

## About genes and Alzheimer's disease

*This fact sheet was developed in collaboration with the Alzheimer's Association Clinical Issues and Interventions Work Group, a team of consulting physicians and specialists.*

People who have experienced Alzheimer's disease in their families often wonder about the importance of genetics. They are worried about inheriting the disease themselves or passing it along to the next generation. Although this is an understandable concern, it is important to know that genes are rarely the direct cause of Alzheimer's. In most cases, genetics may be one of the factors influencing someone's risk for developing the disease.

### Risk factors for Alzheimer's disease

The greatest risk factor associated with Alzheimer's disease is increasing age. The older a person is, the greater the risk of developing the disease.

A family history of Alzheimer's is also a known risk. When all people of the same age are compared, those who have a parent or sibling with the disease are two to three times more likely to develop Alzheimer's than individuals who do not. The likelihood of developing the disease increases as the number of affected relatives increases.

### Background on genes

Each cell in the human body has a complete set of instructions that guide how that person is put together. These instructions are in strands of chemical code called DNA, which is organized into units called chromosomes. Each person has 23 pairs of chromosomes. Half of each pair is passed on from each parent.

Each gene is a tiny section of a chromosome. It directs a cell how to produce a particular protein or other molecule. A variation in a gene can result in a slight difference in the protein produced by that gene and perhaps a difference in the protein's function.

A slight range of variation in a gene is not unusual. Such variations cause differences in hair and eye color. However, normal variations in some genes may statistically alter a person's risk of developing a disease, and certain abnormal variations may directly cause a disease.

### Two forms of Alzheimer's disease

Professionals recognize two forms of Alzheimer's disease. (1) In *familial Alzheimer's disease*, genes directly cause the disease. These cases are very rare and have been identified in a relatively small number of families with many people in multiple generations affected. (2) In *sporadic Alzheimer's disease*, genes do not cause the disease, but they may influence the risk of developing the disease. The word *sporadic* refers to the fact that these cases occur in a less predictable manner and typically in fewer family members. This is the most common form of the disease.

Most cases of familial Alzheimer's disease occur before the age of 60. The vast majority of cases of sporadic Alzheimer's disease occur after 60, and most cases occur in people in their 70s and 80s.

Because of this difference in age at onset, familial Alzheimer's disease is often called *early-onset familial Alzheimer's* or simply *early-onset Alzheimer's*. Sporadic Alzheimer's disease is often called *late-onset sporadic Alzheimer's* or *late-onset Alzheimer's*. However, there are exceptions to these general observations about age at onset. We cannot "guess" at the role of genetics based solely on when someone develops the disease.

### Familial Alzheimer's disease

In familial Alzheimer's disease, a person has inherited an abnormal variation, or *mutation*, in one of three genes that are known causes of the disease: PS1, PS2 and APP. Each of these three genes may contain one of a number of mutations.

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An individual who carries one of the mutated genes has a 50 percent chance of passing it on to his or her children. Those who inherit the mutated gene will almost certainly develop Alzheimer's. Members of the family who do not inherit the mutation are no more likely to get the disease than are other members of the general population.

Studies about the protein products of these Alzheimer-related genes have revealed important clues to the basic biology of Alzheimer's disease and processes that may lead to cell death. While the precise means by which these mutations cause the disease is unknown, all of them influence production of *beta-amyloid* (BAY tuh AM uh loyd), a sticky protein fragment that tends to clump together in the brain and may play an important role in the development of Alzheimer's disease.

### **Sporadic Alzheimer's disease**

Sporadic Alzheimer's disease is not inherited in any simple, direct pattern. There is not a particular gene that guarantees the development of the disease. However, slight variation in certain genes may influence whether someone is more or less susceptible to the disease.

The best-studied susceptibility gene in sporadic Alzheimer's disease is APOE, which is responsible for the production of a protein that transports cholesterol and other fats throughout the body. The protein may also be involved in the structure and function of the fatty membrane surrounding a brain cell. APOE has three common forms:

- APOE-epsilon 2 (APOE-e2) is the least common.
- APOE-e4 is somewhat more common.
- APOE-e3 is by far the most common.

A person inherits one form of the gene from each parent. The form associated with Alzheimer's disease is APOE-e4. People who carry at least one APOE-e4 are at a higher risk of developing Alzheimer's than the people who have no APOE-e4. Research has shown that between 35 and 50 percent of people with Alzheimer's have at least one copy of this form of the gene.

People who have two copies of APOE-e4 have an even higher risk. If these individuals develop the disease, they usually have symptoms at a younger age than people with Alzheimer's who do not carry APOE-e4. However, even individuals with two copies of APOE-e4 do not invariably develop Alzheimer's disease, and many cases of the disease occur in individuals with no copies of APOE-e4.

There is strong evidence that genes other than APOE-e4 affect the development of sporadic Alzheimer's disease. Identifying these genes is an area of active investigation.

### **Genetic testing**

Because of these genetic influences, people often want to know if a genetic test is useful in predicting their chances of developing Alzheimer's. The answer is somewhat different for familial Alzheimer's disease and sporadic Alzheimer's disease.

While genetic testing is available for many of the mutations in the three genes that cause familial Alzheimer's, this testing must be considered very carefully. First, these mutations are very rare. There are only about 200 family lines in the world that are known to carry such mutations.

Second, persons considering this testing should receive genetic counseling before a test is ordered and when the results are disclosed. Because there are no preventive treatments yet available, test results have no practical impact on medical treatment decisions. However, results may significantly affect an individual's psychological well-being and family relationships. Other concerns include employment, health insurance, long-term care insurance, future plans and several other important matters. All of these issues need to be considered very seriously and discussed thoroughly with skilled genetic counselors.

With regard to late-onset sporadic Alzheimer's disease, consensus statements by professional groups—medical, genetic and others—agree that APOE testing is not appropriate for individuals with no symptoms of dementia. Testing positive for APOE-e4, even among individuals with a family history of Alzheimer's disease, does not

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provide any useful information. People who possess APOE-e4 may or may not develop Alzheimer's disease. Similarly, people who do not inherit APOE-e4 may still develop the disease. There are also multiple medical, legal, social and ethical issues involved in receiving such tests. Testing positive may cause problems in getting a job or insurance and may also create a psychological burden.

For individuals with symptoms of dementia, testing for APOE status is of limited value. The information may be helpful to a clinician trying to determine the underlying cause of dementia, but the test results should be interpreted in the context of a complete diagnosis. In a thorough assessment without APOE testing, Alzheimer's disease can be diagnosed with approximately 90 percent accuracy. Therefore, the accuracy of the diagnosis can only be slightly improved with APOE testing. And the test results can provide perhaps unwanted information for the children of the patient about their own genetic makeup.

Genetic testing can be very important, however, in a research setting. Such testing can be done so that the results are kept confidential and not revealed to study participants.

### **For more information**

*Genetic Testing: Ethical Issues in Alzheimer's Disease.* This statement by the Alzheimer's Association Ethics Advisory Panel can be found on the Association Web site at: <http://www.alz.org/Resources/FactSheets/FSGeneticTesting.pdf>.

The National Institute on Aging (NIA) Alzheimer's Disease Genetics Initiative. For information about this study of genes associated with late-onset sporadic Alzheimer's disease, visit our Web site at: <http://www.alz.org/News/03Q3/072203genetics.asp>.

The National Society of Genetic Counselors provides information about counseling and a search feature to help consumers find genetic counselors on their Web site at: <http://www.nsgc.org/>.

The Alzheimer's Association is fighting on your behalf to give everyone a reason to hope. For more information about Alzheimer research, treatment and care, please contact the Alzheimer's Association.

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