

# Apolipoprotein B (APOB) 2 Mutations

## FOR DIAGNOSIS AND SCREENING OF FAMILIAL HYPERCHOLESTEROLEMIA

### Clinical Background

- Disease Overview
  - The interaction between low density lipoprotein (LDL) and the LDL receptor regulates plasma cholesterol.
  - Apolipoprotein B (Apo B) is the main protein of LDL and serves the function of solubilizing cholesterol for transport.
  - The main form of Apo B in plasma, Apo B-100, and a secondary form, Apo B-48, are encoded by a single gene.
  - Mutations in the *APOB* gene induce a conformation change in the Apo B-100 protein which reduces the affinity of LDL for its receptor and may result in hypercholesterolemia/premature atherosclerosis.
  - Up to 15 percent of familial hypercholesterolemia occurs due to ligand defective Apo B-100, also known as familial defective Apo B-100 (FDB).
  - Mutations in the LDL-receptor (LDLR), proprotein convertase subtilisin/kexin type 9 (PCSK9), or *APOB* gene result in largely indistinguishable phenotypes involving familial hypercholesterolemia.
  - Therapeutic approaches for individuals with familial hypercholesterolemia (due to defects in the LDL receptor) and FDB are similar.
- Epidemiology
  - One in 500 European Caucasians has the most common *APOB* gene mutation, R3500Q.
  - A second *APOB* mutation, R3500W, described in a Scottish population has also been identified in 2 percent of Asian FDB patients.
- Genetics
  - Autosomal dominant inheritance
  - Approximately 40 percent of males and 20 percent of females heterozygous for an *APOB* mutation will develop coronary artery disease (CAD).
  - Homozygotes and compound heterozygotes for R3500Q/R3500W are at greater risk for CAD than heterozygotes.

### Indications for Ordering

- Confirm a diagnosis of FDB.
- Identify a cause for inherited hypercholesterolemia
- Screen individuals with a family history of FDB to assess risk of CAD

### Contraindications for Ordering

Screening of asymptomatic minors is not recommended

### Interpretation

- Negative: R3500W and R3500Q were not detected.
- R3500W and R3500Q heterozygotes, homozygotes, or compound heterozygotes: This result is associated with hypercholesterolemia and familial defective Apo B-100 (FDB), with an increased risk of coronary artery disease.

### Methodology

- Mutations in the *APOB* gene, p.R3500Q (c.9775G>A) and R3500W (c.9774C>T), are assayed by polymerase chain reaction (PCR) and fluorescence monitoring using hybridization probes.
- Analytical sensitivity and specificity are 99.9 percent.

### Limitations

- *APOB* gene mutations, other than R3500Q and R3500W, will not be detected.
- Mutations in other genes that may cause familial hypercholesterolemia or an increased risk for CAD are not detected.
- Rare diagnostic errors can occur due to primer-site mutations.

### Related Tests

- Apolipoprotein B/A Ratio (0050028)
- Apolipoprotein B (0050029)
- Apolipoprotein E (*APOE*) 2 Mutations, Cardiovascular Risk (0055566)

### References

1. Austin M, et al. Familial hypercholesterolemia and coronary heart disease: a HuGE association review. *Am J Epidemiol* 2004;160:421–9.
2. Online Mendelian Inheritance in Man. <http://www.ncbi.nlm.nih.gov/omim> (accessed on June 10, 2009).
3. Tybjaerg-Hansen A, et al. Association of mutations in the apolipoprotein B gene with hypercholesterolemia and the risk of ischemic heart disease. *NEJM* 1998;338:1577–84.

## Test Information

0055654

### Apolipoprotein B Mutation Detection

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).