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.1

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 fluid2
- 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

<table>
<thead>
<tr>
<th>APOE Genotype</th>
<th>Estimated Prevalence in American General Population(^a)</th>
<th>Estimated Prevalence in North American AD Population(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>e2/e2</td>
<td>0.2-0.7%</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

\(^a\)Varies by ethnicity.

\(^b\)Prevalence of e4 heterozygotes (both e2/e4 and e3/e4 genotypes).

Sources: Rajan, 2017; Ward, 2012
### Test Interpretation

#### Analytical Sensitivity/Specificity

99%

#### Results

<table>
<thead>
<tr>
<th>Finding</th>
<th>Significance</th>
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<tbody>
<tr>
<td>APOE e2/e2</td>
<td>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</td>
</tr>
<tr>
<td>APOE e2/e3</td>
<td>Not associated with increased risk for AD, but does not exclude a diagnosis of AD</td>
</tr>
<tr>
<td>APOE e3/e3</td>
<td>Not associated with increased risk for AD, but does not exclude a diagnosis of AD</td>
</tr>
<tr>
<td>APOE e2/e4</td>
<td>Adds support to a clinical diagnosis of AD in symptomatic individuals</td>
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<td>APOE e3/e4</td>
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</tr>
<tr>
<td>APOE e4/e4</td>
<td>Adds substantial support to a clinical diagnosis of AD in symptomatic individuals</td>
</tr>
</tbody>
</table>

#### 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


## Additional Resources


## Related Information

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