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
  - R3500W (c.9774C>T)
  - 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)
  - LDL interaction with LDL receptor regulates plasma cholesterol
  - Apo B solubilizes cholesterol for transport – leads to arterial deposition
- Apo B main form is Apo B-100
  - Secondary form is Apo B-48
  - 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