



EDUCATIONAL OBJECTIVE: Readers will recognize the importance of the *IL28B* polymorphism and its implications in treating hepatitis C

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Genetics and hepatitis C: It's good to be 'CC'

ABSTRACT

The interleukin-28B (*IL28B*) gene contains a single-nucleotide polymorphism at location rs12979860 that affects both the natural history of hepatitis C virus infection and the patient's response to treatment, particularly interferon-based regimens with or without protease inhibitors.

KEY POINTS

In *IL28B*, the rs12979860 location can be occupied by either cytosine (C) or thymine (T). The CC genotype is more favorable than the CT or TT genotype.

Testing for the *IL28B* polymorphism is currently available and allows for better outcomes through proper selection of treatment, particularly with interferon-based treatment.

Although newer therapies have shifted toward regimens that do not use interferon, the *IL28B* polymorphism remains clinically significant, especially in light of the potentially prohibitive costs of the newer regimens, and for patients in whom these treatments are contraindicated.

WHAT A DIFFERENCE a single nucleotide can make! The human genome contains more than 3 billion base pairs. Yet having a different nucleotide in only one pair can make a big difference in how we respond to a disease or its treatment.

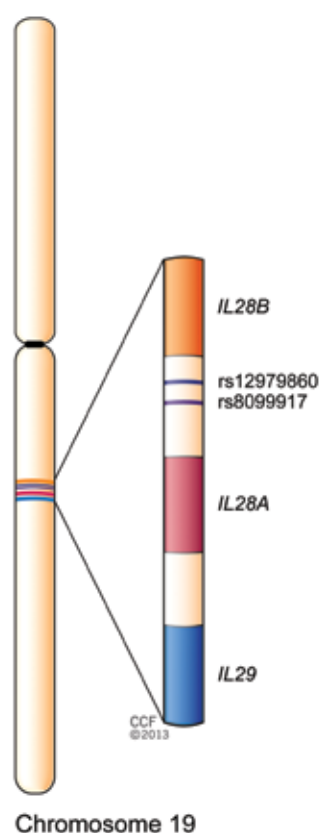
Specifically, in hepatitis C virus infection, people born with the nucleotide cytosine (C) at location rs12979860 in both alleles of the gene that codes for interleukin 28B (the *IL28B* CC genotype) can count themselves luckier than those born with thymine (T) in this location in one of their alleles (the CT genotype) or both of their alleles (the TT genotype). Those with the CC genotype are more likely to clear the virus spontaneously, and even if the infection persists, it is less likely to progress to liver cancer and more likely to respond to treatment with interferon.

Here, we review the *IL28B* polymorphism and its implications in treating hepatitis C.

■ GENETIC POLYMORPHISM AND HUMAN DISEASE

Of the 3 billion base pairs of nucleotides, fewer than 1% differ between individuals, but this 1% is responsible for the diversity of human beings. Differences in genetic sequences among individuals are called *genetic polymorphisms*. A *single-nucleotide polymorphism* is a DNA sequence variation that occurs in a single nucleotide in the genome. For example, two sequenced DNA fragments from different individuals, AAGCCTA and AAGCTTA, contain a difference in a single nucleotide.

Genetic variations such as these underlie some of the differences in our susceptibility to disease, the severity of illness we develop, and our response to treatments. Therefore, identi-



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FIGURE 1. Schematic of the *IL28B* gene.

In hepatitis C virus infection, *IL28B* CC is better than CT or TT

fying genetic polymorphisms may shed light on biologic pathways involved in diseases and may uncover new targets for therapy.¹

Genome-wide association studies have looked at hundreds of thousands of single-nucleotide polymorphisms to try to identify most of the common genetic differences among people and relate them to common chronic diseases such as coronary artery disease,² type 2 diabetes,³ stroke,⁴ breast cancer,⁵ rheumatoid arthritis,⁶ Alzheimer disease,⁷ and, more recently, hepatitis C virus infection.⁸

HEPATITIS C VIRUS: A MAJOR CAUSE OF LIVER DISEASE

Hepatitis C virus infection is a major cause of chronic liver disease and hepatocellular carcinoma and has become the most common indication for liver transplantation in the United States.⁹

This virus has six distinct genotypes throughout the world, with multiple subtypes in each genotype. (A genotype is a classifi-

cation of a virus based on its RNA.⁹) In this review, we will focus on genotype 1; hence, “hepatitis C virus” will refer to hepatitis C virus genotype 1.

Our knowledge of the biology, pathogenesis, and treatment of hepatitis C has been advancing. Originally, fewer than 50% of patients responded to therapy with the combination of pegylated interferon and ribavirin,^{10,11} but since 2011 the response rate has increased to approximately 70% with the approval of the protease inhibitors telaprevir and boceprevir, used in combination with pegylated interferon and ribavirin.^{12–15}

Unfortunately, interferon-based treatment is often complicated by side effects such as fatigue, influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms. An accurate way to predict response would help patients make informed decisions about antiviral treatment, taking into account the risk and possible benefit for individual patients.

GENETIC POLYMORPHISM AND HEPATITIS C VIRUS INFECTION

Genome-wide association studies have identified single-nucleotide polymorphisms in the *IL28B* gene that are associated with differences in response to hepatitis C treatment.⁸

Studying 565,759 polymorphisms in 1,137 patients, researchers at Duke University identified a single-nucleotide polymorphism at location rs12979860 in *IL28B* (FIGURE 1) that was strongly associated with response to combination therapy with pegylated interferon and ribavirin.⁸ The chance of cure with this standard treatment is twice as high in patients who are homozygous for cytosine in this location (the CC genotype) than in those who are heterozygous (CT) or homozygous for thymine in this location (the TT genotype) (TABLE 1).

Adding one of the new protease inhibitors, telaprevir or boceprevir, to the standard hepatitis C treatment substantially improves the cure rates in all three *IL28B* genotypes, but especially in people with CT or TT, in whom the response rate almost triples with the addition of one of these drugs. Those with the CC genotype (who are more likely to be cured with pegylated interferon and ribavirin alone) also achieve an increase (although minimal)

TABLE 1

Rates of response to hepatitis C treatment by interleukin-28B rs12979860 genotype

Genotype	Sustained virologic response rates			
	Pegylated interferon + ribavirin	Protease inhibitor + pegylated interferon + ribavirin	Simeprevir + sofosbuvir + ribavirin	Sofosbuvir + ledipasvir
<i>IL28B</i> CC	78%	82%–90%	100%	100%
<i>IL28B</i> CT	38%	72%	100%	100%
<i>IL28B</i> TT	26%	57%	83%	98%

INFORMATION FROM REFERENCES 8 AND 38–41.

in cure rates when a protease inhibitor is included in the regimen (TABLE 1).^{13–15} Thus, it remains unclear if adding a protease inhibitor to pegylated interferon plus ribavirin in patients with the *IL28B* CC genotype translates into added effectiveness worth the additional cost of the protease inhibitor in previously untreated patients.

Additionally, the effect of the *IL28B* genotype on telaprevir-based triple therapy has been disputed in more recent studies. In a subgroup analysis of the results of a trial that evaluated telaprevir in the treatment of hepatitis C, researchers found that sustained virologic response rates were significantly higher in the telaprevir group, and this was similar across the different *IL28B* polymorphisms.¹⁶

The favorable *IL28B* CC genotype is associated with higher rates of rapid virologic response to antiviral therapy.^{13–15} Of note, almost all patients who achieve a rapid virologic response do well, with a high rate of sustained virologic response even after a shorter duration of therapy (24 vs 48 weeks). Therefore, in addition to predicting response to interferon before starting treatment, the *IL28B* CC genotype may also identify patients who need only a shorter duration of therapy.

Interestingly, the C allele is much more frequent in white than in African American populations, an important observation that explains the racial difference in response to hepatitis C therapy.⁸

Two other research groups, from Asia and Australia, performed independent genome-wide association studies that identified dif-

ferent single-nucleotide polymorphisms (eg, rs8099917) in the same *IL28B* gene as predictors of response to treatment in patients with hepatitis C virus infection.^{17,18} These findings may be explained by linkage disequilibrium, which means that these single-nucleotide polymorphisms are found more frequently together in the same patient due to their proximity to each other. In this review, we will focus on the rs12979860 polymorphism; hence “*IL28B* genotype” will refer to the single-nucleotide polymorphism at rs12979860, unless otherwise specified.

The favorable CC genotype is less common in African Americans than in patients of other ethnicities.¹⁹ Moreover, although *IL28B* CC is associated with a better response rate to interferon-based antiviral therapy across all ethnicities, those of African American descent with the CC genotype are less likely to achieve a sustained virologic response than white or Hispanic Americans.⁸

■ BIOLOGIC ASSOCIATION: *IL28B* POLYMORPHISM AND HEPATITIS C

The interferon lambda family consists of three cytokines:

- Interleukin 29 (interferon lambda 1)
- Interleukin 28A (interferon lambda 2)
- Interleukin 28B (interferon lambda 3).

Production of these three molecules can be triggered by viral infection, and they induce antiviral activity through both innate and adaptive immune pathways. They signal through the IL10R-IL28R receptor complex.^{20–22} This receptor activates the JAK-

A way to predict response would help patients make informed decisions about antiviral treatment

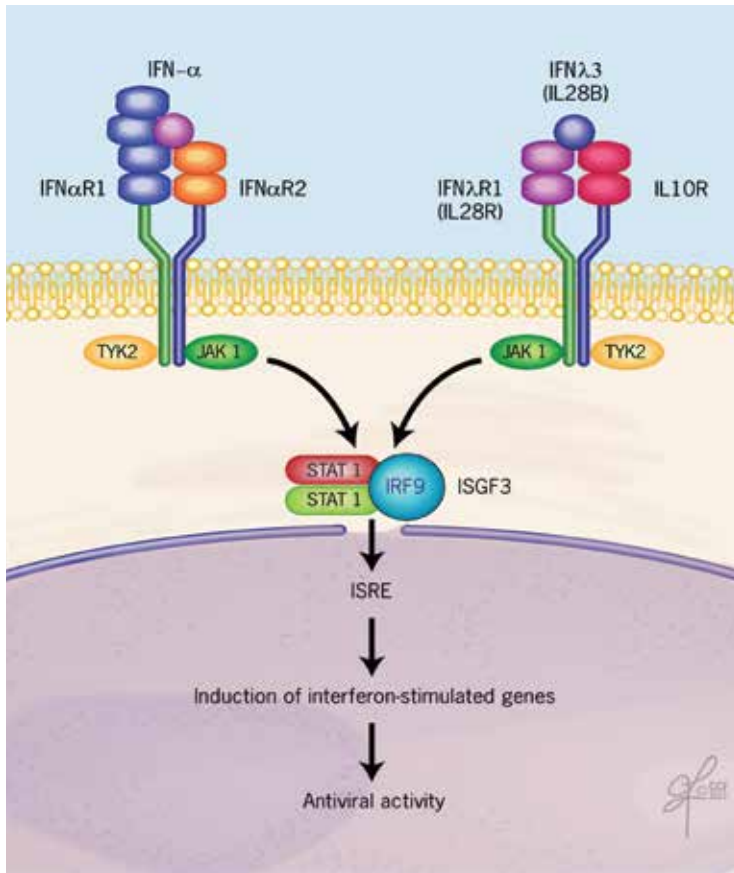


FIGURE 2. Schematic of the interferon pathway in patients with hepatitis C virus infection.

IFN = interferon; IL = interleukin; ISGF3 = interferon-stimulated gene factor 3; ISRE = interferon-stimulated response element; JAK 1 = Janus kinase 1; STAT = signal transducer and activator of transcription; TYK2 = tyrosine kinase 2

STAT (Janus kinase-signal transducer and activator of transcription) pathway, which regulates a large number of interferon-stimulated genes, primarily through the interferon-stimulated response element (FIGURE 2).

A 2013 study found that interferon-stimulated gene expression levels in patients with normal livers were highest in those with the CC genotype, intermediate with CT, and lowest with TT. Interestingly, this pattern was reversed in those with hepatitis C virus infection, indicating a relationship between the *IL28B* genotype and gene expression before infection.²³

The mechanism underlying the association between the *IL28B* polymorphism and response to hepatitis C treatment is not well understood. The unfavorable TT genotype seems to lead to continuous activation of a subset of interferon-

stimulated genes in the presence of intracellular hepatitis C viral RNA. But this level of expression is not sufficient to eliminate the virus from the cells. Instead, it might lead to up-regulation of interferon-inhibitory molecules that suppress JAK-STAT signaling, thereby reducing sensitivity to interferon signaling. Therefore, the hepatocyte not only cannot clear the virus by itself, but also cannot induce strong interferon-stimulated gene expression when interferon is given during therapy.^{20–22}

The recently identified ss469425590 polymorphism, which is located in close proximity to rs12979860 in the *IL28B* gene, is particularly interesting, as it suggests a possible molecular mechanism. The delta G frameshift variant creates a novel gene called *IFNL4*, which is transiently activated in response to hepatitis C virus infection.²⁴ *IFNL4* stimulates STAT1 and STAT2 phosphorylation and induces the expression of interferon-stimulated genes. Increased interferon-stimulated gene expression has been shown to be associated with decreased response to pegylated interferon-ribavirin treatment. These observations suggest that the ss469425590 delta G allele is responsible for the increased activation of interferon-stimulated genes and the lower sustained virologic response rate observed in patients who receive pegylated interferon-ribavirin treatment. It is possible that the activation of interferon-stimulated genes in patients with the ss469425590 delta G/delta G genotype reduces interferon-stimulated gene responsiveness to interferon alpha, which normally activates interferon-stimulated genes and inhibits hepatitis C progression.²⁴

■ *IL28B* POLYMORPHISM AND ACUTE HEPATITIS C VIRUS INFECTION

From 70% to 80% of acute hepatitis C virus infections persist and become chronic, while 20% to 30% spontaneously resolve. Epidemiologic, viral, and host factors have been associated with the differences in viral clearance or persistence, and studies have found that a strong host immune response against the virus favors viral clearance. Thus, variation in the genes involved in the immune response may contribute to one's ability to clear the virus. Consistent with these observations, recent studies have shown that the

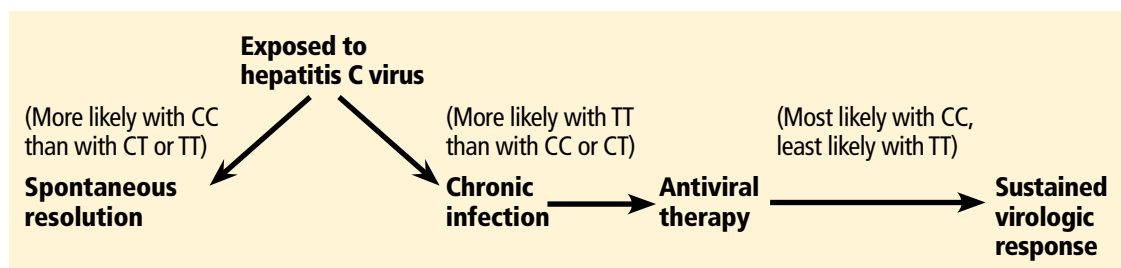


FIGURE 3. *IL28B* rs12979860 polymorphism and the natural history of chronic hepatitis C virus infection.

polymorphism in the *IL28* gene region encoding interferon lambda 3 strongly predicts spontaneous resolution of acute hepatitis C virus infection. People who have the *IL28B* CC genotype are three times more likely to spontaneously clear the virus than those with the CT or TT genotype (FIGURE 3).²⁴

■ *IL28B* POLYMORPHISM AND THE NATURAL HISTORY OF HEPATITIS C

In people in whom hepatitis C virus infection persists, up to 20% develop progressive liver fibrosis and eventually cirrhosis over 10 to 20 years.^{19,25,26} The speed at which fibrosis develops in these patients is variable and unpredictable.²⁵ The relationship between *IL28B* polymorphisms and hepatic fibrosis in patients with chronic hepatitis C virus infection has not been clearly established, although a study indicated that in patients with a known date of infection, the *IL28B* genotype is not associated with progression of hepatic fibrosis.²⁷ Obstacles in this field of study are that it is difficult to determine accurately when the patient contracted the virus, and that serial liver biopsies are needed to investigate the progression of hepatic fibrosis.

Patients with chronic hepatitis C virus infection are also at higher risk of hepatocellular carcinoma compared with the general population.²⁸ An analysis of explanted livers of patients with hepatitis C found that the prevalence of hepatocellular carcinoma in those with the unfavorable TT genotype was significantly higher than with the other genotypes.²⁹ Similarly, an earlier study demonstrated that patients with hepatitis C-associated hepatocellular carcinoma carried the T allele more frequently.³⁰ As with other aspects of *IL28B* associations with hepatitis C, these findings

indicate that the C allele confers a certain degree of protection.

An important implication of these relationships is that they may eventually help identify patients at greater risk, who therefore need earlier intervention.

■ *IL28B* POLYMORPHISM AND LIVER TRANSPLANTATION

Hepatitis C virus infection always recurs after liver transplantation, with serious consequences that include cirrhosis and liver failure. Recurrent hepatitis C virus infection has become an important reason for repeat transplantation in the United States.

Results of treatment with pegylated interferon and ribavirin for recurrent hepatitis C after liver transplantation have been disappointing, with response rates lower than 30% and significant side effects.³¹ Identifying the factors that predict the response to therapy allows for better selection of treatment candidates.

Similar to the way the *IL28B* genotype predicts response to antiviral therapy in the non-transplant setting, the *IL28B* genotypes of both the recipient and the donor are strongly and independently associated with response to interferon-based treatment in patients with hepatitis C after liver transplantation. The *IL28B* CC genotype in either the recipient or the donor is associated with a higher rate of response to pegylated interferon and ribavirin combination therapy after liver transplantation.^{30,32} For example, the response rate to therapy after liver transplantation reaches 86% in CC-donor and CC-recipient livers, compared with 0% in TT-donor and TT-recipient livers.

Additionally, the *IL28B* genotype of the recipient may determine the severity of histologic recurrence of hepatitis C, as indicated by

70% to 80% of hepatitis C virus infections persist, while 20% to 30% spontaneously resolve

progressive hepatic fibrosis. A recipient *IL28B* TT genotype is associated with more severe histologic recurrence of hepatitis C.³³

These data suggest that CC donor livers might be preferentially allocated to patients with hepatitis C virus infection.

■ *IL28B* AND OTHER FACTORS IN HEPATITIS C VIRUS INFECTION

Although it is tempting to think that the *IL28B* polymorphism is the sole predictor of response to antiviral therapy, it is but one of several known factors in the virus and the host.

While *IL28B* polymorphisms are the most important predictor of sustained virologic response with an interferon-based regimen, a rapid virologic response (undetectable viral load at 4 weeks) had superior predictive value and specificity in one study.³⁴ In fact, for patients with chronic hepatitis C infection who achieved a rapid virologic response with pegylated interferon and ribavirin, the *IL28B* polymorphism had no effect on the rate of sustained virologic response. However, it did predict a sustained virologic response in the group who did not achieve rapid virologic response.

In a study of patients with acute hepatitis C infection,³⁵ jaundice and the *IL28* rs12979860 CC genotype both predicted spontaneous clearance. The best predictor of viral persistence was the combination of the CT or TT genotype plus the absence of jaundice, which had a predictive value of 98%.

■ *IL28B* AND THE FUTURE OF HEPATITIS C VIRUS THERAPY

New oral agents were recently approved for treating hepatitis C. As of November 2014, these included simeprevir, sofosbuvir, and ledipasvir.

Simeprevir is a second-generation NS3/4A protease inhibitor approved for use in combination with pegylated interferon and ribavirin. A recent phase 3 trial evaluating simeprevir in patients who had relapsed after prior therapy found sustained virologic response rates to be higher with simeprevir than with placebo, irrespective of *IL28B* status.³⁶ This finding was similar to that of a trial of telaprevir.¹⁶

Sofosbuvir is a nucleotide analogue NS5B polymerase inhibitor that becomes incorpo-

rated into the growing RNA, inducing a chain termination event.³⁷ In phase 3 trials,^{38,39} researchers found an initial rapid decrease in viral load for patients treated with this agent regardless of *IL28B* status.

In the NEUTRINO trial (Sofosbuvir With Peginterferon Alfa 2a and Ribavirin for 12 Weeks in Treatment-Naive Subjects With Chronic Genotype 1, 4, 5, or 6 HCV Infection),³⁸ which used sofosbuvir in combination with interferon and ribavirin, the rate of sustained virologic response was higher in those with the favorable CC genotype (98%) than with a non-CC genotype (87%).

In COSMOS (A Study of TMC435 in Combination With PSI-7977 [GS7977] in Chronic Hepatitis C Genotype 1-Infected Prior Null Responders to Peginterferon/Ribavirin Therapy or HCV Treatment-Naive Patients),³⁹ which used a combination of simeprevir, sofosbuvir, and ribavirin, the rate of sustained virologic response was higher in those with the CC genotype (100%) than with the TT genotype (83%; TABLE 1).

These new medications have radically changed the landscape of hepatitis C therapy and have also unlocked the potential for developing completely interferon-free regimens.

Other new interferon-free regimens such as ledipasvir, daclatasvir, and asunaprevir promise high rates of sustained virologic response, which makes the utility of testing for *IL28B* polymorphisms to predict sustained virologic response very much diminished (TABLE 1).^{40,41} However, these new drugs are expected to be expensive, and *IL28B* polymorphisms may be used to identify candidates who are more likely to respond to pegylated interferon and ribavirin, particularly in resource-poor settings and in developing countries. Additionally, patients who have contraindications to these newer therapies will still likely need an interferon-based regimen, and thus the *IL28B* polymorphism will still be important in predicting treatment response and prognosis.

■ *IL28B* WILL STILL BE RELEVANT IN THE INTERFERON-FREE AGE

The *IL28B* polymorphism is a strong predictor of spontaneous clearance of hepatitis C virus and responsiveness to interferon-based

People with CC are three times more likely to spontaneously clear the virus than those with CT or TT

therapy, and testing for it has demonstrated a great potential to improve patient care. *IL28B* testing has become available for clinical use and may optimize the outcome of hepatitis C treatment by helping us to select the best treatment for individual patients and minimizing the duration of therapy and the side effects associated with interferon-based antiviral medications.

As newer therapies have shifted toward interferon-free regimens that offer very high sustained virologic response rates, the useful-

ness of *IL28B* polymorphism as a clinical test to predict the response rate to antiviral therapy is minimized substantially. It may remain clinically relevant in resource-poor settings and in developing countries, especially in light of the potentially prohibitive costs of the newer regimens, and for patients in whom these treatments are contraindicated. This does not minimize the lesson we learned from the discovery of the *IL28B* gene and the impact on our understanding of the pathogenesis of hepatitis C virus infection. ■

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