

Apolipoprotein B Mutation Analysis

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 is 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
- Contraindication for ordering:
 - Screening of asymptomatic minors is not recommended.

Interpretation

R3500W and R3500Q heterozygotes, homozygotes, or compound heterozygotes: This patient is predicted to have familial defective Apo B-100 (FDB) associated with an increased risk of coronary artery disease.

Methodology

Mutations in the *APOB* gene (R3500Q and R3500W) are assayed by polymerase chain reaction and fluorescence monitoring using hybridization probes.

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.

Related Tests

- Apolipoprotein B/A Ratio (0050028)
- Apolipoprotein B (0050029)
- Apolipoprotein E Mutation Detection for Cardiovascular Risk (0055566)

References

1. Austin, M., et al. Familial hypercholesterolemia and coronary heart disease: a HuGE association review. *Am J Epidemiol* 2004; 160:421-429.
2. Online Mendelian Inheritance in Man, OMIM. Johns Hopkins University, Baltimore, MD. MIM Number: {107730}, 2/1/07. URL: <http://www.ncbi.nlm.nih.gov/omim>.
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; 338:1577-1584.

Test Information

0055654 **Apolipoprotein B Mutation Detection**

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.