

Genetics of Alzheimer's Disease

Alzheimer's disease (AD) is one of the most common neurodegenerative diseases, with more than 20 million cases worldwide.¹ AD is characterized by adult-onset progressive dementia, beginning with subtle memory failure that becomes more severe and is eventually incapacitating.² Neurodegeneration is estimated to start 20-30 years before clinical symptoms become apparent.¹ The most common neuropathological feature of AD is the presence of neurofibrillary tangles and amyloid deposits that form plaques and cerebrovascular accumulations.³ The overall lifetime risk of developing dementia is approximately 10%-12%.²

AD is divided into familial and sporadic forms. AD is considered familial when more than one person in a family is affected, while sporadic refers to AD cases when no other cases have been seen in close family members. Approximately 25% of AD is familial, with the rest sporadic.² AD is further divided into early- and late-onset forms; early-onset denotes onset of the disease before age 65 years, while late-onset denotes onset after age 65 years. Almost all cases of sporadic AD are late-onset, while approximately 90% of familial AD is late-onset. Less than 10% of all AD cases are familial early-onset.^{2,3}

AD is a complex disease, and a number of genes have been discovered that may increase the risk of developing the disease. The most well-established link between AD and genetics is in familial early-onset AD. Three genes have been identified that account for a significant number of familial early-onset AD cases. The *APP* (*amyloid precursor protein*) gene encodes the Amyloid Precursor Protein, which is normally cleaved to form amyloid β . Mutations in *APP* result in incorrect cleavage of the protein, producing a version of amyloid β that is more likely to form plaques.¹ Mutations in *APP* account for 10%-15% of familial early-onset cases.⁴ The *PSEN* (*presenilin*) genes encode proteins that function in the cleavage of Amyloid Precursor Protein. Mutations in both *PSEN1* and *PSEN2* result in incorrect cleavage of *APP*, and are associated with development of familial early-onset AD.¹ Mutations in *PSEN1* are thought to account for 30%-70% of familial early-onset cases, while mutations in *PSEN2* are thought to account for less than 5%.⁴ Familial early-onset AD is inherited in an autosomal dominant manner, meaning that inheritance of one mutant allele of *APP*, *PSEN1*, or *PSEN2* almost always results in development of the disease.⁴ Children of an affected parent have a 50% chance of inheriting the mutation and developing the disease. It is important to note that mutations in *APP*, *PSEN1* and *PSEN2* do not account for all cases of familial early-onset AD, so there are likely other genes not yet described that play an important role in familial early-onset AD.

Sporadic late-onset AD accounts for the majority of all AD cases, and this form can likely be caused by a number of gene mutations, combined with aging and exposure to environmental agents. The most well-established genetic risk factor for development of sporadic late-onset AD is inheritance of the $\epsilon 4$ allele of the *apolipoprotein E* (*APOE*) gene. Although the function of *APOE* in coronary health is well-known, its mode of action in AD progression is unknown.¹ The *APOE* $\epsilon 4$ allele appears to shift onset of AD toward an earlier age.³ Over 50% of people with AD carry at least one *APOE* $\epsilon 4$ allele.² However, the *APOE* $\epsilon 4$ mutation is incompletely penetrant, meaning that presence of the mutation does not always increase risk of developing the disease, and there are likely other mutations that contribute to the development of sporadic late-onset AD. Thus, a person carrying two *APOE* $\epsilon 4$ alleles has a 30% chance of developing sporadic late-onset AD (as opposed to a 100% chance if *APOE* $\epsilon 4$ were completely penetrant and the only mutation necessary).² First degree relatives of a person with sporadic late-onset AD have an approximately 2.5 times greater risk of developing sporadic late-onset AD than those who are not first-degree relatives.²

Genetic testing for the mutations associated with both familial and sporadic AD is available, although the circumstances under which testing is recommended vary. When familial early-onset AD is suspected, genetic testing to detect mutations in *APP*, *PSEN1*, and *PSEN2* can be performed to identify the

molecular lesion.⁴ For predictive testing of family members of a patient who has been diagnosed with familial early-onset AD, the disease causing mutation must be known. Although a large number of patients with sporadic late-onset AD have at least one allele *APOE* ϵ 4, the association of the mutation with the development of the disease is not strong enough to recommend that *APOE* genotyping be used as a predictive test in asymptomatic individuals.² Instead, *APOE* genotyping is most useful as an adjunct diagnostic test in individuals showing symptoms of progressive dementia.^{2,3}

It has been over 100 years since the first cases of AD were described, and since then much has been discovered about the molecular nature of the disease. The genetic control of complex diseases is becoming more apparent as previously unidentified mutations in the human genome are described. As the genetic control of AD is uncovered, improved therapies may also be uncovered.

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