Overview

The apolipoprotein E (APOE) gene, on chromosome 19, is the major genetic source of the common forms of late-onset Alzheimer disease (Alzheimer’s disease). This gene has three allelic variants (2, 3, and 4) and five common genotypes (2/3, 3/3, 2/4, 3/4, and 4/4).

The APOE-4 allele increases the risk and decreases the average age of dementia onset in a dose-related fashion, such that the risk of Alzheimer disease is lowest in patients with the 3/3 genotype, higher for the 3/4 genotype, and highest for the 4/4 genotype.\[1\] The APOE-2 allele lowers the risk of Alzheimer disease.\[2\]

However, APOE-4 accounts for only part of the genetic risk for Alzheimer disease. A family history of dementia, regardless of APOE-4 status, can also increase the risk of developing the disorder. Specifically, persons with a first-degree relative with dementia have a 10-30% increased risk of developing Alzheimer disease.\[3\]

Of note, an investigation in an elderly Swedish population reported that a family history of dementia was associated with an increased risk of dementia and Alzheimer disease only among APOE-4 carriers, suggesting that there might be other familial genetic or environmental factors active in the presence of APOE-4.\[4\]

The underlying mechanism through which APOE influences Alzheimer disease risk has not yet been determined. Scientists have explored several possibilities, including the idea that APOE may play a role in cholesterol transport, neuronal integrity, and amyloid deposition.

Additional studies revealing the true mechanism could eventually lead to more specific treatments for Alzheimer disease. Indeed, studies of asymptomatic APOE-4 carriers show that these persons are more likely to display subtle abnormalities on brain scans, such as positron emission tomography (PET) or magnetic resonance imaging (MRI) scans.\[5\]

Thus, combining information on APOE-4 carrier status with other informative biological-marker data is a promising research strategy for detecting individuals who might be candidates for Alzheimer disease prevention strategies.\[5, 6, 7\]

Clinical Implications

Because the APOE-4 allele is neither necessary nor, by itself, sufficient for developing Alzheimer disease, APOE testing is not generally recommended as a screening tool.

Many experts have suggested that asymptomatic individuals with the APOE-4 allele will never develop the disease and will therefore become unnecessarily concerned about their future cognitive health, while those without the APOE-4 allele will be falsely reassured that they will never develop the disease.\[8\]

Despite such concerns, however, studies of individuals who have learned that they are APOE-4 carriers have not demonstrated higher rates of anxiety or depression. Rather, some APOE-4 carriers are motivated to adapt a healthier
lifestyle to maximize brain health.

Most studies investigating treatment strategies for Alzheimer disease now include APOE testing to determine whether treatment outcomes vary by genotype, with the hope that APOE testing may eventually prove useful as a practical test to predict treatment response.

For now, APOE testing is not generally recommended as a screening tool. However, because the presence of the APOE-4 allele increases the likelihood of a diagnosis of Alzheimer’s disease if the patient already has dementia, APOE testing can be used as an adjunct to other diagnostic tests in patients with dementia.\[8\]

### Contributor Information and Disclosures

**Author**

Gary W Small, MD  Professor of Psychiatry and Biobehavioral Sciences, Parlow-Solomon Professor on Aging, Director of Geriatric Psychiatry, Director of the UCLA Center on Aging, University of California, Los Angeles, David Geffen School of Medicine

Gary W Small, MD is a member of the following medical societies: American Association for Geriatric Psychiatry, American Association of University Professors, American Geriatrics Society, American Psychiatric Association, and Gerontological Society of America

Disclosure: Novartis, Forest Honoraria Speaking and teaching; Novartis Consulting fee Consulting; Dakim Ownership interest Consulting

**Chief Editor**

Bruce Buehler, MD  Professor, Department of Pediatrics and Genetics, Director RSA, University of Nebraska Medical Center

Bruce Buehler, MD is a member of the following medical societies: American Academy for Cerebral Palsy and Developmental Medicine, American Academy of Pediatrics, American Association on Mental Retardation, American College of Medical Genetics, American College of Physician Executives, American Medical Association, and Nebraska Medical Association

Disclosure: Nothing to disclose.

**Additional Contributors**

Mary L Windle, PharmD  Adjunct Associate Professor, University of Nebraska Medical Center College of Pharmacy; Editor-in-Chief, Medscape Drug Reference

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### References


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