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, et al. 2010. Epidemiology of non-alcoholic fatty liver disease. Dig Dis 2010;28(1):155-161
- Falleti E, Cussigh A, 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
- Salameh H, Raff E, et al. *PNPLA3* gene polymorphism is associated with predisposition to and severity of alcoholic liver disease. Am J Gastroenterol. 2015;110(6): 846-856
- Zhang L, You W, 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