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
  o Latinos – 0.57
  o East Asians – 0.38
  o Europeans – 0.23
  o South Asians – 0.22
  o 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
  o Weakness or fatigue
  o Nausea and weight loss
  o Abdominal pain
  o Jaundice
  o Edema and ascites

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

- 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
- 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