

Apolipoprotein E (APOE) 2 Mutations, Cardiovascular Risk

FOR SCREENING OR DIAGNOSTIC CONFIRMATION OF TYPE III HYPERLIPOPROTEINEMIA (HLP III)

Disease Overview

- HLP III is characterized by increased cholesterol and triglyceride levels, presence of B-VLDL, xanthomas, and premature vascular disease, including coronary heart disease (CHD) and peripheral artery disease.
- Identification of this relatively rare lipid disorder may prevent premature coronary heart disease, as patients typically have an excellent response to appropriate drug and dietary therapy.
- Apolipoprotein E (Apo E) is a critical protein component of very low density lipoprotein (VLDL) and chylomicrons; it plays an important role in cholesterol metabolism in the liver.
- The *APOE* gene has three common alleles (e2, e3, e4) encoding three protein isoforms (E2, E3, E4) differing at amino acids positions 112 and 158.
- Apo E2 binds the lipoprotein receptors with only 2 percent of the affinity of the E3 and E4 isoforms. Impaired clearance of chylomicron and VLDL remnants results in increased plasma cholesterol and triglyceride levels.

Epidemiology

HLP III occurs in approximately 1:5,000 individuals and may account for up to 5 percent of premature CHD.

Genetics

- Autosomal recessive inheritance.
- Approximate population frequencies for the common *APOE* alleles: e2 (10 percent), e3 (75 percent), and e4 (15 percent).
- *APOE* e3/e3 is the most common genotype and is considered wild-type.
- Both *APOE* e2 and e4 alleles are associated with increased plasma triglyceride concentrations, but only e2 is associated with HLP III.
- *APOE* e4 is associated with increased plasma cholesterol levels and an increased risk for CHD.
- More than 95 percent of individuals with HLP III have the rare e2/e2 genotype.
- Approximately 1 percent of Caucasians are *APOE* e2 homozygotes, but only 1–5 percent of those individuals will develop disease symptoms.
- Up to 26 percent of individuals heterozygous for both familial hypercholesterolemia and the *APOE* e2 allele will develop HLP III.
- Other genetic and environmental factors likely contribute to the expression of HLP III or CHD.

Indications for Ordering

- To confirm a diagnosis of HLP III.
- Identify a cause for HLP III or premature CHD.
- Screen individuals with a family history of HLP III or premature CHD.

Contraindications for Ordering

- Do not order for a demented patient. Athena Neurosciences, Inc. is the exclusive licensee of U.S. Patent No. 5,508,167 for Alzheimer risk assessment.
- This test is not recommended for asymptomatic patients under 18 years of age.

Interpretation

- e3/e3: Most common (normal) genotype.
- e2/e2: Strong association with HLP III.
- e4/e4: Associated with increased plasma cholesterol levels that may contribute to CHD.
- e2/e3 or e2/e4: Some association with HLP III in patients heterozygous for familial hypercholesterolemia.
- e3/e4: Some association with increased plasma cholesterol levels that may contribute to CHD.

Methodology

- Point mutations in the codons 112 and 158 of the *APOE* gene (e2, e3, e4) are assayed by polymerase chain reaction and fluorescence monitoring using hybridization probes.
- Analytical specificity and sensitivity are 99 percent.
- Clinical sensitivity is approximately 5 percent for individuals with premature CHD and 95 percent for individuals with HLP III.
- Genotyping is the preferred method for distinguishing among the common Apo E isoforms, as it is faster and more reliable than phenotyping.

Limitations

- Rare Apo E isoforms (other than E2, E3, E4) and mutations in other genes that may cause HLP III or an increased risk for CHD are not detected. If rare alleles are suspected, phenotyping by isoelectric focusing may be indicated.
- Rare diagnostic errors may occur due to primer-site mutations.

References

1. Eichner, J.E., et al. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. *Am J Epidemiol* 2002;155:487–95.
2. Online Mendelian Inheritance in Man. <http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=107741> (accessed on July 9, 2009).
3. Apolipoprotein E: laboratory determination and clinical significance. In *Laboratory measurement of lipids, lipoproteins, and apolipoproteins*. N Rifai and GR Warnick, eds. 1994; Washington: AACC Press, 279–304.

Test Information

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

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.