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# Genetics of Alzheimer Disease

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## ABSTRACT

**SUMMARY:** Alzheimer disease prevails as a major cause of disability in the elderly population and ranks as the most common form of dementia that affects 1 of 8 individuals older than 65 years of age. Most AD cases are late in onset and are probably influenced by both genetic and environmental factors. Apart from age, the risk factors include family history; brain injury, both traumatic and vascular; and metabolic diseases, such as diabetes, hypercholesterolemia, and obesity. Based on twin studies, inheritance plays a role in approximately 80% of cases (familial and sporadic).

**ABBREVIATIONS:** AD = Alzheimer disease; APP = amyloid protein precursor; PSEN1 = presenilin 1; PSEN2 = presenilin 2; A $\beta$  = amyloid- $\beta$ ; APOE = apolipoprotein E

While current therapies remain largely limited, advances have been made in clarifying genetic factors related to the development of Alzheimer disease. Autosomal dominant inheritance of 3 genes, *PSEN1*, *PSEN2*, and *APP*, is associated with an early-onset form. Late-onset disease is the most common form and has a risk association with the *APOE*  $\epsilon$ 4 allele. Genetic testing is available for these mutations, and research continues to improve prognostication and may inspire novel treatments.

## WHAT IS ALZHEIMER DISEASE AND HOW IS IT DIAGNOSED?

AD is an irreversible and progressive brain disease that slowly destroys memory and other cognitive functions such as thinking and reasoning and involves behavior abnormalities, which gradually interfere with a person's everyday life and activities. It is now believed that the AD pathophysiologic process starts years before detectable cognitive changes and perhaps decades prior the onset of clinical dementia.<sup>1</sup> The concept of the "AD pathophysiologic process" is thus separated from "AD dementia."

There are 3 distinct clinical stages:

1) In preclinical AD, there are no clinical signs. Measurable changes in the molecular and imaging biomarkers for presymptomatic evaluation are being investigated.

2) In mild cognitive impairment AD, there are mild serial changes in memory and cognitive status that can be detected by careful examination and do not interfere with day-to-day activities. Other causes of dementia should be excluded. Genetic testing for specific mutations can be performed in cases of early-onset familial Alzheimer disease.

3) In Alzheimer dementia, AD is characterized by progressive cognitive decline that interferes with day-to-day activities. The new guidelines propose 4 possible classifications of dementia caused by AD: probable AD dementia; probable AD dementia with an increased level of certainty; possible AD dementia; and probable or possible AD dementia with evidence of an AD pathophysiologic process. Abnormal biomarkers such as elevated CSF levels of  $\tau$  protein and decreased levels of A $\beta$ , decreased glucose uptake on PET imaging, and temporal lobe atrophy on MR imaging may add to the certainty of diagnosis.

## WHAT ARE THE CLINICAL PRESENTATIONS OF ALZHEIMER DISEASE?

Alzheimer disease is the most common form of neurodegenerative dementia that increases in prevalence with age with a lifetime risk of 1 in 10.<sup>1</sup> Like most dementias, the clinical course begins insidiously with a gradual decline in memory classified as mild cognitive impairment and then progresses to involve other symptoms. Executive dysfunction such as poor judgment, behavior disturbances, and changes in mood all may occur in AD.<sup>2</sup> Symptoms span the course of several years to a decade, and mortality is frequently related to deconditioning. Management is mostly supportive with modest functional improvement in some individuals by using an acetylcholinesterase inhibitor or *N*-Methyl-D-aspartate antagonist.

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### Major genetic forms of Alzheimer disease

Gene Name	Locus	AD Type
<i>PSEN1</i>	14q24.3	Early-onset
<i>PSEN2</i>	1q31-q42	Early-onset
<i>APP</i>	21q21	Early-onset
<i>APOE</i> ε4 allele	19q13.2	Late-onset

### WHAT IS THE PATHOPHYSIOLOGY OF AD?

Accumulation of amyloid- $\beta$  protein and  $\tau$  protein within neurofibrillary tangles (abnormally phosphorylated  $\tau$  protein) is the fundamental neuropathologic finding in AD. The amyloid cascade hypothesis proposes that the intracellular deposition of  $A\beta$  is the initiating lesion that may ultimately lead to AD, though the presence of tangles appears essential to dementia. A definite diagnosis is often not evident in the early stages of the disease, especially in the presence of confounding clinical and imaging changes. Abnormalities such as amyloidopathy and tauopathy are not specific individually for AD. Definitive diagnosis is based on the presence of the plaques and tangles and positive staining with  $A\beta$ . When the clinical diagnosis appears reliable, such as in the late stages, autopsy and neuropathologic examination are frequently omitted.<sup>1</sup> Imaging methods involve targeting amyloid protein first with Pittsburgh compound B and most recently with florbetapir, a clinically approved PET imaging  $A\beta$  ligand.<sup>3</sup> However, there is controversy over whether amyloid pathology alone explains AD.<sup>4</sup>

### HOW DO GENES INFLUENCE THE AGE OF ONSET OF AD?

There is a clear genetic influence in the manifestation of AD. Having a first-order relative with AD more than doubles the risk of developing AD in one's lifetime. AD can be thought of as 2 separate entities: a rare early-onset form (early-onset familial Alzheimer disease) before 65 years of age and a common late-onset form (late-onset Alzheimer disease), which manifests at divergent ages. Each involves a different set of genes. There is also a dichotomy between the inheritance patterns, with early-onset familial Alzheimer disease following a more Mendelian pattern, whereas late-onset Alzheimer disease appears to occur in a more sporadic pattern with partial susceptibility conferred by familial history. Three autosomal dominant causal genes have been reliably associated with early-onset familial Alzheimer disease: *presenilin 1*, *presenilin 2*, and *amyloid precursor protein*.<sup>5</sup> Mutations of these 3 genes make up approximately 7 of 10 cases of early-onset familial Alzheimer disease; *PSEN1* is the most common and *PSEN2* is the rarest (Table).<sup>2,5</sup> In patients with late-onset Alzheimer disease, there is a greater risk of AD with the presence of the  $\epsilon 4$  allele of the *apolipoprotein E* gene, whereas other alleles such as  $\epsilon 2$  have a lower risk. Other causes such as trisomy 21 may lead to AD due to an identifiable genetic etiology.

### IS THERE GENETIC TESTING AVAILABLE FOR AD?

Individuals with first-degree relatives with early-onset AD may seek genetic counseling to determine the risk for developing early-onset familial Alzheimer disease. Presently, presymptomatic testing is available for mutations of *APP*, *PSEN1*, and *PSEN2*. There is

also genetic testing to assess the presence of the *APOE*  $\epsilon 4$  allele, but those with relatives with late-onset AD are not advised to pursue testing before symptom development.<sup>5</sup>

### ARE THERE ANY OTHER HYPOTHESIZED GENETIC ASSOCIATIONS WITH AD?

Because AD is one of the most extensively researched conditions, a plethora of putative gene associations have been put forth. There are several databases, such as AlzGene (<http://www.alzgene.org>), that include several hundred genes, linkage studies, and other genomic evidence. A few promising genes are *GAB2*, which is associated with increased  $\tau$  phosphorylation, and *SORL1*, which has an unclear role in AD and has not been well-replicated.<sup>5</sup> Numerous studies are presently examining the possible causative and susceptibility effects of these and many other genes as well as a variety of epigenetic mechanisms to better predict the development of AD.<sup>4</sup> Future work may aid in the earlier diagnosis of AD and may even direct gene-based therapies.

### AD BIOMARKERS

The AD biomarkers are based on the 2 major pathophysiologic pathways of  $A\beta$  and  $\tau$  protein. There are 5 major biomarkers that have been widely studied.<sup>6</sup> The biomarkers of  $A\beta$  accumulation are a low CSF  $A\beta$  42 level and abnormal tracer uptake on PET amyloid plaque imaging. On imaging, <sup>11</sup>C Pittsburgh compound (PiB) has been the most validated tracer for amyloid pathology. A new tracer, florbetapir <sup>18</sup>F, offers the advantage of the longer half-life of <sup>18</sup>F of 110 minutes versus 20 minutes for PiB, potentially offering more extensive use for clinical and research purposes.

The biomarkers for neurodegeneration include elevated levels of total and phosphorylated  $\tau$  protein in the CSF and neuroimaging correlates of hippocampal atrophy on structural MR imaging and symmetric decreased metabolism in the temporoparietal regions on FDG-PET.

### WHAT IS THE ROLE OF STRUCTURAL NEUROIMAGING IN AD?

The traditional role of structural neuroimaging in dementia has been to exclude a treatable cause for cognitive decline such as a subdural hematoma or a tumor. However, with the development of newer technologies, including PET/MR imaging, the role of neuroimaging is being redefined as an aid in the clinical diagnosis of dementias, including AD.

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