Apolipoprotein E Genotyping, Cardiovascular Disease Risk

The APOE gene encodes the apolipoprotein E (apoE) protein, which combines with lipids to form lipoproteins that transport cholesterol and other fats through the bloodstream.

The three most common APOE variants are designated as the e2, e3, and e4 alleles. E3 is the wild type allele, while e2 is associated with an increased risk for early cardiovascular disease (CVD) and hyperlipoproteinemia type III (HLP III) and E4 is associated with Alzheimer disease.

Disease Overview

Incidence of Hyperlipoproteinemia Type III

- 1/5,000
- May account for up to 5% of premature coronary heart disease (CHD)

Clinical Presentation/Treatment of Hyperlipoproteinemia Type III

- Elevated cholesterol, triglycerides, very low density lipoprotein (VLDL)
- Premature CHD, vascular disease, peripheral artery disease
- Xanthomas
- Early identification allows treatment with lipid-lowering agents

Genetics

Gene

APOE

Inheritance of Hyperlipoproteinemia Type III

Autosomal recessive

Structure

ApoE is a critical protein component of VLDL and chylomicrons

Variants

Three common alleles (e2, e3, e4) differ at amino acid positions 112 (130 legacy) and 158 (176 legacy)

- 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%

Tests to Consider

Apolipoprotein E (APOE) Genotyping, Cardiovascular Risk 2013337
Method: Polymerase Chain Reaction/Fluorescence Monitoring

- Determines APOE genotype in context of HLP III for evaluation of premature CHD
- Use for cardiovascular risk assessment only
- Not recommended for asymptomatic individuals <18 years

Apolipoprotein E (APOE) Genotyping, Alzheimer Disease Risk 2013341
Method: Polymerase Chain Reaction/Fluorescence Monitoring

- Determines APOE genotype in context of evaluation for Alzheimer disease (AD)
- Supports a clinical diagnosis of AD in symptomatic individuals
- Not recommended for predictive testing in asymptomatic individuals
- **APOE** 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
- Homozygosity for e2 is present in 1% of White individuals
  - Only genotype associated with HLP III
  - 1-4% of homozygotes will develop HLP III
  - Found in >90% of individuals with HLP III
- **APOE** e3: considered wild type
- **APOE** e4: associated with increased plasma cholesterol

### Test Interpretation

#### Sensitivity/Specificity
- Clinical sensitivity: >90% for individuals with HLP III
- 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 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
- Diagnostic errors can occur due to rare sequence variations
- Rare **APOE** variants and variants in other genes that cause HLP III are not detected
- **APOE** e2 homozygosity is neither sufficient nor necessary to cause HLP III

#### References