect SVR. We assessed genetic predictors of serum lipid and triglyceride levels in 1604 patients with genotype 1 (G1) chronic hepatitis C virus (HCV) infection by genome-wide association study and developed multivariable predictive models of SVR. *IL28B* polymorphisms were the only common genetic variants associated with pretreatment LDL-C level

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in Caucasians (rs12980275, $P = 4.7 \times 10^{-17}$, poor response *IL28B* variants associated with lower LDL-C). The association was dependent on HCV infection, *IL28B* genotype was no longer associated with LDL-C in SVR patients after treatment, while the association remained significant in non-SVR patients ($P < 0.001$). LDL-C was significantly associated with SVR for heterozygous *IL28B* genotype patients ($P < 0.001$) but not for homozygous genotypes. SVR modelling suggested that *IL28B* heterozygotes with LDL-C > 130 mg/dL and HCV RNA ≤600 000 IU/mL may anticipate cure rates >80%, while the absence of these two criteria was associated with an SVR rate of <35%. *IL28B* polymorphisms are the only common genetic variants associated with pretreatment LDL-C in G1-HCV. LDL-C remains significantly associated with SVR for heterozygous *IL28B* genotype patients, where LDL-C and HCV RNA burden may identify those patients with high or low likelihood of cure with pegIFN/RBV therapy.

Keywords

cholesterol; hepatitis C virus; interleukin 28B; lipids; sustained viral response

Introduction

The hepatitis C virus (HCV) is able to co-opt and disrupt host lipid metabolism to facilitate cell entry [1], assembly [2,3], replication and secretion [4–6]. Lower pretreatment serum low-density lipoprotein cholesterol (LDL-C) levels have been associated with poor response to peginterferon/ribavirin (pegIFN/RBV) therapy for patients with chronic hepatitis C (CHC) [7–9]. This lipid-lowering effect of HCV typically corrects after eradication of the virus, supporting the assertion that these clinical effects are virally mediated [7,10,11].

Genome-wide association studies (GWAS) independently identified single nucleotide polymorphisms (SNPs) near the interleukin 28B (*IL28B*) gene (chromosome 19) that are strongly associated with response to pegIFN/RBV treatment for patients infected with genotype-1 HCV [12–14]. The polymorphisms share a haplotype block around the *IL28B* gene with the causal variant(s) yet to be identified. In a candidate gene approach, *IL28B* polymorphism rs12979860 was found to be associated with LDL-C levels in genotype 1 (G1) CHC [15] and has been associated with hepatic steatosis [16,17]. However, the association of other common genetic variants with lipid levels in HCV has not been tested. Furthermore, the relationship between genetic polymorphism and lipid levels during and after treatment and the interactions with sustained viral response (SVR) prediction have not been explored.

We therefore sought to identify whether any other common genetic variants may contribute to serum lipid and triglyceride levels by assessing whole-genome variation by GWAS in the IDEAL pharmacogenomics cohort [18]. The large size and well-characterized nature of the cohort enabled us to analyse LDL-C levels during and after treatment to characterize the host–virus interdependence of this association, which has not previously been studied. Finally, we assessed the clinical utility of LDL-C in the prediction of SVR in the light of *IL28B* genetic associations, modelling specific clinical parameters to help define how LDL-C may be associated with SVR.

Materials and Methods

Study cohort

The IDEAL trial was a multi-centre, randomized control trial comparing efficacy and adverse events in 3070 treatment naïve patients with CHC (ClinicalTrials.gov number, NCT00081770) and has previously been described [18]. Patients chronically infected with

genotype-1 HCV were randomized to one of three treatment arms: peginterferon alfa-2b at standard dose (1.5 μg per kilogram body weight per week); or peginterferon alfa-2b at a lower dose (1.0 μg per kilogram per week), both with ribavirin doses between 800–1400 mg per day; or peginterferon alfa-2a at standard dose (180 μg/week) and ribavirin dose of 1000–1200 mg/day. Study patients with evaluable GWAS samples were predominantly Caucasian males in their forties with mean BMI 28.2 kg/m^2 [standard deviation (SD) 4.8] mean HCV RNA of 6.36 $\log_{10}$ IU/mL (SD 0.62) and 11% had advanced fibrosis (METAVIR fibrosis stages 3 or 4) (Table 1).

The IDEAL cohort has previously been analysed for non-genomic, clinical relationships between serum cholesterol, statin use and SVR [9]. A pharmacogenomics cohort from IDEAL consented to DNA testing (n = 1604) and has been analysed for genetic associations with treatment response [12] and ribavirin-induced haemolytic anaemia [19].

From the pharmacogenomics cohort, patients on statin therapy at any time during the study period (n = 46) were excluded from the GWAS analysis to avoid potential confounding. Patients were included if all covariate data were available for the relevant models and GWAS genotyping quality control protocols were satisfied (n = 1319) [12]. For the SVR analysis in addition to further adjusting for self-declared race rather than genetically inferred ancestry and pegIFN dose received, we considered all patients with covariate data on an intention-to-treat basis, irrespective of treatment compliance, ethnicity or statin therapy (n = 1473).

Genetic analysis

Patients were genotyped using the Illumina Human610-quad BeadChip (Illumina, San Diego, CA, USA). After quality control, 97.5% or 565 759 SNPs were analysed with multivariable linear and logistic regression models. The primary association model used single-marker genotype trend tests in three independent ethnic groups (Caucasians, African Americans and Hispanics). Ethnicity was genetically inferred and a modified Eigenstrat method corrected for population substratification [20].

Clinically important covariates adjusted for in the models included age; gender; body mass index (kg/m^2); baseline HCV viral load ($\log_{10}$ IU/mL); fibrosis (binary variable as METAVIR stage F0–2 *vs* F3–4); inflammation (METAVIR grade 0–1 *vs* 2–3), alanine transaminase (ALT) values, baseline fasting blood glucose levels and respective genetic ancestry subpopulation (or Eigen) sets. Plasma HCV RNA concentrations were measured using the COBAS Taqman assay (lower limit of quantitation of 27 IU/mL; Roche Diagnostics, Indianapolis, IN, USA).

Phenotypes

Fasting levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), LDL-C and triglycerides (TG) were analysed at baseline through GWAS using a linear regression model. Serum lipid measurements were considered as continuous variables, and LDL-C was log transformed to fit a normal distribution.

Serum LDL-C was further analysed by *IL28B* genotype during treatment at 12 weeks (n = 1385), 24 weeks (n = 1045) and 48 weeks (n = 797), then at 24 weeks follow-up post-treatment (n = 1079). Follow-up LDL-C was analysed based on SVR status, defined as undetectable HCV RNA 24 weeks after treatment completion (or 12 weeks after completion if post-treatment 24 week HCV RNA data were missing).

Multivariable logistic regression models of SVR adjusted for pegIFN alfa-2b dose (low *vs* standard dose) in addition to the covariates in the GWAS. Patients were considered on an

intention to treat basis irrespective of treatment adherence, with ethnicity defined by patient declaration rather than inferred from genotype data as in the GWAS. Patients on statins were reincluded and statin use was considered as a covariate.

Statistical analyses

The Bonferroni method corrected for multiple testing with genome-wide significance predefined at $P < 4.4 \times 10^{-8}$ ($\alpha = 0.05$). Student's *T*-test was used to compare LDL levels between *IL28B* genotype (good *vs* poor response genotypes) during treatment and when comparing between SVR and non-SVR patients at follow-up. Linear and logistic regression modelling was conducted with PLINK [21], STATA (Stata-Corp, College Station, TX, USA) and SAS (SAS Institute, Cary, NC, USA) software. The study met local Institutional Review Board requirements and the 1975 Declaration of Helsinki guidelines.

Results

Serum lipid and triglyceride genome-wide association studies

IL28B polymorphisms are the only common variants with genome-wide significant association with baseline serum low-density lipoprotein cholesterol levels—Four SNPs demonstrated genome-wide significant association with pretreatment LDL-C (Table 2). These SNPs are in the region of the *IL28B* gene on chromosome 19 and are all in linkage disequilibrium with the top SNP (Table S1), and all have previously been associated with pegIFN/RBV treatment outcome [12–14].

For the most significant SNP rs12980275, located 2.4 kb downstream from the *IL28B* gene, the G 'poor response' allele was associated with lower serum LDL-C levels across combined ethnic groups (G allele, all ethnicities $P = 4.7 \times 10^{-17}$). In subanalysis by ethnicity, the association was significant in Caucasians ($n = 1017$, $P = 6.9 \times 10^{-16}$; Table S2), but not genome-wide significant in the smaller cohorts of African American ($n = 207$, $P = 0.017$) and Hispanic patients ($n = 95$, $P = 0.63$), although there was a consistent direction of effect. Importantly, no other common genetic variants on genome-wide testing were associated with LDL-C on genome-wide testing.

These results likely reflect an *IL28B* haplotype effect rather than being SNP-specific, given the degree of linkage disequilibrium demonstrated. As the most significant genetic association for LDL-C in the GWAS was from rs12980275, further analysis will focus on this SNP. To minimize confusion in allele description of 'introducing' a new *IL28B* allele, the variant will be discussed in terms of its association with treatment response to pegIFN/RBV as good or poor response. Results will thus be described as 'good response' variants corresponding to patients homozygous for the 'A' allele at rs12980275 (with equivalent direction of effect for the better known 'C' allele at rs12979860; or the 'T' allele at rs8099917) and the presence of the G allele (G/G or A/G) corresponding to 'poor response'.

Low-density lipoprotein cholesterol levels above 130 mg/dL have previously been associated with SVR [9]. For Caucasians, twice as many patients with the good response *IL28B* genotype had LDL-C above this clinical threshold than poor response genotypes (A/A *vs* A/G and G/G, 33.4% *vs* 14.3%, respectively, $P = 9.92 \times 10^{-6}$).

Baseline serum total cholesterol, high-density lipoprotein cholesterol and triglycerides analyses do not demonstrate genome-wide criteria but identify significant candidate genetic associations—No genome-wide significant associations for other lipids or triglyceride levels were found on GWAS. Several previously identified associations satisfy less stringent candidate gene criteria (results for Caucasians

presented in Tables S3–S5). For the HDL-C GWAS, the top SNP (rs3764261, P = 5.80×10^{-7}) was located upstream from the cholesterylester transfer protein (*CETP*) gene which has previously been linked to HDL-C levels [22]. For TG, the second ranked SNP was close to the *APOA5* gene, a gene previously associated with hypertriglyceridemia (rs6589567, P = 4.00×10^{-6}) [23].

Genetic association between IL28B genotype and low-density lipoprotein cholesterol is hepatitis C virus-dependent—Although there were *IL28B* genotype-based differences in mean LDL-C levels at baseline (P = 6.9×10^{-16}), during treatment with exogenous peginterferon there were no significant differences in mean serum LDL-C by *IL28B* genotype (rs12980275; good response genotype *vs* poor response genotype, Fig. 1). We found no differences based on either viral response or *IL28B* genotype when comparing LDL-C levels by on-treatment milestones [early viral responses (EVRs) *vs* LDL-C at 12 weeks and end of treatment responses *vs* week 48 LDL-C level, Tables S8 & S9]. However the potentially confounding effect of exogenous interferon [24] was a limitation for this on-treatment analysis relative to the pretreatment and SVR/non-SVR LDL-C analyses.

For Caucasians, there was a significant *IL28B* genotype-based difference in mean serum LDL-C at 24 weeks follow-up after treatment in non-SVR patients ($P = 0.0002$), but in patients who achieved SVR, *IL28B* was not associated with LDL-C ($P = 0.287$). This was further tested in a multivariable model of follow-up LDL-C, where formal interaction testing confirmed a significant interaction between treatment outcome and *IL28B* (P = 0.02 for interaction term) with no significant relationship in SVR patients (Tables S6 and S7).

Defining the role of low-density lipoprotein cholesterol and IL28B in predicting sustained viral response

Given the recognized genetic association between *IL28B* polymorphisms and treatment response [12–14] and also LDL-C levels and treatment response [8,9], we undertook multivariable modelling to more definitively assess the association of pretreatment LDL-C on SVR in this large genotype-informed cohort. We assessed models before and after the inclusion of host *IL28B* genotype as a covariate and compared each model's performance [r^2 and area under the receiver operating curve (ROC)].

A baseline logistic regression model of SVR adjusted for the covariates of LDL-C, HCV RNA (log10 IU/mL), race, age, gender, significant fibrosis (METAVIR >F2), presence of any steatosis (>0%), fasting blood glucose level, alanine aminotransferase (ALT), low dose pegIFN and statin therapy but did *not* consider *IL28B* genotype. Higher pretreatment LDL-C was significantly associated with better treatment response [OR 1.16 per 10 mg/dL LDL (95%CI 1.11–1.20); $P < 0.0001$] with reasonable model performance (r^2 19.2% ROC 0.721), confirming the previous association with SVR [9]. Including *IL28B* into the model improved the model's predictive performance (r^2 30.6% ROC 78.3%), with significant interaction between LDL-C and *IL28B* (*P*-value for interaction = 0.029), reducing the effect and significance of LDL-C in SVR prediction, which was subsequently explored further.

Low-density lipoprotein cholesterol helps identify heterozygous IL28B genotype patients with high or low chance of sustained viral response—The significance of the association of LDL-C with SVR is dependent upon *IL28B* genotype. For heterozygous patients, LDL-C level was a significant predictor of SVR (per 10 mg/dL increase in LDL-C, OR 1.18 (95% CI 1.11–1.25), $P < 0.001$). In contrast, for patients with homozygous *IL28B* genotypes LDL-C did not aid in predicting response (*IL28B* good/poor response genotypes $P = 0.097$ and $P = 0.308$, respectively; Tables S10–S12).

Other recognized clinical and demographic factors continued to be significant in the prediction of SVR after inclusion of *IL28B* and LDL-C. Significant covariates associated with a better chance of SVR included Caucasian and Hispanic race relative to African American race (OR 2.11, $P < 0.001$ and OR 2.61, $P = 0.008$, respectively), fibrosis stage of ≤F2 (OR 2.48, $P < 0.001$); normal fasting plasma glucose (OR 1.33, $P = 0.001$) and lower HCV RNA (per 1 $\log_{10}$ IU/mL decrease, OR 2.15, $P < 0001$).

Because LDL-C remained a significant predictor of SVR for heterozygous *IL28B* genotype patients, we sought to better define the clinical utility of LDL-C in predicting SVR for this specific patient group. Dichotomizing the cohort into high LDL-C (>130 mg/dL) and low LDL-C (≤130 mg/dL), we considered a number of treatment endpoints. While there was no difference in rapid viral response, significantly higher rates of EVR, end of treatment responses (EOTR), and as expected SVR were seen in patients with LDL >130 mg/dL, while relapse rates were significantly lower (Table 3). Baseline LDL-C either as quartiles or at the 130 mg/dL cut-off point differentiated HCV viraemia across HCV RNA measurement timepoints (treatment weeks 2, 4, 12, Figures S1 & S2). Importantly, however, the LDL-C cut-off did not help to discriminate eventual SVR responses in slow responder patients with partial EVR (>2 log IU/mL reduction in HCV RNA but remaining HCV RNA positive after 12 weeks of therapy) and thus is unlikely to be useful to identify a treatment futility rule.

We further assessed SVR rates observed in the trial compared across a number of important clinical predictors of SVR (Table 4). LDL-C and high/low HCV RNA burden (≤600 000 IU/mL) were key factors. SVR decreased from 71% when comparing patients with high LDL-C and low HCV RNA, to 24% in patients with neither of these factors. In univariate analysis of the trial data, the high/low LDL-C threshold helped to differentiate SVR rates when considered across a number of other clinical factors such as significant fibrosis (>F2 METAVIR stage), African American ethnicity and abnormal fasting blood glucose.

Finally, we sought to consider these variables together in a multivariable model using binary clinical thresholds as might be carried out in clinic. For model parsimony, we assumed no hepatic steatosis and normal glucose. This model confirmed that for *IL28B* heterozygous patients, the LDL-C threshold helped to differentiate the predicted treatment responses across the continuum of clinical and racial factors associated with poor response (R^2 = 0.261, ROC = 76.0%) (Fig. 2). Patients with high LDL-C, low viral load, without advanced fibrosis (≤F2) and non-African American ethnicity had predicted SVR rates of 81%, while for patients without any of these positive treatment prognostic factors anticipated SVR is below 10%.

Discussion

Altered lipid levels in patients infected with HCV have been thought primarily due to disruption of host lipid synthetic pathways mediated by viral factors such as the HCV core [25] and nonstructural (e.g. NS5A) [26] proteins. Through a genome-wide association approach, we have demonstrated host genetics are also critical. *IL28B* polymorphisms are the only common genetic variants significantly associated with host serum LDL-C levels in genotype-1 HCV infection. We thus validate the previously reported candidate gene association of *IL28B* polymorphism with LDL-C levels [15] and are able to extend this, demonstrating for the first time that there are no other common variants associated with LDL-C in genotype-1 HCV infection.

In this retrospective analysis, we have demonstrated that LDL-C's association with SVR is conditional upon *IL28B* genotype. LDL-C has predictive utility for patients with heterozygous *IL28B* genotype only and is not associated with SVR for patients homozygous

for either the good or poor response *IL28B* alleles. In a multivariable model of SVR in *IL28B* heterozygous patients, established cut-offs for LDL (>130 mg/dL) and HCV RNA (≤600 000 IU/mL) provided a clear distinction of patients with high or low predicted SVR rate, independently of fibrosis and race.

Heterozygous *IL28B* genotype is the most common *IL28B* genotype in Caucasians. The heterozygous *IL28B* genotype is less clear in its predictive discrimination of SVR compared with the homozygous genotypes. Our data suggest patients with high LDL-C, low viral load and heterozygous *IL28B* genotype may anticipate much higher rates of SVR with existing pegIFN/RBV therapy. This distinction may be important for planning regimens for patients at more risk of toxicity or in treatment settings where direct acting antivirals (DAAs) may not be available. For the majority of heterozygous patients with low LDL-C and/or high HCV RNA, expected treatment responses to pegIFN/RBV are below the anticipated SVR rates seen with regimens including DAAs. Further prospective testing is necessary to validate the association of SVR with LDL-C and HCV RNA level for pegIFN/RBV regimens and to explore its use in DAA-inclusive regimens. *IL28B* may continue to play a significant, though attenuated role in DAA-inclusive peg-IFN/RBV regimens [27,28]. To define the clinical utility of LDL-C, our SVR modelling concentrated on *IL28B* heterozygous genotype patients based on data from a treatment naive cohort; however, more extensive modelling of SVR in larger cohorts including patients with more advanced fibrosis or prior nonresponse is needed, ideally prospectively.

In the GWAS analysis of other lipid measurements, no novel variants met genome-wide significance criteria; however, two polymorphisms implicated in previous genetic studies satisfied candidate gene criteria for significance. HDL-C was significantly associated with *CETP* variants and genetic variation near the *APOA5* gene with hypertriglyceridaemia [22,23]. This demonstrates that common genetic variants important in non-HCV-infected populations may also have important effects on HDL and TG for patients with HCV.

Our data suggest that *IL28B* polymorphisms influence the biological associations between HCV infection and serum LDL-C, and the clinical utility of LDL-C for predicting treatment response to pegIFN/RBV therapy. Exogenous IFN therapy has been previously observed to decrease serum lipid levels, which may occur via reduced activities of lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) [24]. This may account for the lower LDL-C levels seen during therapy irrespective of host genotype or on-treatment responses. In contrast, LDL-C levels differ in HCV-infected *vs* cured patients, suggesting a direct role for the virus. Furthermore, in HCV-infected patients (whether pretreatment or non-SVR post-treatment) the effect of the virus on LDL-C level differs significantly by host IL28B genotype. The underlying mechanism of how *IL28B* genetic variation is associated with treatment-induced and spontaneous HCV clearance remains unclear, although it is presumed to be immune related. The viral dependency of the association between host genetics and LDL-C and the inverse correlation between HCV RNA levels and LDL-C (Figures S1 & S2), suggests LDL-C is a marker of HCV interference in lipid metabolism, mediated by host genetics.

Increased expression of interferon-stimulated genes (ISGs) provides a possible functional explanation and weak correlation has previously been found between ISG expression and LDL-C levels. Higher levels of ISG expression pretreatment have been associated with nonresponse to treatment [29,30] and have also been correlated with poor response *IL28B* genotype [31,32], although a recent study has suggested these factors may work independently [33]. Unfortunately, ISG expression data were not available in this clinical trial cohort. The functional mechanisms underlying these genetic associations remain undetermined. Further molecular and clinical research is required to understand how host

genotype underlies the complex interaction between the HCV, the host immune system and lipid metabolism.

Conclusions

IL28B polymorphisms are the only common variants associated with LDL-C in G1-HCV. This association is HCV-dependent and was no longer significant after SVR. The clinical utility of serum LDL-C for predicting SVR is apparent only for patients with heterozygous *IL28B* genotype. In multivariable modelling of SVR, LDL-C level was significant for heterozygous *IL28B* patients and may potentially allow better prognostication of treatment response. Established thresholds for LDL-C and HCV RNA levels help to better identify heterozygous *IL28B* genotype patients with high or low anticipated SVR rates to pegIFN/RBV therapy and may help to better individualize care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix 1

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Abbreviations

ALT	alanine aminotransferase
CETP	cholesterylester transfer protein
CHC	chronic hepatitis C
DAA	direct acting antiviral
EOTR	end of treatment responses
EVR	early viral response
G1	genotype 1
GWAS	genome-wide association studies
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HTGL	hepatic triglyceride lipase
IL28B	interleukin 28B
ISG	interferon-stimulated gene
LDL-C	low-density lipoprotein cholesterol
LPL	lipoprotein lipase

pegIFN/RBV	peginterferon/ribavirin
ROC	receiver operating curve
SD	standard deviation
SNP	single nucleotide polymorphisms
SVR	sustained viral response
TC	total cholesterol
TG	triglycerides

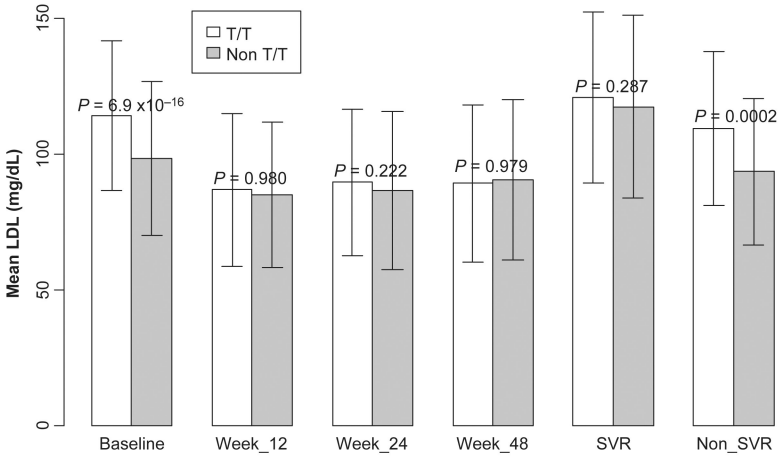

Fig. 1.

Mean serum low-density lipoprotein (LDL) (mM) at baseline, during treatment and at follow-up by host *IL28B* genotype [rs12980275 A/A (white) *vs* non-A/A (grey)] in Caucasians within the IDEAL pharmacogenomics cohort.

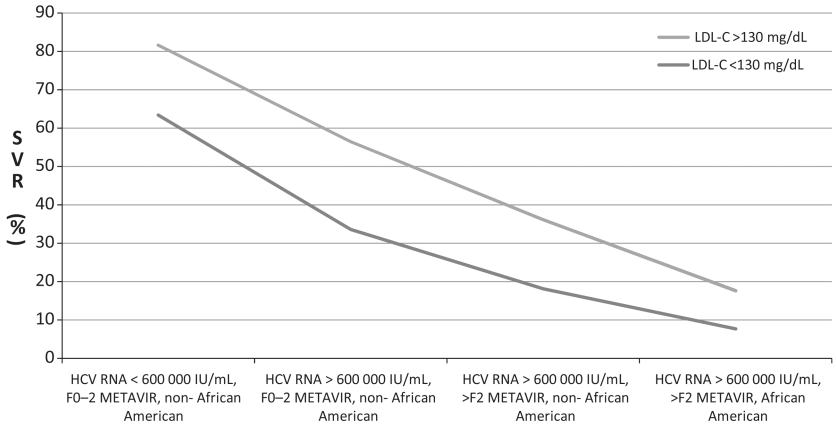

Fig. 2.

Low-density lipoprotein cholesterol (LDL-C) level above 130 mg/dL (light grey line) or below 130 mg/dL (dark grey line) differentiates sustained viral response (SVR) predication for *IL28B* heterozygous patients across the spectrum of adverse clinical predicators including high viral load [hepatitis C virus (HCV) RNA >600 000 IU/mL], advanced fibrosis (>METAVIR F2) and African American race in a logistic regression model of SVR.

Table 1

Clinical characteristics of the study population for genome-wide association studies related to serum lipids

	All	Caucasians	African Americans	Hispanics
N	1319	1017	207	95
Gender (M/F)	803/516	622/395	121/86	60/35
Age, years (mean)	47.4	47.2	49.7	44.3
BMI, kg/m^2 (mean)	28.2	27.8	29.7	29.2
Advanced fibrosis (>F2), *n* (%)	148 (11)	115 (11)	20 (10)	13 (14)
Steatosis (>0%), *n* (%)	810 (61)	607 (60)	134 (65)	69 (73)
Activity grade (% with grade 2–3)	82.6	82.0	85.5	83.2
Baseline viral load (log_{10}) (mean)	6.36	6.36	6.36	6.15
Baseline fasting blood glucose, mm (mean)	5.3	5.2	5.4	5.2
Baseline low-density lipoprotein cholesterol, mg/dL (mean)	103.2	104.0	100.5	98.6
Sustained viral response (%)	51	55	26	51

Table 2

Genome-wide significant associations with pretreatment low-density lipoprotein cholesterol levels

	P-value			
Single nucleotide polymorphism	**Combined (*n* = 1319)**	**Caucasians (*n* = 1017)**	**African Americans (*n* = 207)**	**Hispanics (*n* = 95)**
rs12980275	4.7×10^{-17}	6.9×10^{-16}	0.017	0.63
rs12979860	4.9×10^{-17}	1.3×10^{-15}	0.014	0.26
rs8099917	3.2×10^{-16}	1.2×10^{-15}	0.33	0.086
rs12972991	7.0×10^{-9}	2.0×10^{-8}	0.21	0.48

Table 3

Univariate analysis of on-treatment, end of treatment and sustained viral responses and relapse rates compared by baseline low-density lipoprotein cholesterol (LDL-C) thresholds in *IL28B* heterozygous patients

	Week 4 response (RVR)	Week 12 response (cEVR)	Week 48 response (EOTR)	Week 24 follow-up response (SVR)	Relapse
LDL-C > 130 mg/dL	7.14% (7/98)	55.4% (51/92)	74.1% (60/81)	47.1% (49/104)	18.3% (11/49)
LDL-C ≤ 130 mg/dL	5.12% (32/625)	33.4% (204/611)	47.6% (267/581)	28.7% (185/644)	32.6% (87/267)
Chi-square test *P*-value	0.5594	<0.0001 *	<0.0001	0.0002	0.0432

RVR, rapid viral response; EOTR, end of treatment responses; SVR, sustained viral response; EVR, early viral response; pEVR, partial EVR; cEVR, HCV RNA negative after 12 weeks of therapy.

* The test considers all three levels of EVR (cEVR, pEVR, and no EVR).

Table 4

Univariate analysis of sustained viral response (SVR) rates observed from the IDEAL pharmacogenomics cohort for *IL28B* heterozygous patients with high or low low-density lipoprotein cholesterol (LDL-C) (≤/>130 mg/dL) compared with other prognostic factors associated with SVR

Clinical factor	LDL-C > 130 mg/dL SVR % (*n*/N)	LDL-C ≤ 130 mg/dL SVR % (*n*/N)	*P*-value*
HCV RNA ≤600 000 IU/mL	71% (12/17)	53% (59/112)	0.00014
HCV RNA >600 000 IU/mL	43% 37/87	24% (126/532)	
F0–F2 METAVIR fibrosis	47.9% (45/94)	30.6% (175/571)	0.00033
F3–F4 METAVIR fibrosis	40.0% (4/10)	13.7% (10/73)	
Non-African American	53.8% (42/78)	30.6% (165/533)	0.00008
African American	26.9% (7/26)	18.0% (10/73)	
Normal fasting blood glucose	50.0% (43/86)	31.5% (165/524)	0.00030
Abnormal fasting blood glucose	33.3% (6/18)	16.7% (20/120)	

* Cochran–Mantel–Haenszel test compares SVR rates for high *vs* low LDL-C after adjusting for hepatitis C virus (HCV) RNA level, METAVIR fibrosis, race, abnormal fasting glucose.