Alzheimer's Disease (AD), Inheritance Facts
A Resource Guide

The cause of Alzheimer's disease (AD) is not known. We are gradually learning the part genetics may play in the development of this disease.

Definitions of Key Terms can be found at the end of this fact sheet.

GENES
All living things are made up of basic units. They are called cells. Cells are so tiny that you can only see them with a microscope. Most of the billions of cells in the human body have one nucleus. This acts as a control center. It houses 23 pairs of chromosomes. A chromosome is a thread-like structure found in the cell's nucleus. It carries many genes. We inherit half of each pair of 23 chromosomes from each parent. The genetic material on these chromosomes is the human genome. It is thought that there are about 30,000 genes in the human genome. Genes direct almost every aspect of the construction, operation, and repair of all living things. For example, genes contain information that determines eye and hair color and other traits inherited from our parents.

ANATOMY OF GENES
Genes alone are not all-powerful. Most genes can do little until spurred on by other substances. Genes wait inside the cell's nucleus for other molecules to come along and read their messages. These messages provide the cell with instructions for building a specific protein.

Proteins are essential building blocks in all cells. Bones, teeth, muscles, and blood, for example, are formed from different proteins. They help our bodies grow, work properly, and stay healthy. Amino acids are the building blocks of proteins. A gene provides the code, or blueprint, for the type and order of amino acids needed to build a specific protein. Sometimes a defect in a gene (*genetic mutation*) occurs. This leads to the production of a faulty protein. Faulty proteins can cause cell malfunction, disease, and death. Scientists are studying genes to learn more about the proteins they make and what these proteins do in the body. They hope to discover what illnesses are caused when proteins do not work right.

THE GENETICS OF ALZHEIMER'S DISEASE
Diseases such as cystic fibrosis, muscular dystrophy, and Huntington's disease are single gene disorders. If a person inherits the gene that causes one of these disorders, he or she will usually get the disease. AD, however, is not caused by a single gene. More than one gene mutation can cause AD. Genes on multiple chromosomes are involved.

The two basic types of Alzeheimer's disease are familial and sporadic. **Familial AD** (FAD) is a rare form of AD. It affects less than 10 percent of AD patients. All FAD is early-onset. This means the disease develops before age 65. It is caused by gene mutations in chromosomes 1, 14, and 21. Even if only one of these mutated genes is inherited from a parent, the person will almost always develop early-onset AD. This is called autosomal dominant inheritance. In other words, all offspring in the same generation have a 50/50 chance of developing FAD, if one of their parents had it.

GENES IN LATE-ONSET DISEASE
The majority of AD cases are late-onset. It usually develops after age 65. Late-onset AD has no known cause. The majority of cases are not inherited. However, in some families, clusters of cases are seen. No specific gene has been identified as the cause of late-onset AD. However, genetic factors do seem to play a role in the development of this form of AD. Only one risk factor gene has been identified so far. Researchers have identified an increased risk of developing late-onset AD related to the apolipoprotein E gene (ApoE). It is found

on chromosome 19. This gene codes for a protein that helps carry cholesterol in the bloodstream. The ApoE gene comes in several different forms (*alleles*). Three occur most frequently: ApoE e2, ApoE e3, and ApoE e4.

People inherit one ApoE allele from each parent. Having one or two copies of the e4 allele increases a person's risk of getting AD. That is, having the e4 allele is a risk factor for AD. But it does not mean that AD is certain. Some people with two copies of the e4 allele (the highest risk group) do not develop clinical signs of Alzheimer's disease. But others with no e4s do. The e3 allele is the most common form found in the general population. It may play a neutral role in AD. The rarer e2 allele appears to be associated with a lower risk of AD. The exact risk of AD for any given person cannot be determined based on ApoE status.

Scientists are looking for genetic risk factors for late-onset AD on other chromosomes, as well. They think risk factor genes may lie on regions of chromosomes 9, 10, and 12.

The National Institute on Aging (NIA) has launched a major study to discover remaining genetic risk factors for late-onset AD. Geneticists from the NIA's Alzheimer's Disease Centers are collecting genetic samples from families affected by multiple cases of late-onset AD. Researchers are seeking large families with two or more living relatives with late-onset AD. Families interested in participating in this study can contact the National Cell Repository for Alzheimer's Disease at 1-800-526-2839. Information may also be requested through their website: http://ncrad.iu.edu.

APOE TESTING IN RESEARCH OR DIAGNOSIS

A blood test can identify which ApoE alleles a person has. The ApoE e4 gene is only a risk factor for AD. So, this blood test cannot tell whether a person will develop AD or not. It can only show what risk the person has for developing AD. No test can predict AD for certain.

In diagnosing AD, ApoE testing is not a common practice. The only definite way to diagnose AD is by viewing a brain tissue sample under a microscope. This determines if there are plaques and tangles present. This is usually done after the person dies.

Caregivers can diagnose AD correctly up to 90% of the time. This is done through a complete medical evaluation, including:

- A medical history.
- Lab tests.
- Neuropsychological tests.
- Brain scans.

Caregivers first rule out other diseases and disorders that can cause the same symptoms as AD. If no other cause is identified, a person is said to have "probable" or "possible" AD. In some cases, ApoE testing may be used in combination with these other medical tests. This can strengthen the diagnosis of a suspected case of AD. There is no medical test to establish whether a person is going to develop the disease. ApoE testing as a patient screening (*predictive*) method is not advised.

CONCERNS ABOUT CONFIDENTIALITY

ApoE testing, like all genetic testing, raises ethical, legal, and social questions. **Generally, confidentiality laws protect ApoE information gathered for research purposes.** However, information obtained in ApoE testing may not remain confidential if it becomes part of a person's medical records. Then employers or insurance companies could find out this information. Discrimination could result. For example, employment opportunities or insurance premiums could be affected.

GENETIC COUNSELING

Depending on the study, research volunteers may have the chance to learn the results of their ApoE testing. The meaning of these results is complex. The results of ApoE testing can be hard to understand. They can also be devastating to those tested. The NIA and the Alzheimer's Association recommend that research volunteers and their families have genetic counseling before and after testing, if they have the option of learning their results.

- People who learn that they have an increased risk of getting AD may experience emotional distress and

depression about the future. There is not yet an effective way to prevent or cure the disease. Through counseling, families can learn about the:

- Genetics of AD.
- Tests themselves.
- Possible meanings of the results.

Due to privacy, emotional, and health care issues, the primary goal of genetic counseling is to help people explore and cope with the potential consequences of such knowledge.

The National Society for Genetic Counselors (NSGC) can provide a list of genetic counselors in your area. Search their online database at **www.nsgc.org.** The NSGC does not provide information about specific genetic disorders.

- Experts still do not know how limited information about AD risk can benefit people. Among the issues are:
  - Privacy and confidentiality policies related to genetic information and AD.
  - The small number of genetic counselors trained in neurodegenerative disorders.
  - How the stigma associated with an increased risk for AD may affect people's families and their lives.

RESEARCH QUESTIONS

Learning more about the role of risk factor genes in the development of AD may help scientists identify who would benefit from prevention and treatment efforts. Age is still the most important known risk factor for AD. It continues to be associated with the disease, even when no known genetic factors are present. Research focusing on advancing age may help explain the role that other genes play in most AD cases. Many AD researchers are studying the genetics of AD. Also, researchers, ethicists, and health care providers are developing policies about the proper use of genetic testing and counseling for AD.

FOR MORE INFORMATION

- The Alzheimer's Disease Education and Referral (ADEAR) Center is a service of the NIA. It is funded by the federal government. The ADEAR Center offers information about diagnosis, treatment, patient care, caregiver needs, long-term care, education and training, and AD research. Staff respond to telephone, e-mail, and written requests. They make referrals to local and national resources. Contact:
  - **ADEAR Center, Phone: 1-800-438-4380, Website: www.nia.nih.gov/alzheimers.**
- The Alzheimer's Association is a non-profit supporting AD research. It provides support for families and caregivers of patients with AD. Chapters nationwide provide referrals to local resources and services. They sponsor support groups and educational programs. The Association is also helping identify families who may be able to participate in the NIA's AD Genetics Study. Contact:
  - **Alzheimer's Association, Phone: 1-800-272-3900, E-mail: info@alz.org, Website: www.alz.org.**
- Additional information is available from the National Human Genome Research Institute (NHGRI), part of the NIH.
  - **NHGRI, Website: www.genome.gov.**

KEY TERMS

- **Alleles:** Different forms of the same gene. Two or more alleles can shape each human trait. Each person receives two alleles of a gene. One comes from each parent. This combination is one of many factors that influences processes in the body. On chromosome 19, the ApoE (apolipoprotein E) gene has three common forms or alleles: e2, e3, and e4. The possible combinations in one person are e2/2, e2/3, e2/4, e3/3, e3/4, or e4/4.
- **ApoE Gene:** A gene on chromosome 19. It is involved in making apolipoprotein E. (A substance that helps carry cholesterol in the bloodstream.) The ApoE e4 gene is considered a "risk factor" for AD. It seems to influence the age of onset of the disease.
- **Chromosomes:** Thread-like structures in every cell of the body. Chromosomes carry genes. All healthy people have 46 chromosomes in 23 pairs. Usually, people receive one chromosome in each pair from each parent.
- **Genes:** Basic units of heredity. Each gene is a set of biochemical instructions. It tells a cell how to assemble

one of many different proteins. Each protein has its own specialized role to play in the body.

- **Genetic Mutations:** Permanent changes to genes. Once such change occurs, it can be passed on to children. Early-onset familial AD is relatively rare. It is associated with mutations in genes on chromosomes 1, 14, and 21.
- **Human Genome:** The total genetic information found on the 23 chromosomes inherited from a parent. Through research decoding the human genome, scientists believe humans have between 30,000 to 35,000 genes.
- **Proteins:** Cells translate genetic information into making specific proteins. Proteins determine the physical and chemical characteristics of cells. Proteins are essential to all life processes.

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