

Layton Aging & Alzheimer's Disease Center

Genetics and Alzheimer's Disease

Oregon Health & Science University
3181 SW Sam Jackson Park Road, CR-131
Portland, OR 97239-3098
503.494.6976

Facts About Genes and Alzheimer's Disease

Risk Factors for Alzheimer's Disease (AD)

- The greatest risk factor associated with AD is increasing age.
- A family history of AD is also a risk factor. When people of the same age are compared, those who have a parent or a sibling with AD are 2 – 3 times more likely to develop AD than people who do not.

Two Forms of Alzheimer's Disease

Sporadic AD

- genes, by themselves, do not cause AD, but may influence the risk of developing the disease
- occurs in a less predictable manner and in fewer family members
- most common form of AD
- most cases occur after age 60; often called *late-onset Alzheimer's*

Familial AD

- genes are the direct cause of AD
- occurs in families with many members affected in multiple generations, and is very rare
- most cases occur before the age of 60; often called *early-onset Alzheimer's*

Sporadic Alzheimer's Disease/ late-onset AD

- Not caused by any particular gene that guarantees development of AD;
- slight variations in genes may, however, affect an individual's susceptibility to sporadic AD
- Apolipoprotein E (*APOE*) is the best-studied susceptibility gene
 - there are 3 forms of *APOE*: *APOE-ε2*, *APOE-ε3*, and *APOE-ε4*
 - *APOE-ε4* is associated with AD: people who inherit one *APOE-ε4* (from one parent) or two *APOE-ε4*s (from both parents) have a higher risk of developing AD than people who have no *APOE-ε4*
- However, **it is important to note that:**
 - People with 2 copies of *APOE-ε4* do not invariably develop AD
 - There are many cases of AD in people who have no *APOE-ε4*
- There is strong evidence that other susceptibility genes affect the development of AD. This is the most active area of research in AD.

Familial Alzheimer's Disease/ early-onset AD

- Can be caused by mutations in one of three possible genes
 - the presenilin genes (*PS1* and *PS2*)
 - the amyloid precursor protein gene (*APP*)
- These mutations are inherited

- an individual who carries a mutation has a 50% chance of passing the gene on to children
 - those who inherit the mutation will almost certainly develop AD
- The protein products of the *PS1*, *PS2* and *APP* genes Provide important clues about the biological cause of AD
 - all 3 genes are involved in the production of *β-amyloid*
 - *β-amyloid* is a sticky substance that clumps together in the brain and probably plays a role in the development of AD pathology

Genetic Testing

- Genetic testing is available for mutations in the 3 genes that cause *Familial/early-onset AD*; testing must be considered very carefully
 - these mutations are rare; only about 200 families in the world are known to carry such mutations
 - since no preventive treatment is available, results of testing will have no practical impact on medical treatment decisions
 - test results may have a significant effect on an individual's psychological well-being and family relationships, and may affect employment, health and long-term care insurance matters
 - **It is very important to receive genetic counseling before a test is ordered and when results are obtained, in order to discuss these issues thoroughly with trained genetic counselors.**
- For individuals with no symptoms of dementia, genetic testing is not recommended for *Sporadic/late-onset AD*; a positive test of APOE-ε4 does not provide useful information:
 - people with APOE-ε4 may or may not develop AD
 - people with no APOE-ε4 may still develop AD
 - there are medical, legal, social and ethical issues involved
 - testing positive for APOE-ε4 may cause employment, insurance and psychological problems
- For individuals with dementia symptoms, **APOE testing has limited value**
 - in a thorough assessment, without APOE testing, AD can be diagnosed with approximately 90% accuracy
 - the accuracy of the diagnosis can only be slightly improved with APOE testing
 - test results may provide unwanted information for the children of the AD patient, in terms of their own genetic makeup.
- Genetic testing can be very important in a research setting. Such testing can be done so that results are kept confidential and not revealed to the study participant or their families.

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 www.alz.org/ResourceCenter/ByType/FactSheets.htm.

The Alzheimer's Disease Education and Referral Center (ADEAR) at www.alzheimers.org

Alzheimer's Disease: What Causes It? An interactive information page on AD symptoms, causes, treatment and testing at <http://www.yourgenesyourhealth.org/alz/cause.htm>