

Interleukin 28 B (*IL28B*)-Associated Variants, 2 SNPs

DETECTS DNA VARIANTS ASSOCIATED WITH TREATMENT RESPONSE FOR CHRONIC GENOTYPE 1 HEPATITIS C VIRUS (HCV) INFECTION

Disease Overview

- Hepatitis C is a disease caused by infection with hepatitis C virus (HCV). Transmission may occur from contaminated blood or tissue products, IV drug use, intranasal cocaine use, or organ transplant. Hepatitis C is the most common cause of progressive liver disease, cirrhosis, and hepatocellular carcinoma (HCC) in North America.
- In the United States, hepatitis C causes an estimated 10,000 deaths annually and is responsible for 60–70 percent of chronic hepatitis and up to 50 percent of cirrhosis and HCC. Hepatitis C is also the primary reason for liver transplant in the United States.
- HCV is a small, enveloped, single-stranded RNA virus. Viral genotyping has identified at least six major HCV genotypes that are further subtyped based on sequence identity. HCV genotype 1 (HCV-1), which includes subtypes 1a and 1b, accounts for 75 percent of hepatitis C infections in the United States.
- Approximately 80 percent of those with hepatitis C develop chronic HCV infection. Chronic HCV infection is characterized by the presence of anti-HCV antibodies with increased serum amino transferase (ALT) and detectable levels of viral HCV RNA persisting for more than six months.
- In individuals with chronic infection, the risk of developing cirrhosis ranges from 5 to 25 percent over a period of 25 to 30 years. Persons with HCV-related cirrhosis are at risk of liver failure (30 percent over 10 years) as well as HCC (1–3 percent per year).
- Sustained virological response (SVR), defined as the absence of HCV RNA in serum 24 weeks following completion of therapy represents clearance of the virus and is the most accepted measure of treatment success.
- Current recommended therapy for chronic hepatitis C infection consists of peginterferon (PEG-IFN α) and ribavirin (RBV) combination therapy, and more recently protease inhibitors. The specific therapy regimen, including dosing and duration of therapy, depends on numerous clinical factors and HCV genotype.
- Combination PEG-IFN α /RBV therapy is effective in eliminating HCV RNA in 40–50 percent of individuals with HCV-1 and in 70–90 percent of those with HCV genotype 2 or 3. Triple therapy with protease inhibitors is anticipated to be effective in eliminating HCV RNA in approximately 75 percent of patients with HCV-1. Individuals of European ancestry have a substantially higher probability of treatment response than African-Americans.

- Given the high cost of treatment and significant adverse side effects, which result in discontinuation of hepatitis C therapy in 10–15 percent of those treated, pre-therapeutic identification of factors predicting response is helpful in estimating the likelihood of an SVR. However, the lack of favorable factors should not be used to deny PEG-IFN α /RBV therapy.
- Two single nucleotide polymorphisms (SNPs), rs12979860 and rs8099917, located upstream of the *IL28B* gene, encoding for lambda or type III interferons (IFN- λ), have been independently associated with response to PEG-IFN α /RBV therapy in Caucasians.
- IFN- λ is believed to interact with a cellular trans-membrane receptor to upregulate the JAK-STAT pathway. This results in antiviral activity.

Epidemiology

- Persistent hepatitis C infection affects approximately 180 million individuals worldwide, or approximately 3 percent of the world's population.
- In the United States, approximately 4.1 million individuals, or 1.6 percent of all Americans, have anti-HCV antibodies.
- Estimated allele frequencies for the favorable rs12979860 C allele: Asian: 0.90; Caucasian: 0.75; Hispanic: 0.70; African-American: 0.50.
- Estimated allele frequencies for the favorable rs8099917 T allele: Caucasian: 0.75; Asian: 0.88; unknown in other ethnicities.

Genetics

- The SNP rs12979860 C/C genotype has been associated with a two to threefold greater rate of SVR following PEG-IFN α /RBV therapy in individuals with HCV-1 infection. Individuals with the C/T or TT genotypes are less likely to respond to treatment and achieve SVR.
- The SNP rs12979860 C/C genotype has also been associated with a threefold increase in natural clearance of HCV compared to the C/T and T/T genotypes.
- The SNP rs8099917 T/T genotype has been associated with a higher rate of SVR following PEG-IFN α /RBV therapy in individuals with HCV-1 infection. Individuals with the T/G and G/G genotypes are less likely to respond to treatment and achieve SVR.
- The SNP rs8099917 T/T genotype has also been associated with increased natural clearance of HCV compared to the T/G and G/G genotypes.

Indication for Ordering

Pre-therapeutic prediction of response to PEG-IFN α /RBV therapy for individuals with chronic HCV-1 infection.

Interpretation

- Genotype should be interpreted with clinical information. Individuals lacking favorable genetic factors should not be denied interferon therapy.
- SNP rs12979860
 - C/C genotype: Associated with increased spontaneous clearance of HCV and an increased likelihood of SVR following PEG-IFN α /RBV therapy for HCV-1 infection.
 - C/T or T/T genotypes: Associated with increased risk for nonresponse to PEG-IFN α /RBV therapy for HCV-1 infection.
- SNP rs809917
 - T/T genotype: Associated with increased spontaneous clearance of HCV and an increased likelihood of SVR following PEG-IFN α /RBV therapy for HCV-1 infection.
 - T/G or GG genotypes: Associated with increased risk for nonresponse to PEG-IFN α /RBV therapy for HCV-1 infection.

Methodology

- PCR and fluorescent probe hybridization to detect SNPs rs12979860 C>T and rs809917 G>T.
- Clinical sensitivity and specificity are unknown.
- Analytical sensitivity and specificity for the SNPs detected are 99 percent.

Limitations

- Only the specific SNPs targeted will be detected.
- The tested SNPs are associated with treatment response in Caucasians with chronic genotype 1 HCV infection; the association of these SNPs with treatment in patients of other ethnicities or for other HCV genotypes is unknown.

- Mutations in other genes and non-genetic factors that may affect response to hepatitis C therapy are not detected.
- Rare diagnostic errors can occur due to primer-site mutations.

Related Tests

- Hepatitis C Virus RNA Quantitative, Real-Time PCR with Reflex to Genotype ([2002685](#))
- Hepatitis C Virus RNA Quantitative, Real-Time PCR ([0098268](#))
- Hepatitis C Virus Genotyping by PCR & Sequencing ([0055593](#))

References

1. Ge D, et al. Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; 461(7262):399–401.
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3. Thomas DL, et al. Genetic variation in *IL28B* and spontaneous clearance of hepatitis C virus. *Nature* 2009; 461(7265):798–801.
4. Suppiah V, et al. *IL28B* is associated with response to chronic hepatitis C interferon- α and ribavirin therapy. *Nat Genet* 2009; 41(10):1100–4.
5. Tanaka Y, et al. Genome-wide association of *IL28B* with response to pegylated interferon- α and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009;41(10):1105–9.
6. Rauch A, et al. Genetic variation in *IL28B* is associated with chronic hepatitis C and treatment failure: a genome-wide association study. *Gastroenterol* 2010;138(4):1338–45.

Test Information

2004680 Interleukin 28 B (IL28B)-Associated Variants, 2 SNPs

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.