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

Indications for Ordering

- Supports a clinical diagnosis of Alzheimer disease (AD) in symptomatic individuals
- NOT recommended for predicting risk for AD in asymptomatic individuals
- NOT performed on individuals <18 years or on fetal specimens

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)
- Alleles
  - e2 allele (cysteine at codons 130 and 176)
  - e3 allele (cysteine at codon 130, arginine at codon 176)
  - e4 allele (arginine at codons 130 and 176)

Tests to Consider

Primary test

Apolipoprotein E (*APOE*) Genotyping, Alzheimer Disease Risk 2013341

- Determines *APOE* genotype in context of evaluation for AD
- See 2013337 below for cardiovascular risk assessment
- Genetic counseling and informed consent are strongly recommended prior to ordering and posttest to discuss results

Related test

Apolipoprotein E (*APOE*) Genotyping, Cardiovascular Risk 2013337

- Provides supporting evidence for a diagnosis of type III hyperlipoproteinemia for evaluation of premature coronary heart disease
- Use for cardiovascular disease risk assessment only

Disease Overview

Prevalence of AD

- ≥65 years – 1/9
- ≥85 years – 1/3

Incidence of AD

- 65-74 years – 1/500
- 75-84 years – 1/76
- ≥85 years – 1/25

APOE allele frequencies

- e2 – 10%
- e3 – 75%
- e4 – 15%
  - 30-60% of individuals with AD have at least one e4 allele
  - e4/e4 is found in
    - ~13% of AD population
    - 20% of familial AD population
    - 1-2% of general population

Age of onset – typically >65 years

Symptoms

- Cognitive decline
  - Progressive memory loss
  - Confusion and disorientation
  - Personality changes
  - Problems with executive function
- Neurological findings
  - Seizures
  - Parkinsonism
  - Psychiatric disturbance
- Progression of symptoms can last 8-25 years
- Death typically occurs due to malnutrition, pneumonia, or secondary infections

Diagnostic issues

- Diagnosing AD in symptomatic individuals
  - Probable diagnosis of AD can be made based on combination of clinical findings, neuroimaging, and exclusion of other causes of dementia
    - An antemortem diagnosis of AD is correct 80-90% of the time
    - Presence of e4/e4 *APOE* genotype increases diagnostic certainty to ~97%
  - Diagnosis is confirmed postmortem by neuropathologic examination
  - *APOE* genotyping can be used to support the clinical diagnosis of AD in symptomatic individuals if one or more e4 alleles are present, but e4 is neither necessary nor sufficient to diagnose AD

- Predicting AD risk in asymptomatic individuals
  - *APOE* genotyping is not recommended for predictive testing in asymptomatic individuals due to
    - Low sensitivity and specificity
    - Lack of preventive options
    - Difficulty quantifying individual risk
  - AD risk is multifactorial
    - Determined by multiple genes, age, gender, ethnicity, family history, and environment
  - In rare cases of early onset familial AD, presymptomatic testing is possible if the familial variant is known
    - *APP*, *PSEN1,* and *PSEN2* genes, which are associated with early onset AD, are not included in this test

Pathophysiology

Etiology of AD is largely unknown

- Symptoms are thought to be caused by abnormal accumulation of beta-amyloid plaques and neurofibrillary tangles of tau protein in the brain that cause neuronal damage and death

Genetics

Gene – *APOE*

Inheritance of AD – multifactorial

Inheritance of *APOE* e4 – semidominant

Penetrance – incomplete and age dependent

Variants

- *APOE* e2
  - Associated with decreased risk for AD
- *APOE* e3
  - Most common *APOE* allele in the general population
- *APOE* e4
  - Associated with increased risk for AD

Test Interpretation

Sensitivity/specificity

- Analytical sensitivity/specificity – 99%

Results

- *APOE* e2/e2
  - Not associated with increased risk for AD, but has been associated with increased risk for type III hyperlipoproteinemia
- *APOE* e3/e3 and e2/e3
  - Not associated with increased risk for AD, but does not exclude a diagnosis of AD
- *APOE* e4/e4
  - Adds substantial support to a clinical diagnosis of AD in symptomatic individuals
- *APOE* e2/e4 and e3/e4
  - Adds support to a clinical diagnosis of AD in symptomatic individuals

Limitations

- Presence of one or more *APOE* e4 alleles is considered a risk factor but is not diagnostic for AD
  - *APOE* e4 is neither necessary nor sufficient to diagnose AD
- Other *APOE* alleles and variants in other genes associated with AD are not analyzed
- Diagnostic errors can occur due to rare sequence variations

References

- Alzheimer's Association. 2015 Alzheimer's disease facts and figures (www.alz.org/facts/)
- Bird TD. Alzheimer Disease Overview. 1998 Oct 23 [Updated 2015 Sept 24]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016 (www.ncbi.nlm.nih.gov/books/NBK1161/)