Alzheimer's Disease Genetics

FACT SHEET

Scientists don't yet fully understand what causes Alzheimer's disease (AD). However, the more they learn about AD, the more they realize that **genes*** play an important role in the development of this devastating disease. Research conducted and funded by the National Institute on Aging (NIA) and others is advancing the field of AD genetics.

The Genetics of Disease

Some diseases are caused by a **genetic mutation**, or permanent change, in one specific gene. If a person inherits a genetic mutation that is linked to a certain disease from a parent, then he or she will usually get the disease. Cystic fibrosis, muscular dystrophy, and Huntington's disease are examples of single-gene disorders.

In other diseases, a **genetic variant**, or a change in a gene, may occur, but it doesn't necessarily cause the person to develop the disease. More than one gene variant may be necessary to cause the disease, or the variant may increase a person's risk of developing the disease. When this happens, the changed gene is called a **genetic risk factor**.

The Genetics of Alzheimer's Disease

AD is an irreversible, progressive brain disease characterized by the development of amyloid plaques and neurofibrillary tangles, the loss of connections between nerve cells in the brain, and the death of these nerve cells. AD has two types: early-onset and late-onset. Both types have genetic links.

Early-Onset AD

Early-onset AD is a rare form of AD, affecting only about 5 percent of all people who have AD. It develops in people ages 30 to 60.

Some cases of early-onset AD, called familial AD (FAD), are inherited. FAD is caused by a number of different gene mutations on **chromosomes** 21, 14, and 1, and each of these mutations causes abnormal **proteins** to be formed. Mutations on chromosome

*Terms in bold are defined at the end of this fact sheet.

Alzheimer's Disease Education & Referral (ADEAR) Center
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21 cause the formation of abnormal amyloid precursor protein (APP). A mutation on chromosome 14 causes abnormal presenilin 1 to be made, and a mutation on chromosome 1 leads to abnormal presenilin 2.

Even if only one of these mutated genes is inherited from a parent, the person will almost always develop early-onset AD. This inheritance pattern is referred to as "autosomal dominant" inheritance. In other words, offspring in the same generation have a 50/50 chance of developing FAD if one of their parents had it.

Scientists know that each of these mutations causes an increased amount of the beta-amyloid protein to be formed. Beta-amyloid, a major component of AD plaques, is formed from APP.

These early-onset findings were critical because they showed that genetics were involved in AD, and they helped identify key players in the AD process. The studies also helped explain some of the variation in the age at which AD develops.

Late-Onset AD

Most cases of Alzheimer's are of the late-onset form, developing after age 60. Scientists studying the genetics of AD have found that the mutations seen in early-onset AD are not involved in this form of the disease.

Although a specific gene has not been identified as the cause of late-onset AD, one predisposing genetic risk factor does appear to increase a person's risk of developing the disease. This increased risk is related to the **apolipoprotein E (APOE) gene** found on chromosome 19. APOE contains the instructions needed to make a protein that helps carry cholesterol in the bloodstream. APOE comes in several different forms, or **alleles**. Three forms—APOE ε2, APOE ε3, and APOE ε4—occur most frequently.

- APOE ε2 is relatively rare and may provide some protection against the disease. If AD does occur in a person with this allele, it develops later in life than it would in someone with the APOE ε4 gene.
- APOE ε3 is the most common allele. Researchers think it plays a neutral role in AD—neither decreasing nor increasing risk.
- APOE ε4 occurs in about 40 percent of all people who develop late-onset AD and is present in about 25 to 30 percent of the population. People with AD are more likely to have an APOE ε4 allele than people who do not develop AD. However, many people with AD do not have an APOE ε4 allele.

  Dozens of studies have confirmed that the APOE ε4 allele increases the risk of developing AD, but how that happens is not yet understood. These studies also have helped explain some of the variation in the age at which AD develops, as people who inherit one or two APOE ε4 alleles tend to develop AD at an earlier age than those who do not have any. APOE ε4 is called a risk-factor gene because it increases a person's risk of developing AD. However, inheriting an APOE ε4 allele does not mean that a person will definitely develop AD. Some people with one or two APOE ε4 alleles never get the disease, and others who develop AD do not have any APOE ε4 alleles.

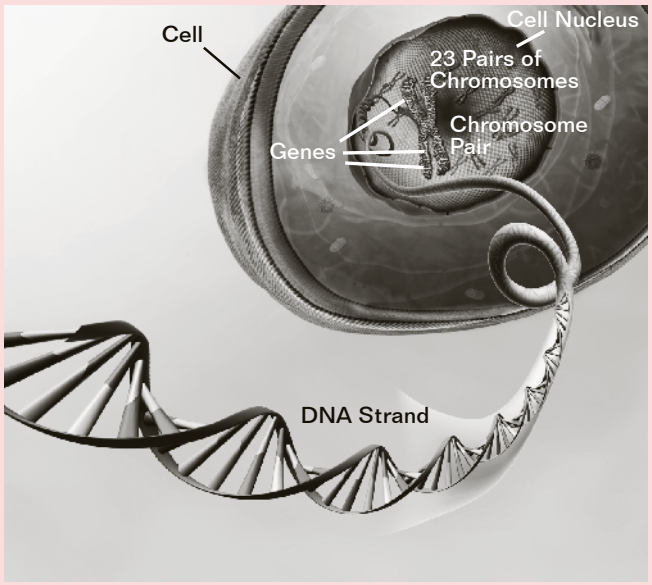
Scientists believe that four to seven other AD risk-factor genes exist and are using a new approach called a **genome-wide association study** (GWAS) to help speed the discovery process. Another possible risk-factor gene, SORL1, was discovered in 2007. This gene is involved in transporting APP within cells, and its association with AD has been identified and confirmed in three separate studies. Researchers found that when SORL1 is present at low levels or in a variant form, beta-amyloid levels increase and may harm neurons.

APOE Testing

A blood test is available that can identify which APOE alleles a person has, but it is not yet possible to predict who will or will not develop AD. Because APOE ε4 is only a risk factor for AD, this blood test cannot say for sure whether a person will develop AD or not. Some researchers believe

DNA, Chromosomes, and Genes

The nucleus of almost every human cell contains a "blueprint" that carries the instructions a cell needs to do its job. The blueprint is made up of **DNA**, which is present in long strands that would stretch to nearly 6 feet in length if attached end to end. The DNA is packed tightly together with **proteins** into compact structures called **chromosomes** in the nucleus of each cell. Each cell has 46 chromosomes in 23 pairs. The DNA in nearly all cells of an individual is identical.



Each chromosome contains many thousands of segments, called **genes**. People inherit two copies of each gene from their parents, except for genes on the X and Y chromosomes, which, among other functions, determine a person's sex. The gene tells the cell how to make specific proteins, which determine the different kinds of cells that make up an organism and direct almost every aspect of the cell's construction, operation, and repair. Even slight alterations in a gene can produce an abnormal protein, which may lead to cell malfunction and, eventually, to disease. Other changes in genes may not cause disease but can increase a person's risk of developing a particular disease.

that screening measures may never be able to predict AD with 100 percent accuracy. However, a small battery of tests for other risk-factor genes might eventually be useful.

At present, APOE testing is used in a research setting to identify study participants who may have an increased risk of developing AD. This knowledge helps scientists look for early brain changes in participants and compare the effectiveness of treatments for people with different APOE profiles.

Most researchers believe that the APOE test is useful for studying AD risk in large groups of people but not for determining any one person's specific risk. Someday, perhaps, screening in otherwise healthy people may be useful if an accurate and reliable test is developed and effective ways to treat or prevent AD become available.

Research Questions

Learning more about the role of APOE ε4 and other risk-factor

Major AD Genetics Research Efforts Underway

As AD genetics research has intensified, it has become clear that scientists need many genetic samples to make further progress. The National Institute on Aging (NIA) has launched two large programs, the Alzheimer's Disease Genetics Study and the Alzheimer's Disease Genetics Consortium, to collect and analyze blood samples and other biological information from thousands of families around the world with members who do and do not have late-onset AD. NIA also funds the National Cell Repository for Alzheimer's Disease (NCRAD), a national resource where clinical information and DNA can be stored and accessed by qualified researchers. Through these programs, AD researchers are working together to develop new technologies and methods and to share data.

The AD Genetics Study is gathering genetic and other information from 1,000 or more families in the United States that include a pair of living siblings (brothers or sisters) who have late-onset AD. Families who meet this criteria are urged to participate and can contact NCRAD (*www.ncrad.org*) for more information.

The AD Genetics Consortium is a collaborative effort of AD geneticists to collect more than 10,000 samples to do GWAS, the DNA analysis studies needed to identify risk-factor genes.

The participation of volunteer families is a critical part of AD genetics research. The more genetic information that researchers can gather and analyze from a wide range of families, the more clues they will have for finding additional risk-factor genes.

genes in the development of AD is a vitally important area of AD research. Understanding more about the genetic underpinnings of the disease will help researchers:

- Answer remaining basic questions about mechanisms—What makes the disease process begin, and why do some people who have memory problems go on to develop AD while others do not?
- Determine how AD risk-factor genes may interact with other genes and lifestyle or environmental factors to affect AD risk in any one person.
- Identify people who are at high risk so they can possibly receive early treatment.
- Focus on new prevention or treatment approaches.

For More Information

Alzheimer's Disease Education and Referral (ADEAR) Center
P.O. Box 8250
Silver Spring, MD 20907-8250
800-438-4380 (toll-free)
www.nia.nih.gov/Alzheimers

A service of the National Institute on Aging (NIA), the ADEAR Center offers information and publications for families, caregivers, and professionals on diagnosis, treatment, patient care, caregiver needs, long-term care, education and training, and research related to AD. Staff members answer telephone, email, and written requests and make referrals to local and national resources. The ADEAR website provides free, online publications in English and Spanish; email alert and online *Connections* newsletter subscriptions; an AD clinical trials database; the AD Library database; and more.

To learn more about the NIA-sponsored AD Genetics Study or to volunteer, contact the **National Cell Repository for Alzheimer's Disease (NCRAD)** toll-free at 800-526-2839. Information also is available on the NCRAD website at *www.ncrad.org*.

Additional information about genetics in health and disease is available from the **National Human Genome Research Institute (NHGRI)**, part of the National Institutes of Health. Visit the NHGRI website at *www.genome.gov*.

The National Library of Medicine's **National Center for Biotechnology Information** also provides genetics information at *www.ncbi.nlm.nih.gov/disease*.

Alzheimer's Association
225 North Michigan Avenue, Floor 17
Chicago, IL 60601-7633
800-272-3900 (toll-free)
866-403-3073 (TDD/toll-free)
www.alz.org

The Alzheimer's Association is a national nonprofit organization with a network of local chapters that provide education and support for people diagnosed with AD, their families, and caregivers. The Association also supports research on AD.

Glossary

- **Allele**—A form of a gene. Each person receives two alleles of a gene, one from each biological parent. This combination is one factor among many that influence a variety of processes in the body. On chromosome 19, the apolipoprotein E (APOE) gene has three common forms or alleles: ε2, ε3, and ε4.
- **Apolipoprotein E (APOE) gene**—A gene on chromosome 19 involved in making a protein that helps carry cholesterol in the bloodstream. The APOE ε4 allele is considered a risk-factor gene for AD and appears to influence the age at which the disease begins.
- **Chromosome**—A compact structure containing DNA and proteins present in nearly all cells of the body. Chromosomes carry genes, which direct the cell to make proteins. Normally, each cell has 46 chromosomes in 23 pairs. Each parent contributes one of each pair of chromosomes.
- **DNA (deoxyribonucleic acid)**—The hereditary material in humans and almost all other organisms. Almost all cells in a person's body have the same DNA. Most DNA is located in the cell nucleus.
- **Gene**—A basic unit of heredity. Genes direct almost every aspect of the construction, operation, and repair of living organisms. Each gene is a set of biochemical instructions that tells a cell how to assemble one of many different proteins. Each protein has its own highly specialized role to play in the body.
- **Genetic mutation**—A permanent change to a gene. Once such a change occurs, it can be passed on to children. The relatively rare, early-onset familial AD is associated with mutations in genes on chromosomes 1, 14, or 21.
- **Genetic risk factor**—A variant in a cell's DNA that does not cause a disease by itself but may increase the chance that a person will develop a disease.
- **Genetic variant**—A change in a gene that may change the risk of a person developing a disease or condition.
- **Genome-wide association study (GWAS)**—A study approach that involves rapidly scanning markers across the complete sets of DNA, or genomes, of many individuals to find genetic variations associated with a particular disease.
- **Protein**—A substance that determines the physical and chemical characteristics of a cell and therefore of an organism. Proteins are essential to all life processes and are created using genetic information.