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, 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.

Genetics

Gene

APOE

Inheritance of Hyperlipoproteinemia Type III

Multifactorial

Penetration

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


Related Information

*Apolipoprotein E (APOE) Genotyping, Alzheimer Disease Risk*