Apolipoprotein E (APOE) Genotyping, Alzheimer Disease

Last Literature Review: October 2021 Last Update: March 2026

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]

The presence of the *APOE* e4 allele has been linked to an increased risk of amyloid-related imaging abnormalities (ARIA), including symptomatic cases, in individuals receiving amyloid-targeting antibody therapies for AD, such as lecanemab and donanemab. The U.S. Food and Drug Administration (FDA) labeling recommends *APOE* genotyping prior to initiating treatment to help assess an individual's ARIA risk (refer to the ARUP Consult Germline Pharmacogenetics topic for more information on pharmacogenetic testing). However, current ARIA management guidelines do not differ between *APOE* e4 carriers and noncarriers.

Featured ARUP Testing

Apolipoprotein E (APOE) Genotyping, Alzheimer Disease 2013341

Method: Polymerase Chain Reaction (PCR) / Fluorescence Monitoring

- Use to assess risk of amyloid-related imaging abnormalities (ARIA) before treating with amyloid-targeting antibody therapies for AD, such as lecanemab or donanemab
- Supports the clinical diagnosis of Alzheimer's disease (AD) in symptomatic individuals
- APOE genotyping may be used for risk assessment, but results have limited clinical utility because APOE status alone does not establish or exclude a diagnosis of AD.
- 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]
- ARIA refers to a spectrum of MRI findings that may be observed in patients treated with amyloid-targeting antibody therapies for AD. It can be characterized by edema and effusion (also known as ARIA-E) and microhemorrhages and superficial siderosis (also known as ARIA-H).

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; associated with a higher risk for ARIA in individuals treated with amyloid-targeting antibody therapies for AD

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, Feldman J, Mirzaa GM, et al, eds. *GeneReviews.* University of Washington, Seattle. Updated Dec 2018; accessed Aug 2024.

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.

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