Apolipoprotein E (APOE) Genotyping, Cardiovascular Disease Risk

Indications for Ordering

- Provides supporting evidence for a diagnosis of type III hyperlipoproteinemia (HLP III) for evaluation of premature coronary heart disease (CHD)
- Identify a genetic cause for HLP III or premature CHD
- Screen individuals with a family history of HLP III or premature CHD
- NOT recommended for asymptomatic individuals <18 years

Test Description

- Polymerase chain reaction and fluorescence monitoring using hybridization probes for APOE gene
- Variants tested
  - c.388T>C (rs429358, p.Cys130Arg)
  - c.526C>T (rs7412, p.Arg176Cys)

Tests to Consider

Primary test
Apolipoprotein E (APOE) Genotyping, Cardiovascular Risk
2013337
- Determines APOE genotype in context of HLP III for evaluation of premature CHD
- Use for cardiovascular risk assessment only

Related test
Apolipoprotein E (APOE) Genotyping, Alzheimer Disease Risk
2013341
- Determines APOE genotype in context of evaluation for Alzheimer disease (AD)
- Supports a clinical diagnosis of AD in symptomatic individuals
- Use for AD risk assessment only

Disease Overview

Incidence of HLP III – 1/5,000
- May account for up to 5% of premature CHD
- APOE allele frequencies
  - e2 (c.388T, p.130Cys and c.526C>T, p.Arg176Cys) – 10%
  - e3 (c.388T, p.130Cys and c.526C, p.176Arg ) – 75%
  - e4 (c.388T>C, p.Cys130Arg and c.526C, p.176Arg) – 15%
  - Homozygosity
    - e2 – 1% of Caucasians (only 1-4% of homozygotes will develop HLP III)

Symptoms of HLP III
- Characterized by
  - Premature CHD, vascular disease, peripheral artery disease
  - Xanthomas
  - Elevated cholesterol, triglycerides, very low density lipoprotein (VLDL)

Screening/detection
Early identification of this disorder is important because lipid-lowering agents usually result in excellent response

Genetics

Gene – APOE

Inheritance – autosomal recessive

Structure/function
- Apo E is a critical protein component of VLDL and chylomicrons
  - Three common protein isoforms (e2, e3, e4) differ at amino acid positions 112 (130 legacy) and 158 (176 legacy)
- Apo e2 binds the lipoprotein receptors with only 2% of the affinity of e3 and e4 isoforms
  - Results in impaired clearance of chylomicron and VLDL remnants
  - Leads to increased plasma cholesterol and triglyceride levels

Variants
- Homozygosity for e2
  - Only genotype associated with HLP III
  - Found in >90% of individuals with HLP III
- APOE e3 – considered wild type
- APOE e4 – increased plasma cholesterol

Test Interpretation

Sensitivity/specificity
- Clinical sensitivity – >90% for individuals with HLP III
  - (Eichner, 2002)
- Analytical sensitivity/specificity – 99%
Results

- **APOE e2/e2** – provides additional evidence for a clinical diagnosis of HLP III; by itself, genotype is not diagnostic for HLP III
- **APOE e3/e3** – most common genotype found in the general population
- **APOE e4/e4** – associated with increased plasma cholesterol levels that may contribute to CHD
- **APOE e2/e3, e2/e4, e3/e4** – no significantly increased risk for HLP III
- **APOE e2/e4 and e3/e4** – some association with increased plasma cholesterol levels and atherosclerosis

Limitations

- Rare **APOE** isoforms and variants in other genes that cause HLP III are not detected
- If rare alleles are suspected, phenotyping by isoelectric focusing may be indicated
- Diagnostic errors can occur due to rare sequence variations
- **APOE e2** homozygosity is neither sufficient nor necessary to cause HPL III

Reference