Apolipoprotein B (APOB) 2 Mutations

Indications for Ordering

• Confirm a diagnosis of familial defective Apo B-100 (FDB)
• Identify genetic cause for inherited hypercholesterolemia
• Screen individuals with a family history of FDB to assess risk of coronary artery disease (CAD)

Test Description

Polymerase chain reaction/fluorescence monitoring using hybridization probes for APOB gene

• Targeted testing for two variants
  o R3500W (c.9774C>T)
  o p.R3500Q (c.9775G>A)

Tests to Consider

Primary test
Apolipoprotein B (APOB) Mutation Detection 0055654

Related Tests

Apolipoprotein B/A Ratio 0050028

• Not usually recommended for cardiovascular disease risk assessment
• May be used concurrently with cholesterol/HDL-C ratio in individuals with elevated triglycerides (>200 mg/dL)

Apolipoprotein B 0050029

• Acceptable non-traditional secondary cardiovascular disease risk screen for specific populations
• May be useful in addition to LDL-C monitoring in individuals with elevated triglycerides

Apolipoprotein E (APOE) Genotyping, Cardiovascular Risk 2013337

• Provides supporting evidence for a diagnosis of type III hyperlipoproteinemia for evaluation of premature coronary heart disease

Disease Overview

Incidence

• R3500Q – 1/500 European Caucasians
• R3500W – described in Scottish population and in ~2% of Asian individuals with FDB
• Up to 15% of familial hypercholesterolemia is due to FDB

Symptoms

• Elevated cholesterol, triglycerides
• Premature CAD

Genetics

Gene – APOB

Inheritance – autosomal dominant

Structure/function

• Apo B is the main protein of low-density lipoprotein (LDL)
  o LDL interaction with LDL receptor regulates plasma cholesterol
  o Apo B solubilizes cholesterol for transport – leads to arterial deposition
• Apo B main form is Apo B-100
  o Secondary form is Apo B-48
  o Surrogate marker for measuring non-LDL-C
• Variants in APOB gene induce conformation change in Apo B-100 protein
  • Reduces affinity of LDL for its receptor
  • May lead to hypercholesterolemia and CAD

Variants

• R3500Q – most common
• R3500W
• ~40% of males and 20% of females heterozygous for an APOB variant will develop CAD
• Variants in LDLR, PCSK9, or APOB gene result in indistinguishable phenotypes for hypercholesterolemia

Test Interpretation

Sensitivity/specificity

• Analytical sensitivity/specificity – 99.9%

Results

• Negative – R3500W and R3500Q not detected
• Positive – R3500W and/or R3500Q detected
  • Associated with hypercholesterolemia and increased risk for CAD
  • Homozygotes and compound heterozygotes for R3500Q/R3500W are at greater risk for CAD than heterozygotes

Limitations

• Other APOB gene variants will not be detected
• Variants in other genes that may cause familial hypercholesterolemia are not detected
• Diagnostic errors can occur due to rare sequence variations
• Not recommended for asymptomatic individuals <18 years