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Alzheimer Overview

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Summary

Disease characteristics. Alzheimer disease (AD) is characterized by adult-onset slowly progressive dementia associated with diffuse cerebral atrophy on neuroimaging studies. It is the most common form of dementia, but less than 5% of families with AD have early-onset familial AD (EOFAD), in which symptoms consistently occur before the age of 65 years.

Laboratory testing/diagnosis. The diagnosis of Alzheimer disease is based on the histological findings of β -amyloid plaques and intraneuronal neurofibrillary tangles. No accurate clinical diagnostic test for AD exists. A significant association with the e4 allele of apolipoprotein E supports the diagnosis of AD in patients with dementia and increases the risk that asymptomatic individuals will eventually develop AD. *ApoE* genotyping, however, is neither fully specific nor sensitive. Three forms of EOFAD caused by mutations in one of three different genes (*APP*, *PSEN1*, *PSEN2*) are recognized. A molecular genetic test of the *PSEN1* gene (chromosomal locus 14q) is available in clinical laboratories.

Genetic counseling. First-degree relatives of individuals with sporadic AD have about a 20% lifetime risk of developing AD. Presumably, when several individuals in a family have AD, the risk is further increased. EOFAD is inherited in an autosomal dominant manner. The risk to offspring of individuals with EOFAD is 50%.

Definition

The term Alzheimer disease refers to dementia which typically begins with subtle and poorly recognized failure of memory slowly becoming more severe and, eventually, incapacitating. Other common symptoms include confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations. Occasionally, seizures, Parkinsonian features, increased muscle tone, myoclonus, incontinence, and mutism occur [Risse et al 1990, Cummings et al 1998]. Death usually results from general inanition, malnutrition, and pneumonia. The typical clinical duration of the disease is 8-10 years, with a range of 1-25 years.

The diagnosis of Alzheimer disease relies upon clinical-neuropathological assessment [Terry et al 1994, Cummings et al 1998]. Neuropathological findings on autopsy examination remain the gold standard for diagnosis of AD. The clinical diagnosis of AD (prior to autopsy confirmation) is correct about 80-90% of the time [Joachim et al 1988, Mayeux et al 1998].

- Clinical signs: slowly progressive dementia
- Neuroimaging studies: gross cerebral cortical atrophy [Kaye 1998]
- Neuropathological findings are microscopic A β -amyloid neuritic plaques, intraneuronal neurofibrillary tangles, and amyloid angiopathy at postmortem examination.

The plaques should stain positively with A β -amyloid antibodies and negative for prion antibodies. The numbers of plaques and tangles must exceed those found in age-matched controls without dementia. Guidelines exist to assess these changes quantitatively [Khachaturian 1985, NIA-Reagan Working Group 1997].

Alzheimer disease needs to be distinguished from other causes of dementia, especially treatable forms of cognitive decline such as depression, chronic drug intoxication, chronic CNS infection, thyroid disease, vitamin deficiencies (especially B12 and thiamine), and normal pressure hydrocephalus [Bird 1998]. Other degenerative disorders associated with dementia such as fronto-temporal dementia, Picks disease, Parkinson's disease, diffuse Lewy body disease, Creutzfeldt-Jakob disease, and *CADASIL* may also be confused with AD. CT and MRI are valuable for identifying other causes of dementia, such as astrocytomas, normal pressure hydrocephalus, and cerebral vascular disease.

Prevalence

AD is the most common cause of dementia in North America and Europe. The prevalence of the disease increases with increasing age. Approximately 10% of all persons over the age of 70 years have significant memory loss and more than half of these individuals have AD. The prevalence of dementia in individuals over the age of 85 years is estimated to be 25 to 45%. Because of increasing longevity, the occurrence of AD in the elderly represents a tremendous medical, economic, and social problem [Max 1993, Ebly et al 1994].

Categories

Alzheimer disease can be categorized as:

- Sporadic AD
- AD associated with Down syndrome
- Familial AD, which can be further subdivided by mode of inheritance and gene or chromosomal locus

Table 1. Categories of Alzheimer Disease

Type	Proportion of all AD
Sporadic	~ 75%
Associated with Down syndrome	< 1%
Familial <ul style="list-style-type: none"> Late-onset familial (AD2) Early-onset familial AD (AD1, AD3, AD4) 	~ 25% <ul style="list-style-type: none"> 15-25% < 5%

Sporadic AD

Patients with sporadic AD meet the diagnostic criteria for AD and have a negative family history. Onset can be anytime in adulthood. The exact pathogenesis of the disease is unknown. A common hypothesis is that sporadic AD is multifactorial and results from a combination of aging, genetic predisposition, and exposure to one or more environmental agents such as head trauma, viruses, and/or toxins [[Cummings et al 1998](#)]. Such environmental agents have not yet been proven to be directly involved in the pathogenesis of AD.

AD Associated with Down Syndrome

Essentially all persons with trisomy 21 develop the neuropathological hallmarks of AD after age 40 years. More than half such individuals also show, if carefully observed or tested, clinical evidence of cognitive decline [[Brugge et al 1994](#)]. The presumed reason for this association is the lifelong over-expression of the amyloid precursor protein (APP) gene on chromosome 21 and the resultant overproduction of A β -amyloid in the brains of persons who are trisomic for this gene.

Familial AD

About 25% of AD is familial. Familial cases appear to have the same clinical and pathological phenotypes as sporadic cases [[Haupt et al 1992](#), [Nochlin et al 1993](#)] and thus are distinguished only by family history or molecular genetic testing. There has been a large volume of research on the molecular and genetic basis of AD that has been summarized by [Rosenberg \(2000\)](#).

Late-onset Familial AD (AD2)

Molecular Genetics

Table 2. Late-onset Familial Alzheimer Disease: Molecular Genetics

Disease Name	Proportion of all AD	Gene Symbol	Locus	Normal Gene Product	Test Availability	Genomic Databases
AD2	15-25%	<i>ApoE</i> (risk factor)	19q13	Apolipoprotein E	Clinical GENETests	OMIM LocusLink HGMD OMIM LocusLink

Investigations have supported the concept that late-onset AD is a complex disorder that may involve multiple susceptibility genes. Although no chromosomal assignment for a gene or genes directly responsible for this form of AD has yet been made, the following information is currently available:

- Well-documented association of late-onset FAD with the e4 allele of Apolipoprotein E chromosomal locus 19q13) [[Corder et al 1993](#)]. *ApoE* e4, by unknown mechanisms, appears to affect age of onset by shifting the onset curve toward an earlier age [[Meyer et al 1998](#)].
- Evidence that a region on chromosome 12 may contain a susceptibility gene for late-onset AD [[Pericak-Vance et al 1997](#)]. This putative gene has not been identified. One subsequent study has confirmed this linkage [[Rogaeva et al 1998](#)] and another has not [[Wu et al 1998](#)].
- An association of α 2 macro-globulin (chromosome 12) with late-onset FAD with both positive and negative association studies [[Blacker et al 1998](#), [Dodel et al 2000](#), [Gibson et al 2000](#)].
- Three groups have found evidence for linkage of late onset FAD to markers on chromosome 10. No gene has been identified [[Bertram et al 2000](#), [Ertekin-Taner et al 2000](#), [Myers et al 2000](#)].

Clinical Features

Many families have multiple affected members, most or all of whom have onset of dementia after the age of 60 or 65 years. Disease duration is typically 8-10 years, but ranges from 2-25 years.

Early-Onset Familial AD (EOFAD)

Molecular Genetics

At least three subtypes of EOFAD (AD1, AD3, AD4) have been identified based on the causative gene. The relative proportion of each subtype and the causative genes are summarized in Table 3 [[Campion et al 1999](#)]. EOFAD and the testing available are described in more detail in the [EOFAD disease profile](#). It is likely that other genes will be identified as a cause of EOFAD because kindreds with autosomal dominant FAD with no known mutations in *PSEN1*, *PSEN2*, or *APP* have been described [[Cruts et al 1998](#)].

Table 3. Early-Onset Familial Alzheimer Disease (EOFAD): Molecular Genetics

Disease Name	Proportion of EOFAD	Gene Symbol	Locus	Normal Gene Product	Testing	Genomic Databases
AD3	20-70%	<i>PSEN1</i>	14q24	Presenilin 1	Clinical GENETests	OMIM LocusLink
AD1	10-15%	<i>APP</i>	21q21.3-q22	Amyloid precursor protein	Research	OMIM LocusLink HGMD
AD4	Rare	<i>PSEN2</i>	1q31-q42	Presenilin 2	Clinical GENETests	OMIM LocusLink

Clinical Features

This category refers to families in which multiple cases of AD occur with the mean age of onset usually before age 65 years, although some studies have used age 60 years or 70 years. Age of onset is usually in the 40's or early 50's, although onset in the 30's and early 60's has been reported. This group comprises less than 5% of all AD [Bird et al 1989]. Campion et al (1999) found a prevalence of early-onset AD in the general population of 41.2 per 100,000 persons at risk (ages 40-59 years). Sixty-one percent of these individuals with early-onset AD had a positive family history and 13% met stringent criteria for autosomal dominant inheritance (i.e., affected individuals in three generations). EOFAD cannot be clinically distinguished from sporadic AD except on the basis of family history and age of onset.

Management

The mainstay of treatment is necessarily supportive and each symptom is managed on an individual basis. In general, affected patients eventually require assisted living arrangements or care in a nursing home. The exact biochemical basis of AD is not well understood. Deficiencies of the brain cholinergic system and of other neurotransmitters are present. There are drugs that increase cholinergic activity by inhibiting acetylcholinesterase that play a role in treatment of AD. A minority of patients show modest but useful behavioral or cognitive benefit. The first such drug was tacrine, but this agent is also hepatotoxic [Knapp et al 1994]. There are newer such drugs with similar pharmacologic action that are not hepatotoxic, such as Aricept (donepezil), Exelon (rivastigmine) [Rogers et al 1996], and Galantamine [Raskind et al 2000, Tariot et al 2000]. Nonsteroidal anti-inflammatory drugs and estrogen are also under study as possible therapeutic agents. Antidepressant medication may improve associated depression. Treatment trials evaluating several different therapeutic strategies are underway; these strategies include use of anti-inflammatory agents, estrogens, nerve growth factors, and antioxidants [Marx 1996, Farlow & Evans 1998]. Thus far, treatment of symptomatic AD with estrogens has not proven beneficial [Mulnard et al 2000, Wang et al 2000]. There is evidence that patients taking HMG-Coenzyme A reductase inhibitors for hypercholesterolemia have a reduced incidence of dementia [Wolozin et al 2000]. Immunization of a AD mouse model with β -amyloid has attenuated the AD pathology and stimulated the search for a possible vaccination approach to the treatment of human AD [Schenk et al 1999].

Diagnosis

Establishing the specific subtype of AD for a given patient usually involves a detailed family history and use of molecular genetic testing.

Family history. A three-generation family history with close attention to the history of individuals with dementia should be obtained. For each affected individual, the age of onset dementia should be noted. Generally, individuals with onset before age 65 years are considered to have early onset AD and those with onset after age 65 years are considered to have late onset AD. Medical records of affected family members including reports of neuroimaging studies and autopsy examinations should be obtained.

- The diagnosis of EOFAD is made in families with multiple cases of AD in which the mean age of onset is before age 65 years.
- The diagnosis of late-onset FAD is made in families with multiple cases of AD in which and the mean age of onset is after age 65 years.

Molecular Genetic Testing

Late-onset familial AD. The association of *ApoE* e4 with late-onset AD is well-documented, but the usefulness of *ApoE* testing in clinical diagnosis and risk assessment remains unclear [Roses 1995, Statements and Guidelines Regarding Genetic Testing]. *ApoE* e4 is neither necessary nor sufficient as a cause of AD. *ApoE* genotyping may have an adjunct role in the diagnosis of AD because a large proportion of individuals with e4 alleles who are demented have been found to have neuropathological confirmation of AD at autopsy [Saunders et al 1996, National Institute on Aging/Alzheimer's Association Working Group 1996, Welsh-Bonner et al 1997, Maveux et al 1998]. *ApoE* genotyping was not found to be of significant diagnostic use in identifying AD in a community based sample with late-onset dementia [Tsuang et al 2000].

Presence of an e4 allele in an individual with dementia increases the probability that AD is the cause of the dementia. Table 4 shows the association between *ApoE* genotypes and AD [Jarvik et al 1996]. A significant proportion of patients with AD have an e4 allele (i.e., genotypes 2/4, 3/4, 4/4). The association between *ApoE* e4 and AD is greatest when the patient has a positive family history of dementia. The last column of Table 4 largely represents late-onset familial AD. Also note that the strongest association between e4 and AD, relative to the normal control population, is with the 4/4 genotype. That genotype occurs in about 1% of the normal control population and in nearly 19% of the familial AD population. In individuals who have the clinical diagnosis of AD, the probability that AD is the correct diagnosis is increased to about 97% in the presence of the *ApoE* 4/4 genotype [Saunders et al 1996]. Note that about 42% of persons with AD do not have an e4 allele. Thus, *ApoE* testing is not specific for AD. The absence of an e4 allele does not rule out the diagnosis of AD [Bird 1995, Maveux et al 1998]. Breitner et al (1999) have estimated lifetime risks for developing AD based on gender and *ApoE* genotype.

See [Testing at-risk asymptomatic individuals](#) under Genetic Counseling.

Table 4. Percent of *ApoE* Genotypes in Controls and Patients with AD

<i>ApoE</i> Genotype	Normal Controls (n = 304)	All Patients with AD (n = 233)	Patients with AD and Positive Family History of Dementia ¹ (n = 85)
2/2	1.3%	0%	0%
2/3	12.5%	3.4%	3.5%
2/4	4.9%	4.3%	8.2%
3/3	59.9%	38.2%	23.5%
3/4	20.7%	41.2%	45.9%
4/4	0.7%	12.9%	18.8%

Modified from Jarvik et al (1996).

1. Most families would be considered to have late-onset familial AD.

Another way to look at this association between AD and *ApoE4* is with *ApoE4* allele frequencies as shown in Table 5.

Table 5. *ApoE* Allele Frequencies in Controls and Patients with AD

<i>ApoE</i> Allele	Normal Controls (n=304)	All Patients with AD (n=233)	Patients with AD and Positive Family History of Dementia (n=85)
2	9.0%	3.9%	5.9%
3	76.5%	60.5%	48.2%
4	13.7%	35.6%	45.9%

Modified from [Jarvik et al \(1996\)](#).

Early-onset familial Alzheimer disease. The three known subtypes of EOFAD, called AD3, AD1, and AD4 [[Levy-Lahad & Bird 1996](#), [Tsuang et al 1999](#)] can only be distinguished by molecular genetic testing. Testing for mutations in the *PSEN1* gene detects 30-60% of individuals with AD3 and is available in clinical laboratories. Clinical molecular genetic testing is not available for mutations in the *APP* or *PSEN2* genes.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. This section deals with genetic risk assessment and the use of genetic testing to clarify genetic status. It is not meant to address all personal or cultural issues that individuals might face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see [GENETests](#). —ED.

Since AD is genetically heterogeneous, genetic counseling of persons with AD and their family members must be tailored to the information available for that family.

Modes of Inheritance

Alzheimer disease is most commonly inherited in a multifactorial manner. Early-onset familial Alzheimer disease (EOFAD) is quite rare but usually inherited in an autosomal dominant manner.

Risk to Family Members: Sporadic Alzheimer Disease

Genetic counseling for people with the sporadic type of AD and their family members must be empiric and relatively nonspecific. It should be pointed out that AD is common and that the overall lifetime risk of developing dementia is approximately 10-12%.

Parents, sibs and offspring of a proband. First-degree relatives of a person with AD have a cumulative lifetime risk of developing AD of about 15-30%, which is typically reported as a 20-25% risk [[Farrer et al 1989](#), [Silverman et al 1994](#)]. Disagreement exists as to whether the age of onset of the affected person changes the risk to first-degree relatives. One study found that early onset AD increased the risk [[Silverman et al 1994](#)], while another study did not [[Farrer et al 1989](#)]. The number of additional affected family members probably increases the risk to close relatives, but the magnitude of that increase is unclear unless the pattern in the family is characteristic of autosomal dominant inheritance.

While there is an association of AD with the e4 allele of apolipoprotein E (*ApoE*), the *ApoE* genotype is not useful for prediction of AD in asymptomatic persons. The greatest risk appears to be in females who are homozygous for the e4 allele [[Breitner et al 1999](#)].

Risk to Family Members: Late-Onset Familial Alzheimer Disease

Many families have multiple affected members, all of whom have onset of dementia after the age of 65 or 70 years.

Parents, sibs and offspring of a proband. Having two, three, or more affected family members probably raises the risk to other first-degree relatives in excess of that noted above for sporadic cases, although the exact magnitude of the risk is not clear. [Heston et al \(1981\)](#) found a 35-45% risk of dementia in persons with a sib with onset of AD at less than age 70 years of age and an affected parent. [Bird et al \(1993\)](#) also reported preliminary data suggesting that offspring of parents with conjugal AD (i.e., both parents affected) had an increased risk of dementia.

Risk to Family Members: Early-Onset Familial Alzheimer Disease (EOFAD)

Parents of a proband. Most individuals diagnosed as having early-onset familial Alzheimer disease (EOFAD) will have an affected parent, although occasionally the family history will be negative. Family history may be "negative" because of alternate paternity, adoption, early death of a parent, failure to recognize early-onset familial Alzheimer disease (EOFAD) in family members, late onset in a parent, reduced penetrance of the mutant allele in an asymptomatic parent, or a new mutation for early-onset familial Alzheimer disease (EOFAD). New mutations causing early-onset familial Alzheimer disease (EOFAD) are rare.

Sibs of a proband. The risk to sibs depends upon the genetic status of the proband's parent. If one of the proband's parents has a mutant allele, then the risk to the sibs to inherit the mutant allele is 50%.

Offspring of a proband. Individuals with early-onset familial Alzheimer disease (EOFAD) have a 50% chance of transmitting the mutant allele to each child.

Other family members of a proband. The risk to other family members depends upon the status of the proband's parents. If a parent is found to have a disease causing mutation, his or her family members are at risk.

Related Genetic Counseling Issues

***ApoE* testing.** In contrast to the utility of *ApoE* testing as an adjunct diagnostic test, there is general agreement that *ApoE* testing should not be used for predictive testing for AD in asymptomatic persons. Although a young asymptomatic person with the 4/4*ApoE* genotype may have an approximately 30% lifetime risk of developing AD [[Breitner 1996](#)], this estimate is not generally considered clinically useful. This risk also depends on gender of the subject. [Breitner et al \(1999\)](#) have shown that females with an *ApoE* 4/4 genotype have a 45% probability of developing AD by age 73 years, whereas the risk is 25% for males with a 4/4 genotype. Furthermore, these risks are lower and the likely age of onset is later for persons with only one (peak age 87 years) or no (peak age 95 years) *E4* allele.

Down syndrome. Family members of persons with Down syndrome are not at increased risk for AD.

Testing of At-Risk Asymptomatic Family Members

Testing of at-risk asymptomatic adults. Testing of asymptomatic adults at-risk for early-onset familial Alzheimer disease (EOFAD) caused by mutations in the *PSEN1* (presenilin 1) gene is available clinically. Testing for AD1 and AD4 caused by mutations in *APP* gene and *PSEN2* gene respectively is available only on a research basis. Results of testing at-risk asymptomatic adults can only be interpreted after an affected family member's disease-causing mutation has been identified. It should be remembered that testing of asymptomatic at-risk individuals with non-specific or equivocal symptoms is predictive testing, not diagnostic testing.

Testing of at-risk asymptomatic children. Consensus holds that children at risk for adult onset disorders should not have testing in the absence of symptoms. The principle reasons against testing children who do not have symptoms are that it removes their choice to know or not know this information, raises the possibility of stigmatization within the family and in other social settings, and could have serious educational and career implications. (See also the National Society of Genetic Counselors [resolution](#) on genetic testing of children and the American Society of Human Genetics and American College of Medical Genetics [points to consider](#): ethical, legal, and psychosocial implications of genetic testing in children and adolescents.)

DNA Banking

DNA Banking is the storage of DNA, which has typically been extracted from white blood cells, for possible future use. Since it is likely that testing methodologies, our understanding of genes, mutations and diseases will improve in the future, consideration should be given to banking DNA particularly when:

- Molecular genetic testing is not available. For example, the gene responsible has not yet been identified, the disease causing mutations have not yet been elucidated or testing is available on a research or linkage basis only.
- Molecular genetic testing is not informative. For example, linkage testing was not informative or the sensitivity of currently available testing is less than 100%.
- Interpretation of results is difficult. For example, if an affected family member chooses not to be tested, interpretation of a "negative" result in at risk family members is difficult. An affected family member who chooses not to be tested may be willing to have DNA banked for future use by other family members.

For laboratories offering DNA banking, see [GENETests](#).

Prenatal Testing

It is possible to perform prenatal diagnosis by analyzing fetal DNA extracted from cells obtained by chorionic villus sampling (CVS) at 9-11 weeks gestation or amniocentesis at 16-18 weeks gestation for mutations in the presenilin 1 (*PSEN1*) gene for those families with early-onset familial Alzheimer disease in which a disease causing mutation has been identified in an affected family member. Requests for prenatal diagnosis of adult onset diseases are difficult situations requiring careful genetic counseling. The continuation of pregnancies in which test results are positive becomes a significant issue because issues related to testing of at-risk asymptomatic children pertain.

Resources

GeneClinics provides information about selected national organizations and resources for the benefit of the reader. GeneClinics is not responsible for information provided by other organizations. —ED.

- **Alzheimer's Association National Headquarters**

919 North Michigan Avenue, Suite 1000
Chicago, IL 60611-1676
Phone: 800-272-3900; 312-335-8700
Fax: 312-335-1110
Email: info@alz.org
Web: www.alz.org

- **NCBI Genes and Disease Web page**

www.ncbi.nlm.nih.gov/disease/Alzheimer.html

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- 22 Jun 2001: Au revisions (ca)
- 07 Jul 2000: Au/internal updates (ca)
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