

# Apolipoprotein E Mutation Analysis for Cardiovascular Risk

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

## Clinical Background

- 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 dominant
  - Approximate population frequencies for the common APOE alleles: e2 (10%), e3 (75%), e4 (15%)
  - Apo e3/e3 is the most common genotype and considered wildtype.
  - 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

- Confirm a diagnosis of HLP III.
- Identify a cause for HLP III or premature CAD.
- Screen individuals with a family history of HLP III or premature CAD.
- Contraindication for ordering:  
Assessment of Alzheimer disease

## 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 is 99.9 percent.
- 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 CAD, are not detected.

## References

1. Eichner, J.E., et al. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. *Am J Epidemiol* 2002;155:487-495.
2. Online Mendelian Inheritance in Man, OMIM. Johns Hopkins University, Baltimore, MD. MIM Number: {107741}, 2/1/07. URL: <http://www.ncbi.nlm.nih.gov/omim>.
3. LL, et al. Apolipoprotein E: laboratory determination and clinical significance. In *Laboratory measurement of lipids, lipoproteins, and apolipoproteins*. N Rifai and GR Warnick, eds. 1994; Washington: AACCC Press, 279-304.

## Test Information

**0055566**

**Apolipoprotein E Mutation Detection for Cardiovascular Risk**

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