Alzheimer's Disease Genetics

Fact Sheet

Scientists do not yet fully understand what causes Alzheimer's disease (AD). However, the more they learn about AD, the more they become aware of the important function *genes** play in the development of this devastating disease.

Genes

All living things are made up of basic units called cells, which are so tiny that you can only see them through the lens of a strong microscope. Most of the billions of cells in the human body have one nucleus that acts as a control center, housing

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

Alzheimer's Disease Education & Referral (ADEAR) Center
A Service of the
National Institute on Aging
National Institutes of Health
U.S. Department of Health and Human Services

our 23 pairs of *chromosomes*. A chromosome is a thread-like structure found in the cell's nucleus, which can carry hundreds, sometimes thousands, of genes. In humans, one of each pair of 23 chromosomes is inherited from each parent. The genetic material on these chromosomes is collectively referred to as the *human genome*. Scientists now believe 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. In addition, genes ensure that we have two hands and can use them to do things, like play the piano.

Genes alone are not all-powerful. Most genes can do little until spurred on by other substances. Although they are necessary in their own right, genes basically 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*.

Fact Sheet

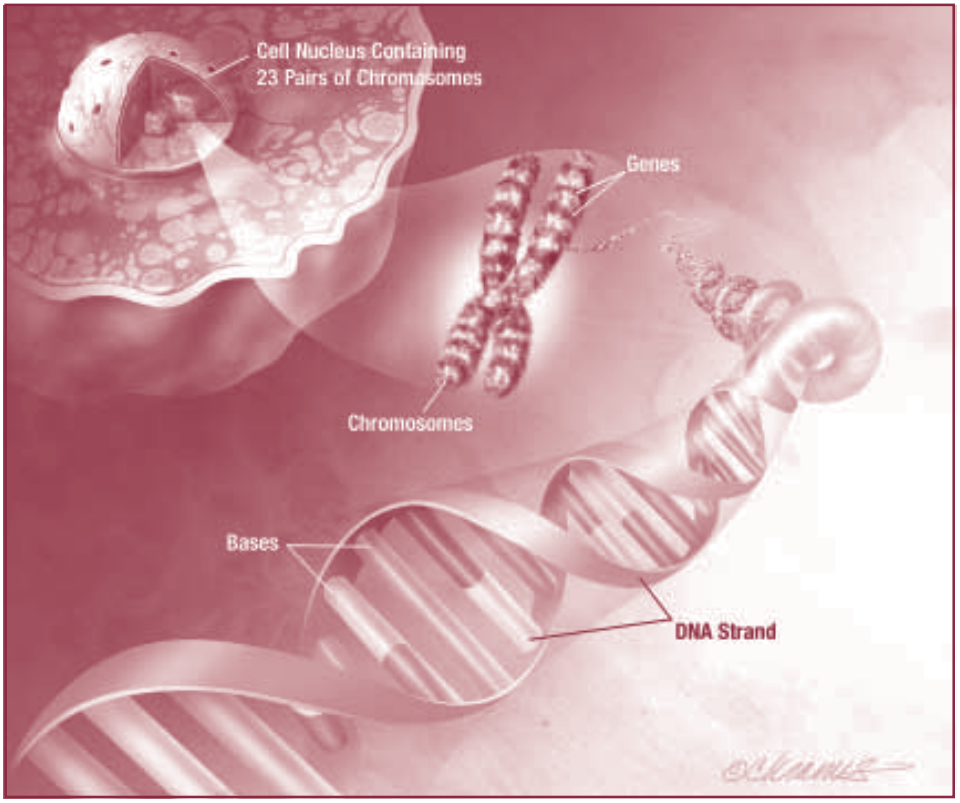

Illustration from the booklet, *Alzheimer's Disease: Unraveling the Mystery*, available from the ADEAR Center. Illustrator: Christy Krames.

Proteins are essential building blocks in all cells. Bones and 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 *genetic mutation* (or defect in a gene) can occur, leading 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 actually do in the body. They also hope to

discover what illnesses are caused when proteins don't 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 mutated gene that causes one of these disorders, he or she will usually get the disease. AD, on the other hand, is not caused by a single gene. More than one gene mutation can cause AD, and genes on multiple chromosomes are involved.

The two types of AD are early-onset and late-onset, depending on whether the disease starts before or after the age of 65. Less than 5 percent of AD is early-onset, and this form of the disease often runs in families. Many forms of early-onset AD are caused by gene mutations on chromosomes 1, 14, or 21. Like the other diseases mentioned above, even if only one of these mutated genes is inherited from a parent, the person will usually develop early-onset AD. This inheritance pattern is referred to as autosomal dominant inheritance: all children have a 50/50 chance of

developing early-onset AD if one of their parents had it.

Genes in Late-onset Disease

The majority of AD cases are late-onset, usually developing after age 65. Late-onset AD has no known cause and shows no obvious inheritance pattern. However, in some families, clusters of cases are seen. Although a specific gene has not been identified as the cause of late-onset AD, genetic factors do appear 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 (APOE) gene* 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, or *alleles*, but three occur most frequently: APOE ε2, APOE ε3, and APOE ε4.

People inherit one APOE allele from each parent. Having one or two copies of the ε4 allele increases a person's risk of getting AD. That is,

having the ε4 allele is a risk factor for AD, but it does not mean that AD is certain. Some people with two copies of the ε4 allele (the highest risk group) do not develop clinical signs of Alzheimer's disease, while others with no ε4s do. The ε3 allele is the most common form found in the general population and may play a neutral role in AD. The rarer ε2 allele appears to be associated with a lower risk of AD. The exact degree of risk of AD for any given person cannot be determined based on APOE status. Therefore, the APOE ε4 gene is called a risk factor gene for late-onset AD.

Scientists are looking for genetic risk factors for late-onset AD on other chromosomes as well. They think that additional 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 working to collect 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 is available that can identify which APOE alleles a person has. However, because the APOE ε4 gene is only a risk factor for AD, this blood test cannot tell whether a person will develop AD or not. Instead of a yes or no answer, the best information a person can get from this genetic test for APOE is maybe or maybe not. Although some people want to know whether they will get AD later in life, this type of prediction is not yet possible. In fact, some researchers believe that screening measures may never be able to predict AD with 100 percent accuracy.

In a research setting, APOE testing may be used to identify study

volunteers who may be at a higher risk of getting AD. In this way, researchers can look for early brain changes in some patients. This test also helps researchers compare the effectiveness of treatments for patients 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 one person's individual risk. Predictive screening in otherwise healthy people will be useful if an accurate/reliable test is developed and effective ways to treat or prevent AD are available.

In diagnosing AD, APOE testing is not a common practice. The only definite way to diagnose AD is by viewing a sample of a person's brain tissue under a microscope to determine if there are plaques and tangles present. This is usually done after the person dies. However, through a complete medical evaluation (including a medical history, laboratory tests, neuropsychological tests, and brain scans), well-trained doctors can diagnose AD correctly up to 90 percent of the time. Doctors look to rule out other diseases and disorders

that can cause the same symptoms of 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 to strengthen the diagnosis of a suspected case of AD. Currently, there is no medical test to establish if a person without the symptoms of AD is going to develop the disease. APOE testing as a patient screening (predictive) method is not recommended.

Concerns About Confidentiality

APOE testing, and indeed all genetic testing, raises ethical, legal, and social questions for which we have few answers. Generally, confidentiality laws protect APOE information gathered for research purposes. On the other hand, information obtained in APOE testing may not remain confidential if it becomes part of a person's medical records. Thereafter, employers, insurance companies, and other health care organizations could find out this information, and discrimination could result. For example, employment opportunities or insurance premiums could be affected.

Genetic Counseling

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

People who learn through testing that they have an increased risk of getting AD may experience emotional distress and depression about the future, because there is not yet an effective way to prevent or cure the disease. Through counseling, families can learn about the genetics of AD, the tests themselves, and 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, as well as information about creating a family history. Search their online database at *www.nsgc.org/consumer/index.asp*. 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, and the small number of genetic counselors now trained in neurodegenerative disorders. In addition, little is known about how stigma associated with an increased risk for AD may affect people's families and their lives.

Research Questions

Learning more about the role of APOE ε4 and other risk factor genes in the development of AD may help scientists identify who would benefit from prevention and treatment efforts. Age, still the most important known risk factor for AD, 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. In addition, researchers, ethicists, and health care providers are developing policies about the appropriate use of genetic testing and counseling for AD.

For More Information

Accurate, current information about AD and its risk factors is important to patients and their families, health professionals, and the public. The Alzheimer's Disease Education and Referral (ADEAR) Center is a service of the NIA and 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 and make referrals to local and national resources. Contact:

ADEAR Center
PO Box 8250
Silver Spring, MD 20907-8250

1-800-438-4380
Fax: 301-495-3334
E-mail: *adear@alzheimers.org*
Website: *www.alzheimers.org*

The Alzheimer's Association is a nonprofit organization supporting AD research and providing support for families and caregivers of patients with AD. Chapters nationwide provide referrals to local resources and services, and 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. For information on the Association, contact:

Alzheimer's Association
225 N. Michigan Avenue, Suite 1700
Chicago, IL 60611-1676
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. Visit the NHGRI website at *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 from each parent. This combination is one factor among many that influences 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. Thus, the possible combinations in one person are ε2/2, ε2/3, ε2/4, ε3/3, ε3/4, or ε4/4.

APOE Gene – a gene on chromosome 19 involved in making ApoE, a substance that helps carry cholesterol in the bloodstream. The APOE ε4 gene is considered a "risk factor" gene for AD and appears to influence the age of onset of the disease.

Chromosomes – thread-like structures in every cell of the human 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 that 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 Mutations – permanent changes to genes. Once such 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, 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 specific proteins. Proteins determine the physical and chemical characteristics of cells and therefore organisms. Proteins are essential to all life processes.

The National Library of Medicine's National Center for Biotechnology Information also maintains genetic information at: *http://www.ncbi.nlm.nih.gov/disease.*

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