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Alzheimer's Disease Genetics Fact Sheet

Español

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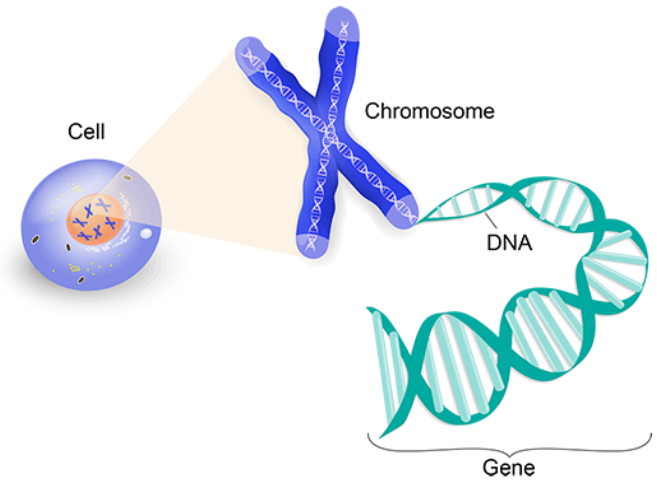
Many people wonder if Alzheimer's disease runs in their family. Is it in your genes? This question isn't easy to answer. Researchers have identified several genetic variants that are associated with Alzheimer's and may increase or decrease a person's risk of developing the disease. What does that mean? Let's first learn about the role of genes.

What are genes?

Human cells contain the instructions needed for a cell to do its job. These instructions are made up of DNA, which is packed tightly into structures called chromosomes. Each chromosome has thousands of segments called genes.



Genes are passed down from a person's biological parents. They carry information that defines traits such as eye color and height. Genes also play a role in keeping the body's cells healthy.

Variations in genes — even small changes to a gene — can affect the likelihood of a person developing a disease such as Alzheimer's.

Do changes in genes cause diseases?

Permanent changes in one or more specific genes are called genetic variants. Some of these variants are quite common in the human population. While most genetic variants don't cause diseases, some do. In some cases, a

person inherits a genetic variant that will almost certainly lead to that individual developing a disease. Sickle cell anemia, cystic fibrosis, and some cases of early-onset Alzheimer's are examples of inherited genetic disorders. However, other variants may simply increase, or even decrease, a person's risk of developing that disease. Identifying genetic variants and their effects can help researchers uncover the most effective ways to treat or prevent diseases in an individual.

Additionally, factors such as exercise, diet, chemicals, or smoking can have positive or negative effects by changing the way certain genes work. In the field of epigenetics, researchers are studying how such factors can alter a cell's DNA in ways that affect gene activity.

Genetic research is a component of precision medicine, an emerging approach that considers individual variability in genes, environment, and lifestyle. Precision medicine will enable researchers and doctors to predict more accurately which treatment and prevention strategies will work in particular groups of people.

Genes and Alzheimer's disease

In most cases, Alzheimer's does not have a single genetic cause. Instead, it can be influenced by multiple genes in combination with lifestyle and environmental factors. Consequently, a person may carry more than one genetic variant or group of variants that can either increase or reduce the risk of Alzheimer's.

Importantly, people who develop Alzheimer's do not always have a history of the disease in their families. Still, those who have a parent or sibling diagnosed with the disease have a higher risk of developing Alzheimer's than those without that association.

Share this infographic and help spread the word about Alzheimer's genetics.

Genetic variants that affect Alzheimer's disease risk

In 2010, we knew of just 10 genetic areas associated with Alzheimer's. Today, thanks in large part to the work of NIH-funded researchers, we know of at least 80 genetic areas associated with this disease. Understanding which genes play a role — and what role they play — may help identify new methods to prevent, delay, or treat dementia.

One well-known gene that influences Alzheimer's risk is the apolipoprotein E (*APOE*) gene. The *APOE* gene is involved in making a protein that helps carry cholesterol and other types of fat in the bloodstream. Problems in this process are thought to contribute to the development of Alzheimer's. *APOE* comes in several forms, called alleles (e.g., *ε2, ε3*).

- *APOE ε2* may provide some protection against the disease. If Alzheimer's occurs in a person with this allele, it usually develops later in life than it would in someone with the *APOE ε4* gene. Roughly 5% to 10% of people have this allele.
- *APOE ε3*, the most common allele, is believed to have a neutral effect on the disease — neither decreasing nor increasing risk of Alzheimer's.

- *APOE ε4* increases risk for Alzheimer's and is associated with an earlier age of disease onset in certain populations. About 15% to 25% of people have this allele, and 2% to 5% carry two copies.

Each person inherits two *APOE* alleles, one from each biological parent, meaning people can have one of six possible combinations: 2/2, 2/3, 2/4, 3/3, 3/4, and 4/4. Having two copies of *APOE ε4* is associated with a higher risk of Alzheimer's than having one copy. While inheriting *APOE ε4* increases a person's risk of Alzheimer's, some people with an *APOE ε4* allele never develop the disease.

Researchers are also finding other rare genetic variants, in addition to *APOE ε2*, that appear to provide some protection against developing Alzheimer's.

However, prevalence and risk associated with *APOE* and other genetic variants may not be the same across all population groups. Research suggests that the degree of risk may be affected by genetic ancestry — the global geographic region from which a person is biologically descended — and differ among people of African, Asian, American Indian, and European descent. More research is needed to better understand how certain genetic variants might affect a person's or group's risk for Alzheimer's and to identify treatment and prevention strategies that will work best for that particular group.

Genetic variants that cause Alzheimer's disease

Of the genetic variants so far associated with Alzheimer's, three rare single-gene variants are known to cause the disease:

- Amyloid precursor protein (*APP*) on chromosome 21
- Presenilin 1 (*PSEN1*) on chromosome 14
- Presenilin 2 (*PSEN2*) on chromosome 1

A child whose biological parent carries a genetic variant for one of these three genes has a 50/50 chance of inheriting that altered version of the gene. If the variant is inherited, the child has a very strong probability of developing Alzheimer's before age 65 and sometimes much earlier. When someone develops Alzheimer's before age 65, it's known as "early-onset Alzheimer's" or sometimes "younger-onset Alzheimer's" or "earlier-onset Alzheimer's." Less than 10% of all people with Alzheimer's develop symptoms this early. Of those who do, 10% to 15% can be attributed to changes in *APP*, *PSEN1*, and *PSEN2*.

Changes in these three genes result in the production of abnormal proteins that are associated with the disease. Each of these mutations contributes to the breakdown of APP, a protein that's function isn't completely understood. The breakdown of APP is part of a process that makes harmful forms of sticky amyloid fragments. These fragments cluster to form plaques in the brain, which is a hallmark of Alzheimer's.

In addition to the three genetic variants that are known to cause Alzheimer's, people with Down syndrome have an extra copy of chromosome 21, which carries the APP gene, and a higher risk of developing early-onset Alzheimer's. Estimates suggest that 50% or more of people living with Down syndrome will develop Alzheimer's with symptoms appearing in their 50s and 60s. Learn more about Alzheimer's disease in people with Down syndrome.

Genetic testing for Alzheimer's disease

Genetic tests are not routinely used in clinical settings to diagnose or predict the risk of developing Alzheimer's or a related dementia.

In some cases, if a person has symptoms at an early age with a strong family history of Alzheimer's, a neurologist or other medical specialist may order a genetic test for *APP*, *PSEN1*, and *PSEN2*.

Although *APOE* testing is also available, the results cannot fully predict who will or won't develop Alzheimer's. Rather, this type of testing is used primarily in research settings to identify study participants who may have an increased risk of developing Alzheimer's. This approach helps scientists look for early brain changes and compare the effectiveness of possible treatments for people with different *APOE* profiles.

Some people learn their *APOE* status through consumer genetic testing. These products are available for a fee and provide some information around the results and what they mean. While at-home genetic tests are convenient, people considering them may also benefit from talking with a doctor or genetic counselor to better understand this type of test and their test results.

General information about genetic testing can be found at:

- Genetic Testing
- What is Direct-to-Consumer Genetic Testing?
- Getting a Genetic Test
- Genetic Testing FAQ

Understanding Alzheimer's genetics in diverse populations

Research shows the rates of dementia **vary among different racial and ethnic groups**. While the concepts of race and ethnicity are socially defined, these social definitions offer researchers another way of looking at risk factors that may affect certain groups. These risk factors can include external influences, such as the environment, education, and income levels, as well as biological factors like genetics.

One way researchers are using genetics to advance health disparities research is to look at genetic ancestry. Genetic ancestry refers to the region from which a person is biologically descended. People of the same race and ethnicity may share genetic ancestry, but this is not always the case. Large genetic research studies can help scientists identify unique factors that are linked to genetic ancestry. Understanding these factors in

> diverse populations is important to identifying ways to prevent,

Alzheimer’s genetics research

Discovering as much as possible about the role of Alzheimer’s genetic risk and protective factors across populations is an important area of research. NIA funds several major genetics research programs. Understanding more about the genetic basis of the disease will help researchers:

- Answer a number of basic questions, such as: What makes the disease process begin? Why do some people with memory and other thinking problems develop Alzheimer’s while others don’t?
- Determine how genetic risk and protective factors may interact with other genes and lifestyle or environmental influences to affect Alzheimer’s risk in any one person.
- Identify people who are at high risk of developing Alzheimer’s so they can benefit from new interventions and treatments as much and as soon as possible.
- Explain differences in Alzheimer’s risks and protections among racial groups and genders.
- Use individual gene discoveries to develop potential therapies to prevent or treat the disease.

Research needs volunteers of all different races, ethnicities, ancestries, ages, and genders to participate in clinical trials and studies. Talk with a doctor if you’re interested in participating in Alzheimer’s research or search the Alzheimers.gov Clinical Trials Finder to find a study near you or online.

You may also be interested in

- Learning more about the causes of Alzheimer's
- Finding out about assessing risk for Alzheimer's
- Discovering the changes that happen in the brain in Alzheimer's

For more information about Alzheimer's disease genetics

NIA Alzheimer’s and related Dementias Education and Referral (ADEAR) Center
800-438-4380
adear@nia.nih.gov
www.nia.nih.gov/alzheimers
The NIA ADEAR Center offers information and free print publications about Alzheimer’s and related dementias for

families, caregivers, and health professionals. ADEAR Center staff answer telephone, email, and written requests and make referrals to local and national resources.

Alzheimers.gov
www.alzheimers.gov
Explore the Alzheimers.gov website for information and resources on Alzheimer's and related dementias from across the federal government.

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