

# Apolipoprotein E (APOE) Genotyping, Alzheimer Disease Risk

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.<sup>1</sup>

## 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<sup>2</sup>
- 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.<sup>3</sup>
- 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.<sup>4</sup>

### 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

<i>APOE</i> Genotype	Estimated Prevalence in American General Population <sup>a5</sup>	Estimated Prevalence in North American AD Population <sup>6</sup>
e2/e2	0.2-0.7%	Not specified

<sup>a</sup>Varies by ethnicity.

<sup>b</sup>Prevalence of e4 heterozygotes (both e2/e4 and e3/e4 genotypes).

Sources: Rajan, 2017<sup>5</sup>; Ward, 2012<sup>6</sup>

## Featured ARUP Testing

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

**Method:** Polymerase Chain Reaction/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.

<i>APOE</i> Genotype	Estimated Prevalence in American General Population <sup>a5</sup>	Estimated Prevalence in North American AD Population <sup>6</sup>
e2/e3	10-15%	Not specified
e3/e3	45-63%	Not specified
e2/e4	2-6%	56% <sup>b</sup>
e3/e4	21-29%	
e4/e4	2-5%	11%

<sup>a</sup>Varies by ethnicity.

<sup>b</sup>Prevalence of e4 heterozygotes (both e2/e4 and e3/e4 genotypes).

Sources: Rajan, 2017<sup>5</sup>; Ward, 2012<sup>6</sup>

## Test Interpretation

### Analytical Sensitivity/Specificity

99%

### Results

Finding	Significance
<i>APOE</i> 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
<i>APOE</i> e2/e3	Not associated with increased risk for AD, but does not exclude a diagnosis of AD
<i>APOE</i> e3/e3	Not associated with increased risk for AD, but does not exclude a diagnosis of AD
<i>APOE</i> e2/e4	Adds support to a clinical diagnosis of AD in symptomatic individuals
<i>APOE</i> e3/e4	Adds support to a clinical diagnosis of AD in symptomatic individuals
<i>APOE</i> 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, editors. GeneReviews, University of Washington; 1993-2021. [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](#)

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