



## Alzheimer Disease Overview

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### Summary

The purpose of this overview is to:

1. Describe the clinical characteristics of Alzheimer disease (AD);
2. Review the genetic causes of AD;
3. Provide an evaluation strategy to identify the genetic cause of AD in a proband (when possible);
4. Inform genetic counseling of family members of an individual with AD.

### 1. Clinical Characteristics of Alzheimer Disease

Alzheimer disease (AD) is characterized by dementia that typically begins with subtle and poorly recognized failure of memory (often called mild cognitive impairment or MCI) and slowly becomes more severe and, eventually, incapacitating. Other common findings include confusion, poor judgment, language disturbance, visual complaints, agitation, withdrawal, and hallucinations. Occasionally, seizures, Parkinsonian features, increased muscle tone, myoclonus, incontinence, and mutism occur. Death usually results from general inanition, malnutrition, and pneumonia. The typical clinical duration of the disease is eight to ten years, with a range from one to 25 years.

Approximately 95% of all AD is late onset (age >60-65 years) and 5% is early onset (age <60-65 years).

Establishing the diagnosis of Alzheimer disease relies on clinical-neuropathologic assessment. Neuropathologic findings of  $\beta$ -amyloid plaques, intraneuronal neurofibrillary tangles (containing tau protein), and amyloid angiopathy remain the gold standard for diagnosis.

- The plaques should stain positively with  $\beta$ -amyloid antibodies and negative for prion antibodies (which are diagnostic of prion diseases).
- The numbers of plaques and tangles must exceed those found in age-matched controls without dementia. Guidelines for the quantitative assessment of these changes exist [Montine et al 2012].
- Aggregation of alpha-synuclein in the form of Lewy bodies may also be found in neurons in the amygdala; frequently there is accumulation of TDP-43 protein [James et al 2016, Lemstra et al 2017].

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The clinical diagnosis of AD, based on clinical signs of slowly progressive dementia and neuroimaging findings of gross cerebral cortical atrophy, is correct approximately 80%-90% of the time. Greater precision can be obtained by use of more sophisticated studies such as amyloid PET imaging, CSF concentrations of amyloid and tau, and (in the near future) tau PET imaging and plasma concentration of  $\beta$  amyloid [Dubois et al 2014, Gabelle et al 2015, Sutphen et al 2015, Mattsson et al 2018].

**Differential diagnosis of Alzheimer disease** includes the following:

- **Treatable forms of cognitive decline** including depression, chronic drug intoxication, chronic CNS infection, thyroid disease, vitamin deficiencies (especially B<sub>12</sub> and thiamine), CNS angiitis, and normal-pressure hydrocephalus [Bird & Miller 2008]. CT and MRI can identify some of these other causes of dementia, including neoplasms, normal-pressure hydrocephalus, and cerebral vascular disease.
- **Other degenerative disorders associated with dementia**, such as frontotemporal dementia (including frontotemporal dementia with parkinsonism-17; FTDP-17), Picks disease, [Parkinson disease](#), diffuse Lewy body disease (LBD), Creutzfeldt-Jakob disease, and [CADASIL](#) [Loy et al 2014, Ferrari et al 2018].

## 2. Causes of Alzheimer Disease

**Table 1.** Causes of Alzheimer Disease

Cause	% of Cases
Late-onset familial <sup>1</sup> (age >60-65 years)	15%-25%
Early-onset familial <sup>1</sup> (age <60-65 years)	<2%
Down syndrome <sup>2</sup>	<1%
Unknown (includes genetic/environment interactions)	~75%

1.  $\geq 3$  persons in a family with AD

2. Essentially all persons with Down syndrome (trisomy 21) develop the neuropathologic hallmarks of AD after age 40 years [McCarron et al 2017]. If carefully observed or tested, more than half of individuals with DS also show clinical evidence of cognitive decline. The presumed reason for this association is the lifelong overexpression of *APP* on chromosome 21 encoding the amyloid precursor protein and the resultant overproduction of  $\beta$ -amyloid in the brains of persons who are trisomic for this gene.

### Familial Alzheimer Disease

Approximately 25% of all AD is familial (i.e.,  $\geq 3$  persons in a family have AD) and 75% is nonfamilial (i.e., an individual with AD and no known family history of AD). Because familial AD and nonfamilial AD appear to have the same clinical and pathologic phenotypes, they can only be distinguished by family history and/or by molecular genetic testing.

#### Late-Onset Familial AD

Investigations have supported the concept that late-onset AD (age >60-65 years) is a complex disorder that may involve multiple susceptibility genes [Van Cauwenberghe et al 2016].

While the association of the *APOE* e4 allele with AD is significant, *APOE* genotyping is neither fully specific nor sensitive. While *APOE* genotyping may have an adjunct role in the diagnosis of AD in symptomatic individuals, it appears to have little role at this time in predictive testing of asymptomatic individuals. As reviewed and summarized by Van Cauwenberghe et al [2016], the gene *APOE* has three major allelic variants – e2, e3, and e4 – which encode different isoforms of the protein ApoE. The presence of the *APOE* e4 allele in the heterozygous state (*APOE* e3/e4) or the homozygous state (*APOE* e4/e4) increases the risk for early-onset and late-onset AD but is not sufficient to cause disease. Only 20%-25% of individuals in the general population are heterozygous or homozygous for the e4 allele compared to 20%-65% of individuals with AD. The risk effect is estimated to be threefold for heterozygotes (*APOE* e3/e4) and 15-fold for homozygotes (*APOE* e4/e4). Using data from

community-based samples, Qian et al [2017] determined that a heterozygote for an *APO* e4 allele has about a 10%-20% chance of developing AD by age 75, whereas an *APO* e4 homozygote has about a 25%-35% risk.

Approximately 42% of persons with AD do **not** have an *APOE* e4 allele. The absence of an *APOE* e4 allele does not rule out the diagnosis of AD.

Of note, the *APOE* e2 allele appears to have a protective effect [Iacono et al 2015].

## Susceptibility Genes

Research studies have identified variants in ~20 genes that increase the risk of AD slightly (i.e., <2%). Many of these genes have a role in brain development, cytoskeletal organization, and immune function. Variants in these susceptibility genes differ from variants in genes known to cause Alzheimer disease as no variant in any of these genes "causes" AD; therefore, these genes should not be included in any diagnostic testing (see Evaluation Strategies).

Furthermore, it should be noted that while various combinations of variants in these genes have been proposed as markers for genetic risk of developing AD (so-called "polygenic risk scores") [Desikan et al 2017, Tan et al 2017, Tosto et al 2017], at present these risk scores are of no known clinical utility.

The following list of susceptibility genes is based on reviews by Naj et al [2014], Del-Aguila et al [2015], Ridge et al [2016], Van Cauwenberghe et al [2016], and Yokoyama et al [2016]: *ABCA7*, *AKAP9*, *BIN1*, *CASS4*, *CD2AP*, *CD33*, *CLU*, *EPHA1*, *FERMT2*, *HLA-DRB5/DRB1*, *INPP5D*, *MEF2C*, *MS4A6A/MS4A4E*, *PICALM*, *PLD3*, *PTK2B*, *SORL1*, *TREM2* (see NOTE), and *UNC5C*.

NOTE: The *TREM2* p.Arg47His variant is a statistically significant risk factor for late-onset AD [Guerreiro et al 2013, Jonsson et al 2013]. Although this variant in the heterozygous state is rare in the general population (0.5%-1%), it results in an odds ratio of about 3.0 for the occurrence of AD. In a large family, apparent interaction of this variant with the *APOE* e4 allele increased the risk for late-onset AD [Korvatska et al 2015].

See [Table 2 \(pdf\)](#) for potential functional contribution to Alzheimer disease risk.

## Early-Onset Familial AD

Early-onset familial AD (EOFAD) refers to AD that occurs in multiple members of a family with a mean onset usually before age 65 years. The dementia phenotype is similar to that of late-onset AD, sometimes with a long prodrome [Schellenberg & Montine 2012]. The genes causative of EOFAD and associated ages of onset are summarized in Table 3.

**Table 3.** Early-Onset Familial Alzheimer Disease (EOFAD)

Gene <sup>1</sup>	Proportion of EOFAD <sup>2</sup>	Age of Onset (yrs)	Other
<i>APP</i>	10%-15%	Usually 40s & 50s, occasionally 60s (range 30-65) <sup>3</sup>	
<i>PSEN1</i>	20%-70%	Usually 40s or early 50s (range 30s-early 60s); onset after age 65 thought to be rare	<ul style="list-style-type: none"> <li>• Relatively rapid progression over 6-7 yrs is common.</li> <li>• Often associated w/seizures, myoclonus, &amp; language deficits <sup>4</sup></li> <li>• Founder variants identified in residents of the state of Antioquia, Colombia <sup>5</sup> &amp; in Caribbean Hispanics <sup>6</sup></li> </ul>

Table 3. continued from previous page.

Gene <sup>1</sup>	Proportion of EOFAD <sup>2</sup>	Age of Onset (yrs)	Other
<i>PSEN2</i>	~5%	40-75	<ul style="list-style-type: none"> <li>• Mean duration: 11 yrs</li> <li>• Reduced penetrance (i.e., asymptomatic heterozygotes age &gt;80 yrs) reported <sup>7</sup></li> <li>• Founder variant identified in the Volga German population</li> </ul>
Unknown	20%-40% <sup>8</sup>		No major new gene for EOFAD has been identified because of overlap in the clinical presentation of AD and FTD caused by pathogenic variants in <i>MAPT</i> , <i>GRN</i> , <i>C9orf72</i> .

AD = Alzheimer disease; FTD = frontotemporal dementia

1. Genes are in alphabetic order.

2. Schellenberg & Montine [2012]

3. Pilotto et al [2013]

4. Larner [2013], Ryman et al [2014]

5. Lalli et al [2014]

6. Lee et al [2014]

7. Jayadev et al [2010]

8. It is likely that pathogenic variants in other genes causative of EOFAD will be identified because kindreds with autosomal dominant FAD with no known pathogenic variants in *PSEN1*, *PSEN2*, or *APP* have been described [Pasanen et al 2018].

### 3. Evaluation Strategies to Identify the Genetic Cause of Alzheimer Disease in a Proband

Establishing a specific genetic cause of Alzheimer disease (AD):

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling (Section 4);
- Usually involves a medical history, physical examination, and laboratory testing to exclude disorders included in the differential diagnosis (see Section 1), family history, and genomic/genetic testing.

The two most important indicators of a genetic form of AD are age of onset (Table 3) and positive family history of dementia.

- There is no specific age cutoff and the general rule is that in a single individual diagnosed with AD, the earlier the onset, the more likely a genetic cause. Onset before 50 years has the highest likelihood of a genetic cause and after 70 years the lowest.
- A positive family history ( $\geq 3$  affected persons) of early-onset dementia increases the probability of a genetic cause.

**Family history.** A three-generation family history should be taken, with attention to relatives with manifestations of AD and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing.

**Molecular genetic testing approaches** can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing or genome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

Because of the significant overlap in clinical manifestations and age of onset in AD, single-gene testing (i.e., sequence analysis, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

A **multigene panel** (see NOTE) that includes *APOE* (specifically for detection and interpretation of the e4 allele) and all three genes listed in Table 3 is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (5) Because Alzheimer disease susceptibility genes (Table 2) are not "causative," they should not be included in a multigene panel.

NOTE: Some laboratories offer multigene panels for "neurodegenerative disorders." While the genes included in such panels are likely to vary significantly by laboratory, often the genes known to cause the disorders mentioned in the differential diagnosis of AD (see Section 1), such as Parkinson disease, FTD, ALS, and prion-related disorders, are included. Because the clinical diagnosis of AD is usually "possible" or "probable" rather than "definite," it frequently is reasonable to use such a multigene panel.

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

**Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be considered if a multigene panel does not identify a cause for the findings that prompted testing. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

## 4. Inform Genetic Counseling of Family Members of an Individual with Alzheimer Disease

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

### Risk to Family Members – Nonfamilial Alzheimer Disease

Genetic counseling for people with late-onset nonfamilial AD (i.e., an individual with AD and no known family history) and their family members must be empiric and relatively nonspecific. First-degree relatives of a person with nonfamilial AD have a cumulative lifetime risk of developing AD of approximately 15%-39%, which is typically reported as a 20%-25% risk [Farrer et al 1989, Silverman et al 1994, Lautenschlager et al 1996]. This risk is approximately two to three times that of the background risk (~27% vs 10.4%) [Cupples et al 2004].

Disagreement exists as to whether the age of onset of AD in a person with nonfamilial AD changes the risk to first-degree relatives. Silverman et al [2005] found that the risk to relatives of a proband with nonfamilial AD decreases with increasing age of onset of the proband.

## Risk to Family Members – Late-Onset Familial Alzheimer Disease (LOFAD)

Inheritance of LOFAD (i.e.,  $\geq 3$  persons in a family have AD) is thought to be multifactorial and potentially involve multiple susceptibility genes [Van Cauwenberghe et al 2016]. First-degree relatives of a person with LOFAD have a cumulative lifetime risk of developing AD of ~15%-25%, which is ~1.5-2 times the risk of the general population. When both parents have AD (i.e., conjugal AD) risk to their children is at least twice that of the general population risk [Jayadev et al 2008].

## Risk to Family Members – *APP*-, *PSEN1*-, or *PSEN2*-Related Early-Onset Familial Alzheimer Disease (EOFAD)

EOFAD in which an individual has a pathogenic variant in *APP*, *PSEN1*, or *PSEN2* represents an autosomal dominant disease. This section refers only to families having a known EOFAD-causing *APP*, *PSEN1*, or *PSEN2* pathogenic variant. Guidelines for counseling these families have been published [Goldman et al 2011].

### Parents of a proband

- Most individuals diagnosed as having *APP*-, *PSEN1*-, or *PSEN2*-related EOFAD have had an affected parent.
  - Because the onset of EOFAD is typically in early adulthood and the progression is rapid, affected parents are not alive at the time of diagnosis of their children.
  - Occasionally, neither parent is identified as having had AD, but a second-degree relative (e.g., an uncle, aunt, and/or grandparent) has or had EOFAD. In this instance, a parent of the proband is presumed to be heterozygous for a familial AD-causing pathogenic variant associated with reduced (age-related) penetrance.
- A proband with EOFAD may have the disorder as the result of a *de novo* pathogenic variant, although this has not been documented.
- The family history of some individuals diagnosed with EOFAD may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or reduced (age-related) penetrance. Therefore, an apparently negative family history cannot be considered confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

**Sibs of a proband.** The risk to sibs depends on the clinical/genetic status of the parents:

- If a parent of the proband was affected and/or is known to be heterozygous for an *APP*-, *PSEN1*-, or *PSEN2*-related EOFAD pathogenic variant, the risk to sibs of having inherited the variant is 50%.
- Sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for EOFAD because of the possibility of reduced (age-related) penetrance in a parent.

**Offspring of a proband.** Each child of an individual with *APP*-, *PSEN1*-, or *PSEN2*-related EOFAD has a 50% chance of inheriting the EOFAD-causing pathogenic variant.

**Other family members.** The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

## Related Genetic Counseling Issues

**Predictive testing for *APP*-, *PSEN1*-, or *PSEN2*-related EOFAD (i.e., testing of asymptomatic at-risk individuals)**

- Predictive testing for asymptomatic adults at risk for *APP*-, *PSEN1*-, or *PSEN2*-related EOFAD is possible if the pathogenic variant has been identified in an affected family member. It should be remembered that

testing of asymptomatic at-risk individuals with nonspecific or equivocal symptoms is predictive testing, not diagnostic testing.

- Potential consequences of such testing (including, but not limited to, socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

### **Predictive testing for *APP*-, *PSEN1*-, or *PSEN2*-related EOFAD in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)**

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors [position statement](#) on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics [policy statement](#): ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of EOFAD, it is appropriate to consider testing of symptomatic individuals regardless of age.

***APOE* genotyping.** At this time, it is generally agreed that *APOE* genotyping has little role in predictive testing. The presence of one or two copies of the *APOE* e4 allele increases the lifetime risk of AD in an asymptomatic individual but does not constitute a diagnosis of AD (i.e., an individual may have one or two copies of the *APOE* e4 allele and never develop AD). Likewise, absence of one or two copies of the *APOE* e4 allele does not eliminate the risk for AD in an asymptomatic individual (~42% of persons with AD do not have an *APOE* e4 allele).

- ***APOE* e4/e4**
  - A young asymptomatic female who is homozygous for the *APOE* e4 allele has a 40%-45% probability of developing AD by age 75 years, compared with 10%-15% probability in the general female population.
  - A young asymptomatic homozygous male has a 25%-30% risk of developing AD by age 80 years, compared with 10%-15% probability in the general male population [Breitner et al 1999, Qian et al 2017, Liu & Caselli 2018].
- ***APOE* e3/e4.** For an asymptomatic person heterozygous for an *APOE* e4 allele, the lifetime risk of developing AD is lower (15%-25%) and the likely age of onset is later (peak age 80s) [Breitner et al 1999, Neu et al 2017, Qian et al 2017].

See the [Statement of The Alzheimer's Foundation of America \(AFA\) and AFA's Medical, Scientific and Memory Screening Advisory Board on Genetic Testing to Determine Risk of Alzheimer's Disease](#) and Frank et al [2018] for further discussion of predictive testing for AD.

## **Resources**

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).*

- **Alzheimer's Association**

225 North Michigan Avenue

Fl 17

Chicago IL 60601-7633

**Phone:** 800-272-3900 (Toll-free 24/7 Helpline); 866-403-3073 (Toll-free 24/7 Helpline - TDD);  
312-335-8700

**Fax:** 866-335-5886 (toll-free)

**Email:** [info@alz.org](mailto:info@alz.org)

[www.alz.org](http://www.alz.org)

- **Alzheimer's Disease Education and Referral Center (ADEAR)**

PO Box 8250

Silver Spring MD 20907

**Phone:** 800-438-4380 (toll-free)

**Fax:** 301-495-3334

**Email:** [adear@alzheimers.org](mailto:adear@alzheimers.org)

[www.nia.nih.gov/alzheimers](http://www.nia.nih.gov/alzheimers)

- **National Library of Medicine Genetics Home Reference**

[Alzheimer Disease](#)

- **NCBI Genes and Disease**

[Alzheimer Disease](#)

- **National Institute on Aging**

31 Center Drive

Building 31, Room 5C27

MSC 2292

Bethesda MD 20892

**Phone:** 301-496-1752; 800-222-2225 (toll-free); 800-222-4225 (toll-free TTY)

**Fax:** 301-496-1072

[www.nia.nih.gov](http://www.nia.nih.gov)

## Chapter Notes

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