Apolipoprotein E (APOE) Genotyping, Alzheimer Disease Risk

Last Literature Review: October 2021 Last Update: June 2023

Alzheimer's disease (AD) is the most common type of dementia, characterized by a progressive cognitive decline that affects aspects such as memory, problem-solving skills, multistep tasks, planning, and personality. Most individuals with AD have symptom onset at 60-65 years of age or later (termed late-onset AD), while only 5% of cases are early-onset (before 60-65 years of age). AD is a multifactorial condition, meaning multiple genetic and environmental factors may contribute to its development. It has been well established that the e4 allele of the *APOE* gene is more prevalent in individuals with AD, however, the presence of the e4 allele is neither required nor sufficient for a diagnosis. Identification of the e4 allele in an individual suspected to have AD can be used to support a suspected clinical diagnosis.[1]

Featured ARUP Testing

Apolipoprotein E (APOE) Genotyping, Alzheimer Disease Risk 2013341

Method: Polymerase Chain Reaction (PCR)/Fluorescence Monitoring

- Use to support a clinical diagnosis of AD in symptomatic individuals
- Use for AD risk assessment only
- Genetic counseling and informed consent are strongly recommended both before ordering and posttest to discuss results.

Disease Overview

Diagnosis

- Clinical diagnosis of AD is typically suspected based on symptoms of slowly progressive dementia, neuroimaging findings of gross cerebral cortical atrophy, and exclusion of other causes of dementia.
- Additional studies that can support a clinical diagnosis of AD include amyloid positron emission tomography (PET) imaging and measurements of amyloid and tau in cerebral spinal fluid[2]
- Confirmatory diagnostic testing for AD can only be performed postmortem, with the identification of hallmark neuropathologic findings such as beta (β)-amyloid plaques and intraneuronal neurofibrillary tangles containing tau protein.[3]
- Many genes beyond *APOE* have been identified in association with late-onset AD, but their effect on disease risk is minimal. The clinical utility of testing for genetic factors to predict the risk of late-onset AD has not been established.[4]

Incidence

Approximately 6.2 million Americans are currently living with AD, including about one in nine people over the age of 65.

Genetics

Gene Tested

APOE

Variants Tested

- 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)

Inheritance

AD is a multifactorial condition. The e4 allele of *APOE* is semidominant with incomplete penetrance.

Prevalence

APOE Genotype	Estimated Prevalence in American General Population[a][5]	Estimated Prevalence in North American AD Population[6]
e2/e2	0.2-0.7%	Not specified
e2/e3	10-15%	Not specified
e3/e3	45-63%	Not specified
e2/e4	2-6%	56%[b]
e3/e4	21-29%	
e4/e4	2-5%	11%

[a]Varies by ethnicity.

[b]Prevalence of e4 heterozygotes (both e2/e4 and e3/e4 genotypes).

Sources: Rajan, 2017[5]; Ward, 2012[6]

Test Interpretation

Analytical Sensitivity/Specificity

99%

Results

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

Limitations

- The presence of one or more *APOE* e4 alleles is considered a risk factor but is not diagnostic for AD.
- Only the *APOE* alleles e2, e3, and e4 will be detected; other *APOE* alleles and variants in other genes associated with AD are not analyzed.
- Diagnostic errors can occur due to rare sequence variations.

References

1. Bird TD. Alzheimer disease overview. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews.* University of Washington, Seattle. Last update Dec 2018; accessed Oct 2021.

2. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014;13(6):614-629.

3. Montine TJ, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach. *Acta Neuropathol*. 2012;123(1):1-11.

4. Van Cauwenberghe C, Van Broeckhoven C, Sleegers K. The genetic landscape of Alzheimer disease: clinical implications and perspectives. *Genet Med*. 2016;18(5):421-430.

5. Rajan KB, Barnes LL, Wilson RS, et al. Racial differences in the association between apolipoprotein E risk alleles and overall and total cardiovascular mortality over 18 years. *J Am Geriatr Soc*. 2017;65(11):2425-2430.

6. Ward A, Crean S, Mercaldi CJ, et al. Prevalence of apolipoprotein E4 genotype and homozygotes (APOE e4/4) among patients diagnosed with Alzheimer's disease: a systematic review and meta-analysis. *Neuroepidemiology*. 2012;38(1):1-17.

Additional Resources

Alzheimer's Association. Alzheimer's and dementia facts and figures. Accessed: Oct 2021.

Related Information

Apolipoprotein E Genotyping, Cardiovascular Disease Risk
Early-Onset Alzheimer's Disease
Early-Onset Alzheimer's Panel, Sequencing

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com