

“My mother has Alzheimer’s disease. Am I next?”

With a growing number of people affected by Alzheimer’s disease (AD) and greater public awareness surrounding it, worried relatives of individuals with AD are increasingly asking, “What is my risk of developing Alzheimer’s?” For family members, many of whom are in the caregiver role, even the smallest sign of forgetfulness can trigger fear about developing this progressive, fatal disease.

In this issue of *In Brief*, we discuss the role of genetics in younger-onset (early-onset) and late-onset AD.

Risk at the Population Level

The greatest known risk factor for AD is advancing age, with an estimated 95 percent of all cases occurring in individuals who are 65 years or older.¹ The estimated lifetime risk for AD at age 65 is 17 percent for women and 9 percent for men.² For the vast majority of cases, experts believe AD is caused by a combination of genetic, lifestyle, and environmental factors with exact causative factors just beginning to be understood.³ Individuals who have a parent, brother, sister, or child with AD (i.e., familial AD) are more likely to develop the disease, and the risk increases if more than one family member has the disease. However, only an estimated 1 percent of AD cases develop due to gene mutations (i.e., autosomal dominant AD or autosomal dominant familial AD), which typically result in younger-onset AD (defined as when symptoms occur before age 65).⁴ Alzheimer’s disease may also occur without a previous family history.

Younger-Onset Alzheimer’s Disease Can Be Due to Genetic Profile

Younger-onset AD may be sporadic, familial, or autosomal dominant in nature. Less than 1 percent of all AD cases and approximately 13 percent of all younger-onset cases are younger-onset autosomal dominant cases.^{5,6} Approximately 95 to 100 percent of these autosomal dominant younger-onset AD cases are the result of specific mutations or duplications to any of the following three specific genes: amyloid precursor protein (APP), presenilin 1 (PSEN1), or presenilin 2 (PSEN2).⁵ Children of parents with the specific genes have a 50 percent chance of inheriting the dominant mutation.⁷ If inherited, it is nearly certain that the individual will develop younger-onset AD, sometimes as early as age 30.⁴ In addition, a small number of younger-onset cases have been influenced by the APOE4 gene. (See Table 1.)

Table 1. Genes and Alzheimer’s disease

Gene	Inheritance Pattern	Typical Age of Onset	Penetrance
APP	Autosomal dominant	30–65 yr	100%
PSEN1	Autosomal dominant	30–65 yr	100%
PSEN2	Autosomal dominant	30–65 yr	~95%
APOE (e4 allele)	Familial/sporadic	40–90 yr ⁶	Increases risk, but may or may not result in AD

Late-Onset Alzheimer’s Disease

Late-onset AD occurs in individuals age 65 or older. Researchers have not found a specific gene directly linked to late-onset AD (e.g., late-onset AD has not been shown to be autosomal dominant in nature), but have identified several genes that act as genetic risk factors.⁶ These susceptibility genes can have an impact on their own, with variations acting to increase or decrease to varying degrees the risk of developing AD, but not directly causing or preventing onset in all cases.

APOE gene

The identified gene with the greatest impact on the risk of developing late-onset AD is the apolipoprotein E (APOE) gene. APOE is found on chromosome 19 and provides the blueprint for a protein that transports cholesterol in the bloodstream.⁸ Everyone inherits one of three forms (alleles) of the APOE gene from each parent: e2, e3, or e4.

The APOE alleles affect the risk of developing AD differently:

- Individuals who inherit the e4 allele have a higher risk of developing AD than those with the e3 form. Alternatively, the e2 allele may actually decrease risk compared to the e3 form.
- Those who inherit one copy of the e4 form have a three-fold higher risk of developing AD than those without the e4 form, while those who inherit two copies of the e4 form have an 8- to 12-fold higher risk.^{9,10,11}
- Those with the e4 allele are more likely to develop AD at a younger age than those with e2 or e3 forms.¹²
- Researchers estimate that between 40 and 65 percent of people diagnosed with AD have one or two copies of the APOE-e4 gene.^{8,13,14}

Table 2. APOE gene, risk of AD and estimated U.S. prevalence

APOE Form	Alzheimer's Risk	% of Population (U.S.)
e2/e2	↓	0.5
e2/e3	↓	11
e2/e4	↑	2
e3/e3	Average risk	61
e3/e4	↑	23
e4/e4	↑ Greatest risk	2

Bottom Line for Your Patients with Normal Cognition

Many risk factors are involved with AD, with advancing age being the most significant. For the vast majority of asymptomatic patients, having a sibling, parent, or grandparent with AD increases their risk, but does not definitively mean they will develop the disease. However, knowing that these patients' chances of developing AD are higher than others provides an opportunity to educate them on key lifestyle changes that may help lower their risk of cognitive decline. Current research suggests that engaging in regular exercise, quitting smoking, eating a heart-healthy diet, and participating in formal education may improve brain health and reduce the risk of cognitive decline.³

References

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