Apolipoprotein E Genotyping, Cardiovascular Disease Risk

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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, e4 is associated with Alzheimer disease, and e2 is associated with an increased risk for early cardiovascular disease (CVD) and hyperlipoproteinemia type III (HLP III).

HLP III accounts for up to 5% of premature coronary heart disease (CHD) and may also present with elevated cholesterol, triglycerides, and very low density lipoprotein (VLDL). Early identification allows for treatment with lipid-lowering agents.

Featured ARUP Testing

Apolipoprotein E (APOE) Genotyping, Cardiovascular Risk 2013337

Method: Polymerase Chain Reaction (PCR)/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

Genetics

Gene

APOE

Inheritance of Hyperlipoproteinemia Type III

Multifactorial

Penetrance

1-5% percent of individuals homozygous for the e2 allele develop HPL III

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%
- *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[1]
- 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 HPL III

References

1. Eichner JE, Dunn T, Perveen G, et al. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. *Am J Epidemiol*. 2002;155(6):487-495.

Related Information

Apolipoprotein E (APOE) Genotyping, Alzheimer Disease Risk

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