
Genetic Testing

With the growth in public awareness of Alzheimer's disease and other dementias, many people have questions about the genetics that drive disease and the value of genetic testing for Alzheimer's or other dementia risk or the need to understand genetics in order to make treatment decisions.

THINGS TO KNOW WHEN CONSIDERING GENETIC TESTING FOR DISEASE RISK

The genetics of Alzheimer's disease and related dementias (such as frontotemporal dementia, Lewy body dementia, etc.) varies from one disorder to another. The Alzheimer's Association cautions against routine genetic testing of healthy individuals for risk of Alzheimer's or other dementia until an individual has received genetic counseling and understands the information necessary to make an informed decision, including the social and economic factors that could be impacted by having this genetic information. Genes are only one factor. At this time, genetic tests that determine susceptibility or risk for Alzheimer's or other dementia are primarily of value in a research setting or for clinical trials, for example in studies investigating the role of genes in disease onset and progression.

The APOE-ε4 form of the APOE gene is the strongest known genetic predictor of risk for Alzheimer's, with the APOE-ε3 and APOE-ε2 forms having the lower risks. However, there are several variations in the inheritance of APOE-ε4 that need to be considered to determine an individual's risk. The risk for Alzheimer's from APOE-ε4 can vary across populations. For example, in general, Europeans can have a higher risk than individuals that have some African ancestry such as African Americans and Caribbean Hispanic individuals. Some African countries have the lowest reported risk due to APOE-ε4. Many people in the US have ancestors from several population backgrounds and have inherited DNA from multiple ancestries. Thus, to know the risk for Alzheimer's from APOE-ε4, an individual needs to know from which ancestor their APOE-ε4 gene was inherited. Also, as everyone has two copies of the APOE gene, it is important to know the combination of the three forms a person has, i.e. (APOE-ε2, APOE-ε3 or APOE-ε4). It is important to discuss these factors with a genetic counselor to really understand the genetic risk from APOE-ε4. Testing positive for APOE-ε4 may not mean the same for Alzheimer's risk across all racial and ethnic groups.

A person genuinely concerned about their dementia risk, or the risk of a loved one, based on family history or symptoms should consider adopting healthier habits

regardless of genetic status. Growing evidence indicates that people can reduce their risk of cognitive decline and possibly dementia by adopting healthier habits that support cardiovascular health and other health factors, such as eating a heart-healthy diet, engaging in physical activity, improving sleeping habits, and remaining mentally and socially active.

THINGS TO KNOW WHEN CONSIDERING GENETIC TESTING FOR TREATMENT DECISIONS

Outside of understanding risk, there may be specific instances when an individual living with Alzheimer's should discuss genetic testing with their physician, as the results could impact a treatment decision. New treatments that target the underlying biology of Alzheimer's disease are beginning to emerge. The presence or absence of the $\epsilon 4$ form of the APOE gene may be used to determine a course of treatment, as the genetic information may inform the risk for specific treatment-related side effects. In addition, a physician may utilize genetic testing as part of the diagnostic process for more rare types of dementia and in order to assess the best course of treatment. As noted above, genetic testing must be considered carefully by an individual, their family and their physician, but could be used to help individuals make informed decisions about their treatment. The Alzheimer's Association strongly recommends that people receive genetic counseling before a test is ordered and when the results are obtained as part of any diagnostic or treatment process.

AVAILABLE GENETIC TESTS

Genetic testing services have become more widely available. Some tests may be conducted through laboratory services, and some at-home genetic tests don't require physician approval. Genetic testing for disease risk outside of a research setting or genetic testing for the purposes of treatment decisions must be considered carefully by an individual, in consultation with their family and physician. It is important to realize that obtaining genetic results is just information, and is not the same as having understanding and knowledge what that information means. It is important to discuss any information you receive with a qualified professional.

Things to think about when considering genetic testing for Alzheimer's or another dementia include existing protections and rights around disclosure of results that might affect one's employment, health insurance, long-term care insurance, and how results may affect other members of the family. Learning genetic testing results may also invite other issues, such as anxiety about getting a disease or discrimination.

Individuals who are considering genetic testing for any reason should receive genetic

counseling before a test is ordered and when the results are obtained. A genetic counselor can help make an informed decision about testing and can interpret the results and help navigate next steps. A genetic counselor may be found through the [National Society of Genetic Counselors \(nsgc.org\)](https://www.nsgc.org).

BACKGROUND INFORMATION ABOUT RISK GENES AND DETERMINISTIC GENES

The cause of Alzheimer's disease remains unknown, but some risk factors – characteristics that increase the incidence of the disease – have been identified. The greatest risk factor for Alzheimer's disease is age, with females having a greater risk for AD than males.

Scientists have found that genetics are a contributing factor in Alzheimer's disease. Genetics related to Alzheimer's can be considered two major categories: risk genes and deterministic genes. Risk genes increase the likelihood of developing a disease, but do not guarantee it will happen. Deterministic genes directly cause a disease; they virtually guarantee that anyone who inherits one will develop the disorder if they live to the estimated age of onset.

More than 100 risk genes are suspected to confer greater susceptibility for developing late-onset (age 65 or older) Alzheimer's disease, the most common form of the disease. The gene with the largest known impact on risk in White, European-descended populations is APOE (on chromosome 19), which encodes the protein apolipoprotein E. People with one copy of APOE-ε4 have a greater risk (about threefold) of developing Alzheimer's disease than people with other forms of the gene, and people with two copies of APOE-ε4 have an even greater risk.

A small minority of Alzheimer's disease cases are caused by deterministic genes. In general, these are of the younger-onset (sometimes called early-onset) form, in which symptoms appear before age 65, sometimes as young as in one's 30s or 40s. A proportion of these early-onset cases are linked to mutations identified in three genes: APP (on chromosome 21), PSEN1 (on chromosome 14) and PSEN2 (on chromosome 1). This is also referred to as Dominantly Inherited or Autosomal Dominant Alzheimer's disease (DIAD or ADAD). If someone has one of these gene mutations, there is a high degree of certainty (approaching 99 percent) they will develop the disease. Such cases of Alzheimer's disease are very rare, accounting for about two-tenths of one percent of dementia cases worldwide.

Families with Dominantly Inherited Alzheimer's disease are usually well aware of their unusual history with the disease, as about 50% of the people in the family tree

develop Alzheimer's, usually before age 60 and quite often at a much younger age. For members of these rare families, a genetic test could indicate whether an individual carries the gene mutation and will develop the disease. Some members of these families may wish to know their genetic status (for planning and decision-making), but others may not. For individuals from families in which dementia is of the late-onset type, or in which there is only one additional affected individual, screening for the deterministic genes is not recommended.

Besides Alzheimer's disease, determinant genes can cause other types of dementia, such as frontotemporal or Lewy body dementia. Many of these genes are inherited across families with a strong family history in all previous generations. Additionally, as they age, those affected by Down syndrome have a greatly increased risk of developing a type of dementia that's either the same as or very similar to Alzheimer's disease. According to the National Down Syndrome Society, about 30% of people with Down syndrome who are in their 50s have Alzheimer's dementia. About 50% of people with Down syndrome in their 60s have Alzheimer's dementia. Scientists think that the increased risk of dementia — like other health issues associated with Down syndrome — results from the extra genes present. One of the chromosome 21 genes of greatest interest in the Down syndrome/Alzheimer's connection codes amyloid precursor protein (APP). The fact that APP is strongly implicated in Alzheimer's through makes the intersection of Down syndrome and Alzheimer's a strong focus of research.

— Alzheimer's Association Medical and Scientific Advisory Group, reviewed October 2023