

Nonalcoholic Fatty Liver Disease Susceptibility (PNPLA3) Genotyping

Indications for Ordering

Screen for genetic susceptibility to:

- Nonalcoholic fatty liver disease (NAFLD)
- Cirrhosis progression in alcoholic liver disease (ALD)

Test Description

- Polymerase chain reaction (PCR) followed by high-resolution melt analysis
- Variant tested: *PNPLA3* c.444C>G; p.I148M (rs738409)

Tests to Consider

Primary Test

[Non-Alcoholic Fatty Liver Disease Susceptibility \(PNPLA3\) Genotyping 2014599](#)

- Assess genetic risk for NAFLD and cirrhosis progression in ALD

Related Test

[Liver Fibrosis, Non-Alcoholic Fatty Liver Disease \(Echosens\) 2012521](#)

Disease Overview

Prevalence

- Allele frequency of c.444C>G; p.I148M varies by ethnicity
 - Latinos: 0.57
 - East Asians: 0.38
 - Europeans: 0.23
 - South Asians: 0.22
 - African Americans: 0.14
- Prevalence of NAFLD: ~20-30% in the U.S. (Bellentani, 2010)

Symptoms

- May present with the progression of liver disease and can include:
 - Weakness or fatigue
 - Nausea and weight loss
 - Abdominal pain
 - Jaundice
 - Edema and ascites

Pathophysiology

- NAFLD
 - *PNPLA3* I148M variant leads to reduced function of adiponutrin protein
 - Results in accumulation of excessive triglycerides in hepatocytes
 - Risk factors include:
 - Male gender
 - Increasing age
 - Obesity
 - Diabetes
 - Insulin resistance
 - Associated with insulin resistance, dyslipidemia, and other adverse metabolic outcomes
 - May cause an inflammatory response in the liver (steatohepatitis) that can progress to fibrosis, cirrhosis, and liver cancer
- ALD
 - Spectrum includes alcoholic fatty liver disease, alcoholic hepatitis, and alcoholic cirrhosis
 - Individuals with alcoholic cirrhosis are at higher risk for hepatocellular carcinoma (HCC)
 - *PNPLA3* I148M variant is associated with liver disease progression, including development of cirrhosis and HCC

Genetics

Gene: *PNPLA3*

Variant: I148M

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity: unknown
- Analytical sensitivity/specificity: >99%

Results

- Positive: c.444C>G; p.I148M variant detected
 - Increased risk for NAFLD as well as more aggressive and more severe disease
 - Odds ratio (OR) for heterozygotes: 1.63 (95% CI: 1.35-1.98) (Zhang, 2015)
 - OR for homozygotes: 3.57 (95% CI: 2.42-5.26) (Zhang, 2015)
 - Association is independent of body mass index, diabetes, alcohol consumption, or ethnicity
 - Increased risk for alcoholic cirrhosis among heavy drinkers
 - OR for heterozygotes: 2.09 (95% CI: 1.79-2.44) (Salameh, 2015)
 - OR for homozygotes: 3.37 (95% CI: 2.49-4.58) (Salameh, 2015)
- Negative: c.444C>G; p.I148M variant not detected
 - Other genetic or environmental risk factors not detected by this assay may be present

Limitations

- Variants other than *PNPLA3* c.444C>G; p.I148M are not evaluated.
- Diagnostic errors can occur due to rare sequence variations.

References

- Bellentani S, Scaglioni F, Marino M, et al. [Epidemiology of non-alcoholic fatty liver disease](#). *Dig Dis*. 2010;28(1):155-161. PubMed
- Falletti E, Cussigh A, Cmet S, et al. [PNPLA3 rs738409 and TM6SF2 rs58542926 variants increase the risk of hepatocellular carcinoma in alcoholic cirrhosis](#). *Dig Liver Dis*. 2016;48(1):69-75. PubMed
- Salameh H, Raff E, Erwin A, et al. [PNPLA3 gene polymorphism is associated with predisposition to and severity of alcoholic liver disease](#). *Am J Gastroenterol*. 2015;110(6):846-856. PubMed
- Zhang L, You W, Zhang H, et al. [PNPLA3 polymorphisms \(rs738409\) and non-alcoholic fatty liver disease risk and related phenotypes: a meta-analysis](#). *J Gastroenterol Hepatol*. 2015;30(5):821-829. PubMed