# Interferon-lambda Genotype and Low Serum Low-Density Lipoprotein Cholesterol Levels in Patients with Chronic Hepatitis C Infection

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**Recently, genetic polymorphisms occurring in the interferon (IFN)-lambda gene region were associated with response to IFN-based treatment of hepatitis C infection. Both infection with the hepatitis C virus and IFN therapy are associated with decreased serum cholesterol and high cholesterol has been associated with increased likelihood to respond to IFN. We sought to determine if the IFN-lambda gene variant was also associated with serum lipid levels in chronic hepatitis C patients. We compared genotypes of the rs12979860 polymorphism, located proximal to the *IL28* gene, with serum lipid and apolipoprotein levels in 746 subjects with chronic hepatitis C virus infection, not currently undergoing treatment, using multivariable analysis of variance. Levels of total cholesterol ($P = 6.0 \times 10^{-4}$), apolipoprotein B ($P = 1.3 \times 10^{-6}$) and low-density lipoprotein (LDL) cholesterol ($P = 8.9 \times 10^{-10}$) were significantly higher in subjects carrying the rs12979860 CC responder genotype compared with those with the CT or TT genotype. Levels of triglycerides ($P = 0.03$), apolipoprotein A-I ($P = 0.06$), and apolipoprotein E ($P = 0.01$) were slightly lower in the rs12979860 CC genotype group, whereas levels of high-density lipoprotein cholesterol ($P = 0.78$) and apolipoprotein C-III ($P = 0.74$) did not vary by rs12979860 genotype. *Conclusion:* Our results suggest that low levels of LDL cholesterol in chronic hepatitis C patients may be a marker of host endogenous IFN response to hepatitis C and that subjects with the rs12979860 CC responder genotype may have a lower endogenous IFN response to the virus. (HEPATOLOGY 2010;51:1904-1911)**

*Abbreviations: CHC, chronic hepatitis C; HCV, hepatitis C virus; HDL, high-density lipoprotein; IFN, interferon; LDL, low-density lipoprotein; PEG-IFN, pegylated interferon; RBV, ribavirin; SNP, single-nucleotide polymorphism; SVR, sustained virologic response.*

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There is a growing body of epidemiological literature to support an association between hepatitis C virus (HCV) infection and alterations in host serum lipid levels. A consistent, strong association exists between chronic hepatitis C (CHC) infection and low levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein B, the main protein constituent of LDL and very low-density lipoprotein.[1-10] Moreover, there may be clinical implications for HCV-associated dyslipidemia. Low lipid levels in HCV infection have been correlated with steatosis,[11,12] more advanced liver fibrosis,[11,13-15] and nonresponse to interferon (IFN) treatment.[16-23]

Recently, several highly correlated common single-nucleotide polymorphisms (SNPs) on a linkage disequilibrium block encompassing two IFN-lambda genes, encoding type III IFN-lambda 2 (*IL28A*) and IFN-lambda 3 (*IL28B*) have been implicated in response to pegylated IFN-alpha among CHC patients.[24-26] CHC patients with the CC genotype of rs12979860 were more than twice as likely to respond to treatment than those without this genotype. In addition, this same genotype was paradoxically associated with higher serum HCV-RNA levels. The identification of the causal genetic variant underlying this association and its function remain to be determined; however, given the genomic location of the associated SNPs, the causal variant is likely to influence levels or activity of one or both of these IFN-lambdas. Treatment with type 1 IFNs has been shown to affect the metabolism of LDL,[27,28] resulting in a marked decline in serum LDL cholesterol levels. Little is known about the effect of type III IFNs on lipid metabolism. We sought to determine the association between the IFN-lambda rs12979860 polymorphism and serum lipid levels in a cohort of patients with chronic HCV infection in order to further evaluate the interrelationship of IFN-lambda and HCV hypolipidemia.

## Patients and Methods

***Patient Population.*** Subjects for the current study were drawn from two sources. Most came from the Duke Hepatology Clinical Research Database and Repository,[29] which consists primarily of patients referred to the Duke Liver Clinic with a diagnosis of HCV infection. Some, but not all patients took part in clinical trials or received treatment as part of standard of care, whereas others had not received any treatment. At the time of enrollment, informed consent was obtained for the collection and storage of serum, liver tissue, and peripheral blood for DNA extraction. The database includes clinical and demographic data extracted from medical records, laboratory reports, and, for those patients enrolled in clinical trials, case report forms. A second cohort of patients was from a recently completed multicenter phase II clinical trial to assess the effectiveness of farglitazar, a peroxisome proliferator-activated receptor-gamma agonist, as an antifibrotic agent among CHC patients who were nonresponsive to prior IFN-based therapy (NCT 00244751). Samples and patient data collected at baseline were used in the current study, and all patients gave consent for genetic studies.

HCV status was confirmed by the presence of detectable serum HCV-RNA and HCV genotypes determined by the INNOLIPA HCV assay (Innogenetics, Zwijnaarde, Belgium).[30] Liver fibrosis was scored using the METAVIR system (F0-F4). Patients who had undergone treatment with standard of care pegylated interferon/ribavirin (PEG-IFN/RBV), either as part of a clinical trial or regular care, were classified according to whether they had a sustained virologic response (SVR), defined as having undetectable HCV-RNA levels 24 weeks after cessation of treatment, or non-SVR, defined as detectable HCV-RNA levels at 24 weeks after cessation of treatment. HCV-RNA levels in the Duke serum samples were measured using either the National Genetics Institute SuperQuant assay (Culver City, Los Angeles, CA) or the Cobas Taqman HCV Test (Roche Molecular Systems, Pleasanton, CA) and for the farglitazar samples using quantitative real-time polymerase chain reaction assay (Quest Diagnostics, Northridge, CA). Viral load was classified as low ($<$600,000 IU/mL) or high ($\geq$600,000 IU/mL) for analysis. Body mass index (kg/m$^2$) was calculated from height and weight at enrollment.

All samples used for analysis of lipids were from subjects not currently undergoing treatment for HCV. Patients with prior effective treatment, and thus no longer chronically infected with HCV, were not used in the current study. Frozen serum samples were analyzed at a laboratory certified by the National Heart, Lung, and Blood Institute/Centers for Disease Control and Prevention Lipid Standardization Program (N. Rifai, Children's Hospital, Boston, MA). Standard lipids (triglycerides and total, high-density lipoprotein [HDL], and LDL cholesterol) were measured directly with reagents from Roche Diagnostics (Indianapolis, IN). Apolipoprotein A-I, B, C-III, and E were measured using immunoturbidometric assays (DiaSorin, Stillwater, MN). Samples from the Duke cohort were collected under nonfasting conditions, whereas those

**Table 1. Characteristics of Chronic HCV Patients in Duke and Farglitazar Cohorts**

| Variable | Duke (n = 634) | Farglitazar (n = 112) | *P* Value* |
|---|---|---|---|
| Sex, male (%) | 391 (62) | 72 (64) | |
| Race (%) | | | <0.01 |
| Caucasian | 452 (71) | 100 (89) | |
| African American | 182 (29) | 12 (11) | |
| METAVIR fibrosis stage (%), n = 633 | | | <0.01 |
| F0-1 | 146 (28) | 40 (36) | |
| F2 | 203 (39) | 54 (49) | |
| F3-4 | 173 (33) | 17 (15) | |
| HCV genotype (%) | | | <0.01 |
| 1 | 539 (85) | 112 (100) | |
| 2/3 | 95 (15) | 0 (0) | |
| rs12979860 genotype (%) | | | |
| TT | 127 (20) | 23 (21) | |
| TC | 322 (51) | 60 (54) | |
| CC | 185 (29) | 29 (26) | |
| Age (years), mean ± SD | 49.5 ± 8.5 | 51.5 ± 6.9 | |
| Body mass index (kg/m$^2$), mean ± SD (n = 664) | 28.8 ± 5.7 | 28.9 ± 4.5 | |
| Total cholesterol (mg/dL), mean ± SD (n = 577) | 175.0 ± 40.8 | – | |
| HDL cholesterol (mg/dL), mean ± SD (n = 577) | 47.4 ± 16.4 | – | |
| LDL cholesterol (mg/dL), mean ± SD | 102.0 ± 35.7 | 94.0 ± 30.8 | <0.01 |
| Apolipoprotein A-I (mg/dL), mean ± SD | 137.0 ± 29.9 | 138.7 ± 29.2 | |
| Apolipoprotein B (mg/dL), mean ± SD | 79.0 ± 23.4 | 72.4 ± 18.6 | <0.01 |
| Triglycerides (mg/dL), median (IQR) | 115.6 (2.0) | 95.6 (1.7) | <0.01 |
| Apolipoprotein C-III (mg/dL), median (IQR) | 9.2 (1.6) | 10.8 (1.5) | <0.01 |
| Apolipoprotein E (mg/dL), median (IQR) (n = 577) | 4.2 (1.5) | – | |

Abbreviation: IQR, interquartile range; SD, standard deviation.
*Significant difference between populations.

from the farglitazar study were collected under fasting conditions.

There were 634 subjects from the Duke cohort and 112 from the farglitazar study who had serum, DNA, and clinical data available. We excluded subjects coinfected with hepatitis B virus or human immunodeficiency virus type 1; subjects who had undergone liver transplantation; race other than Caucasian or African American; HCV genotypes other than 1, 2, or 3; and the <1% of subjects with poor quality DNA, defined as >10% failed genotypes in prior test-genotyping across a minimum of 10 SNPs. We excluded patients who had their lipids measured after attaining an SVR to treatment, as well as patients with unknown date of serum collection.

This study, the database, and the repository were approved by the Duke University Institutional Review Board. All patients provided written informed consent and the study was conducted in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

***Genotyping.*** The genomic region associated with HCV response in Ge et al.[24] contains several highly correlated SNPs around the *IL28B* gene. We selected the most strongly associated SNP, rs12979860, located upstream of this gene for genotyping in our cohort using the 5′ nuclease assay with allele specific TaqMan probes.[31] Genotyping was performed at the Duke Institute for Genome Sciences and Policy Genotyping Core. Genotyping calls were manually inspected and verified prior to release. Hardy-Weinberg Equilibrium was assessed in Caucasians and African Americans separately.

***Statistical Analysis.*** SAS statistical software, version 9.1 (SAS Institute, Cary, NC) was used to perform linear regression analysis of rs12979860 genotypes associated with lipids; rs12979860 genotypes were coded to test a recessive model, comparing subjects homozygous (CC) with those with one or no copies of the C allele (CT/TT). Triglyceride, apolipoprotein C-III, and apolipoprotein E levels were natural log (ln)-transformed prior to analysis. Primary analysis of the association between rs12979860 and lipids controlled for cohort type, age, sex, race, and HCV genotype. The amount of variance in lipid levels explained by rs12979860 was determined by the partial $r^2$ statistic. Homogeneity of genotype effects across strata was tested by introducing an interaction term. Differences in lipid levels by HCV genotype were examined using analysis of variance. To assess the effect of pretreatment lipids compared with rs12979860 genotype as a predictor of response to PEG-IFN/RBV treatment, a multivariable logistic regression model was run controlling for age, sex, race, and fibrosis.

**Table 2. Association Between rs12979860 Genotype and Lipid Levels in 746 Chronic HCV Patients**

| Lipid | TT/TC (n = 532) | CC (n = 214) | *P* Value |
|---|---|---|---|
| Total cholesterol* (mg/dL) | 168.5 ± 3.7 | 181.7 ± 4.5 | $6.0 \times 10^{-4}$ |
| Triglycerides† (mg/dL) | 105.6 ± 6.3 | 93.1 ± 7.3 | 0.03 |
| HDL cholesterol* (mg/dL) | 47.6 ± 1.4 | 47.2 ± 1.7 | 0.78 |
| LDL cholesterol (mg/dL) | 92.6 ± 3.3 | 110.3 ± 3.9 | $8.9 \times 10^{-10}$ |
| Apolipoprotein C-III† (mg/dL) | 10.4 ± 0.4 | 10.1 ± 0.5 | 0.74 |
| Apolipoprotein A-I (mg/dL) | 141.0 ± 2.6 | 136.8 ± 3.1 | 0.06 |
| Apolipoprotein B (mg/dL) | 71.1 ± 2.2 | 80.3 ± 2.5 | $1.3 \times 10^{-6}$ |
| Apolipoprotein E*,† (mg/dL) | 4.4 ± 0.1 | 4.0 ± 0.2 | 0.01 |

Values are reported as the least-squares mean ± standard error and are adjusted for cohort, age, sex, race, and HCV genotype.

*Data available only in a subset of the population (117 TT, 299 TC, 161 CC).

†Normalized by way of log transformation before analysis.

## Results

***Association of rs12979860 Genotype with Serum Lipid Levels.*** A description of the two CHC cohorts used in our analysis of serum lipid levels is shown in Table 1. Total cholesterol, HDL cholesterol, and apolipoprotein E levels were measured on only a subset of subjects (n = 577). Frequencies of the rs12979860 allele differed by race and were consistent with those reported (Caucasian C = 0.61, T = 0.39; African American C = 0.36, T = 0.64). Deviation from Hardy-Weinberg Equilibrium was only nominally significant ($P = 0.05$) in Caucasians.

Results for the two cohorts were similar (Supporting Table 1) and therefore, the cohorts were combined for further analysis. Table 2 illustrates the mean serum lipid levels of the entire cohort by rs12979860 genotype (CC versus TT/TC), adjusting for cohort, age, sex, race, and HCV genotype. The most significant differences were for LDL cholesterol, apolipoprotein B, and total cholesterol levels. Subjects with the rs12979860 TT/TC genotype had significantly lower LDL cholesterol levels ($P = 8.9 \times 10^{-10}$), lower apolipoprotein B ($P = 1.3 \times 10^{-6}$), and lower total cholesterol ($P = 0.0006$) levels compared with subjects with the CC genotypes. Nominally significant associations between rs12979860 TT/TC and higher triglycerides, apolipoprotein E, and apolipoprotein A-I were also found. The rs12979860 genotype was the strongest factor associated with LDL cholesterol and accounted for 5% of the variation in this trait in this cohort of patients with CHC. Additional models were run controlling for body mass index and METAVIR fibrosis score on the subset of 566 subjects with these data available, and for viral load on the subset of 336 subjects with these data, but inclusion of these additional variables in the model did not alter the association (data not shown).

***Association of Serum Lipids and rs12979860 Genotype With HCV Genotype.*** Next, we assessed for differences in serum lipid levels according to HCV genotype. Only total cholesterol, LDL cholesterol, and apolipoprotein B levels varied significantly by HCV genotype: patients with HCV genotype 3 had the

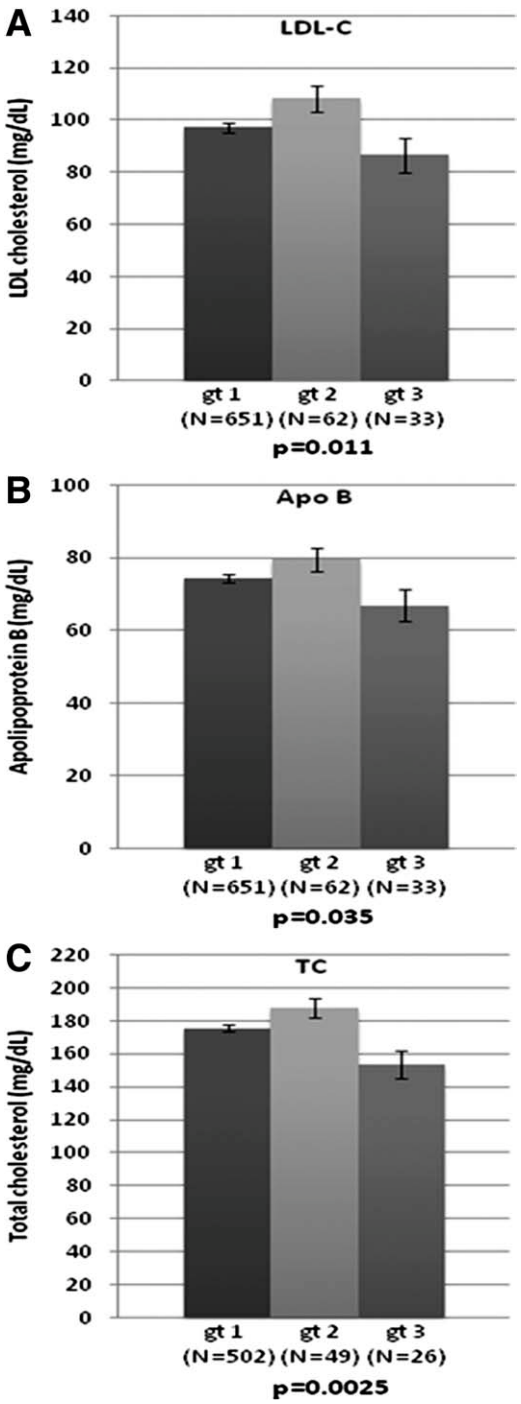


Fig. 1. Differences in LDL cholesterol, apolipoprotein B levels, and total cholesterol by HCV genotype in patients with chronic HCV infection. (A) LDL cholesterol. (B) Apolipoprotein B. (C) Total cholesterol. Means and standard error bars are adjusted for cohort, age, sex, and race.

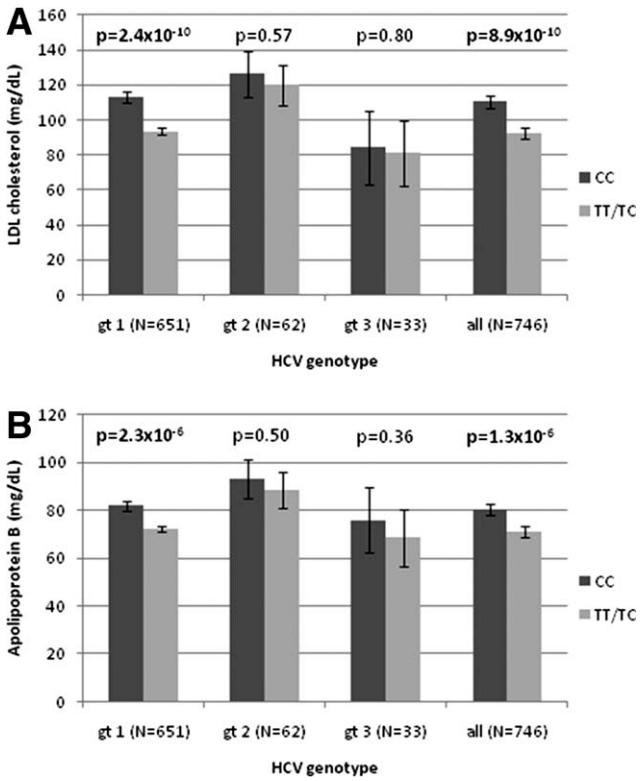


Fig. 2. Effect of rs12979860 genotype (CC versus TT/TC) on levels of LDL cholesterol and apolipoprotein B, stratified by HCV genotype (gt 1, gt 2, gt 3). (A) LDL cholesterol (LDL-C). (B) Apolipoprotein B. Means and standard error bars are adjusted for cohort, age, sex, and race. Pooled analysis was additionally controlled for HCV genotype.

lowest total cholesterol, LDL cholesterol, and apolipoprotein B levels, followed by genotype 1, and finally genotype 2 (Fig. 1). However, the rs12979860 genotype also varied by HCV genotype in our cohort,[32] but the association between rs12979860 genotype and serum lipid levels did not vary significantly by HCV genotype (rs12979860 genotype by HCV genotype interaction $P = 0.22$ for LDL cholesterol; $P = 0.76$ for apolipoprotein B). As seen in Fig. 2, a significant association between rs12979860 and both LDL cholesterol and apolipoprotein B levels was found among patients infected with HCV genotype 1. Patients with HCV genotypes 2 and 3 showed a similar trend, but the association failed to reach significance.

***Effect of Pretreatment Lipid Levels on Treatment Response to PEG-IFN/RBV.*** Pretreatment lipids were available on 261 chronic HCV patients who had received PEG-IFN/RBV treatment, 203 of whom had complete data on treatment response and other covariates. To avoid complex relationships introduced by HCV genotype, we used only the 182 HCV genotype 1 patients to determine the association between pretreatment lipid levels and treatment response and whether an observed association was due to the effects of rs12979860 genotype. Characteristics of responders and nonresponders are given in Supporting Table 2. Both high levels of LDL cholesterol and rs12979860 CC genotype were associated with SVR to treatment when examined individually in their own multivariable models. However, inclusion of both of these predictors in the same multivariable model resulted in an attenuation of the effect of LDL cholesterol such that its association with treatment response was no longer significant, while the effect of the rs12979860 genotype on treatment response remained highly significant (Table 3).

## Discussion

The presence of low serum cholesterol levels in patients with CHC has been well-documented. In a large cohort of CHC patients, we now report for the first time that an IFN-lambda gene variant recently associated with response to IFN therapy[24-26] was also strongly associated with serum lipoproteins. The rs12979860 CC responder genotype was most significantly associated with higher levels of LDL cholesterol, apolipoprotein B, and total cholesterol. These associations reflect the same underlying relationship, because most of total cholesterol is carried by LDL cholesterol, and apolipoprotein B is the main apolipoprotein constituent of LDL cholesterol. These associations were independent of important covariates and may explain 5% of the variation in LDL cholesterol levels among chronic HCV patients. Furthermore, known proxies of the rs12979860 SNP are not genetic contributors

**Table 3. Odds Ratios Associated With LDL Cholesterol and rs12979860 as Predictors of SVR to PEG-IFN/RBV Among 182 Chronic HCV Genotype 1 Patients With Complete Data**

| Predictor | Adjusted Odds Ratio* (95% Confidence Interval) | *P* Value | Adjusted Odds Ratio† (95% Confidence Interval) | *P* Value |
|---|---|---|---|---|
| LDL cholesterol (per mg/dL) | 2.01 (1.32-3.05) | $1.1 \times 10^{-3}$ | 1.56 (0.99-2.47) | 0.06 |
| rs12979860 CC | 8.11 (3.05-21.58) | $2.8 \times 10^{-5}$ | 5.81 (2.07-16.25) | $8.0 \times 10^{-4}$ |

Odds ratios are for LDL cholesterol (per one standard deviation increase) and rs12979860 (CC versus CT/TT).
*Included either LDL cholesterol or rs12979860 genotype along with the following covariates: age, sex, race, and fibrosis.
†Included both LDL cholesterol and rs12979860 genotype in the model with the other covariates.

to LDL cholesterol in healthy non-HCV-infected populations.[33]

The rs12979860 polymorphism lies in a region between two IFN-lambda genes, *IL28A* and *IL28B*, harboring multiple highly correlated gene variants. The causal genetic variant underlying the observed genetic associations at this locus is not yet known, but so far rs12979860 appears to be a strong predictor of HCV treatment response. The causal variant is likely to influence activity or levels of the nearby IFN-lambda genes. The data are consistent with observations by others that responders to treatment are characterized as having a lower baseline immune response to HCV.[34,35] This could also explain the paradoxical association of the response genotype with higher viral load in the study by Ge et al.[24] and in a follow-up report on the cohort used in the current study.[32] Our data on rs12979860 genotype association with lipids support this theory as well. Administration of the exogenous IFNs alpha, beta, and gamma in the setting of treatment for chronic HCV infection and other conditions has been shown to lower LDL cholesterol and raise triglyceride levels in very low-density lipoprotein, concomitant with suppression of lipoprotein lipase.[28,36-38] The effect of IFN-lambdas on serum lipids has not been explored, although it is believed that IFN-lambdas stimulate an IFN signaling gene response through a common pathway with type 1 IFNs.[39] It is not unreasonable to expect that the effect of IFN on lipids extends to endogenous IFNs as well. As such, we hypothesize that the IFN-lambda rs12979860 CC responder genotype, which was associated with both increased likelihood of treatment response and higher LDL cholesterol levels in our cohort, is associated with lower IFN-lambda activity or lower intrahepatic IFN signaling gene expression.

Our study also confirmed the observation by others that higher pretreatment levels of LDL cholesterol predict increased response to standard of care PEG-IFN/RBV in CHC patients.[16-23] However, we note that this association may largely result from the confounding effects of IFN-lambda, because inclusion of rs12979860 genotype in the model resulted in a substantial attenuation of the association. Hence, whereas LDL cholesterol levels may not provide any independent clinical use beyond the IL28 genotype for predicting treatment response, they may serve as a marker of endogenous IFN response to HCV infection.

Our analyses carefully controlled for many factors that may confound the observed associations. Nonetheless, there were several limitations to acknowledge. First, the research incorporated an observational study design in which serum lipid levels were measured from stored samples taken at a single point in time. The majority were nonfasting samples and as such, triglyceride levels may be increased from fasting levels. However, the direct measures of HDL cholesterol, LDL cholesterol, and all of the apolipoproteins are not appreciably affected in the fed state.[40] In any case, the misclassification bias associated with this measurement error would be nondifferential with respect to rs12979860 genotype resulting in a conservative estimate of association. Indeed, examination of the fasting samples by themselves yielded slightly stronger association (data not shown). Second, statins and other lipid-lowering medications are known to lower LDL cholesterol in healthy populations. We did not have accurate data on the use of lipid-lowering therapies in our cohort, but statins have been infrequently used in HCV patients.[41] Furthermore, medication use is unlikely to confound the association, because use of these therapies is unlikely to be dependent on a person's IL28 genotype. Another limitation of our study is the relatively small numbers of patients infected with HCV genotypes 2 and 3, which reduces the power to detect main effects among these groups or differences in effect between HCV genotypes.

The rs12979860 genotype explains only 5% of the variation in LDL cholesterol levels among HCV-infected subjects in our study, but has no effect on LDL cholesterol levels among non-HCV-infected subjects.[33] Although this is more than the variation explained by every gene polymorphism discovered to date in non-HCV-infected subjects,[33] it does not account for much of the variation in HCV-associated LDL cholesterol. Just how much of the variation in LDL cholesterol levels is due to IFN response versus direct viral perturbation of the host lipid metabolism pathway versus other factors remains to be determined. The viral life cycle of HCV is tightly linked to host cholesterol metabolism,[42] and experimental evidence suggests that HCV exploits hepatocyte cholesterol metabolism pathways for cellular entry, replication, assembly, and secretion.[43-47]

In conclusion, our research has shown an association between rs12979860 genotype and host serum lipid levels, suggesting a relationship between endogenous IFN response and lipids. Additional studies are warranted to assess the use of serum lipids as a marker of host IFN response to HCV.

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