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Early-Onset Familial Alzheimer Disease – RETIRED CHAPTER, FOR HISTORICAL REFERENCE ONLY

Synonym: EOFAD

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Summary

NOTE: THIS PUBLICATION HAS BEEN RETIRED. THIS ARCHIVAL VERSION IS FOR HISTORICAL REFERENCE ONLY, AND THE INFORMATION MAY BE OUT OF DATE.

Clinical characteristics

Alzheimer disease (AD) is characterized by adult-onset progressive dementia associated with cerebral cortical atrophy, beta-amyloid plaque formation, and intraneuronal neurofibrillary tangles. AD typically begins with subtle memory failure that becomes more severe and is eventually incapacitating. Other common findings include confusion, poor judgment, language disturbance, agitation, withdrawal, hallucinations, seizures, Parkinsonian features, increased muscle tone, myoclonus, incontinence, and mutism. Familial AD (FAD) characterizes families that have more than one member with AD and usually implies multiple affected persons in more than one generation. Early-onset FAD (EOFAD) refers to families in which onset is consistently before age 60 to 65 years and often before age 55 years.

Diagnosis/testing

EOFAD is diagnosed in families with multiple affected individuals with mean age of onset before 65 years and/or with a documented pathogenic variant in one of the genes known to be associated with EOFAD. The three clinically indistinguishable subtypes of EOFAD based on the underlying genetic mechanism are: Alzheimer disease type 1 (AD1), caused by mutation of *APP* (10%-15% of EOFAD); Alzheimer disease type 3 (AD3), caused by mutation of *PSEN1*, (30%-70% of EOFAD); and Alzheimer disease type 4 (AD4), caused by mutation of *PSEN2* (<5% of EOFAD). Kindreds with autosomal dominant EOFAD with no identifiable pathogenic variants in *PSEN1*, *PSEN2*, or *APP* have been described; thus, it is likely that variants in additional genes are causative.

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Management

Treatment of manifestations: Supportive; symptoms of depression, aggression, sleep disturbance, seizures, and hallucinations are managed on an individual basis; affected individuals eventually require assisted living/nursing home care; agents that increase cholinergic activity, such as Aricept® (donepezil), Exelon® (rivastigmine), and Reminy® (galatamine), show modest but variable benefit; memantine, an NMDA receptor antagonist, is approved for use in AD; physical and occupational therapy help manage activities of daily living.

Surveillance: Monthly monitoring to identify and manage secondary complications.

Agents/circumstances to avoid: Sudden changes in environment; over-sedation.

Genetic counseling

EOFAD is inherited in an autosomal dominant manner. Most individuals with EOFAD had an affected parent; occasionally, neither parent is identified as having had the disease, but a second-degree relative (e.g., an uncle, aunt, and/or grandparent) has or had EOFAD. Each child of an individual with EOFAD has a 50% chance of inheriting the pathogenic variant and developing EOFAD. Prenatal testing for pregnancies at increased risk for is possible if the pathogenic variant in the family is known; however, prenatal testing for adult-onset disorders is uncommon.

Diagnosis

Clinical Diagnosis

Alzheimer disease (AD) (see Alzheimer Disease Overview) is diagnosed in individuals with the following:

- Adult-onset slowly progressive dementia
- Absence of other causes of dementia
- Cerebral cortical atrophy by neuroimaging studies
- Beta-amyloid neuritic plaques and intraneuronal neurofibrillary tangles at post-mortem examination (see diagnostic criteria, National Institute on Aging Working Group [1998]).

Early-onset familial Alzheimer disease (EOFAD) is diagnosed in families that have more than one member with AD (usually multiple affected persons in more than one generation) in which the age of onset is consistently before age 60 to 65 years and often before age 55 years.

Molecular Genetic Testing

Genes. Pathogenic variants in three genes are known to be associated with early-onset familial Alzheimer disease:

- ***PSEN1.*** Pathogenic variants are associated with Alzheimer disease type 3 (AD3) [Larner & Doran 2006], which accounts for 30%-70% of EOFAD [Cruts & Van Broeckhoven 1998, Campion et al 1999, Rogaeva et al 2001, Lleó et al 2002, Janssen et al 2003].
- ***APP.*** Pathogenic variants are associated with Alzheimer disease type 1 (AD1) [Van Broeckhoven 1995], which accounts for no more than 10%-15% of EOFAD [Campion et al 1999].
- ***PSEN2.*** Pathogenic variants are associated with Alzheimer disease type 4 (AD4), which accounts for less than 5% of all EOFAD. AD4 has been identified in a few families (most are of Volga German ancestry) living in the United States, in three Italian kindreds [Bird et al 1988], in two Italian kindreds [Finckh et al 2000, Marcon et al 2004], and in two Spanish families [Beyer et al 1998, Lleó et al 2001].

Other loci. Kindreds with autosomal dominant EOFAD who have no identifiable pathogenic variants in *PSEN1*, *PSEN2*, or *APP* have been described; thus, it is likely that variants in additional genes are causative [Cruts et al 1998, Janssen et al 2003].

PSEN1

- **Targeted analysis for pathogenic variants.** A 4555-bp deletion spanning exon 9 is found in the Finnish population [Crook et al 1998, Prihar et al 1999, Verkkoniemi et al 2000]; this variant is rarely observed in other populations.
- **Sequence analysis** of the coding region and associated intronic regions detects pathogenic missense variants known to result in EOFAD. This method also detects pathogenic splice site variants that result in transcripts lacking exon 9 [Perez-Tur et al 1995].
- **Deletion/duplication analysis** for screening the entire gene to detect rare exon or whole-gene deletions [Smith et al 2001]. This testing can also detect the 4555-bp deletion in the Finnish population.

APP

- **Sequence analysis/scanning for pathogenic variants.** All pathogenic variants, except for rare duplications (see following bullet), are only known to occur in exons 16 and 17. Most variants are missense or nonsense; one indel is reported (Table 2). Sequence analysis is often limited to these exons because they encode the proteolytically cleaved A-beta peptide (see Molecular Genetics, ***APP***). For this reason, laboratories sequencing only exons 16 and 17 may be listed as sequencing select exons or as sequencing the entire coding region; contacting the laboratory directly is advised.
- **Deletion/duplication analysis** (including FISH analysis). Duplication of *APP* represents fewer than 1% of *APP* pathogenic variants [Rovelet-Lecrux et al 2006].

PSEN2

- **Sequence analysis** of the coding region detects pathogenic missense variants known to cause EOFAD.

Table 1. Genetic Testing Used in Early-Onset Familial Alzheimer Disease

Gene [1]	Proportion of EOFAD Attributed to Pathogenic Variants in Gene	Method	Pathogenic Variants Detected [2]	Variant Detection Frequency by Gene & Method [3]
PSEN1	30%-70% [4]	Targeted analysis for pathogenic variants	4555-bp deletion of exon 9 (Finnish founder variant) [5]	100% for the targeted variant
		Sequence analysis [6]	Sequence variants	~98%
		Deletion/duplication analysis [7]	Partial- and whole-gene deletions, including exon 9 Finnish founder deletion	100% for deletions, which are rare
APP	10%-15%	Sequence analysis [6] / scanning [8] of exons 16 and 17 for pathogenic variants	Sequence variants in exons 16 and 17	99%
		Deletion/duplication analysis [7]	Partial- and whole-gene duplications	100% for the targeted duplication

Table 1. continued from previous page.

Gene [1]	Proportion of EOFAD Attributed to Pathogenic Variants in Gene	Method	Pathogenic Variants Detected [2]	Variant Detection Frequency by Gene & Method [3]
PSEN2	<5%	Sequence analysis [6]	Sequence variants	~100%

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants.
3. The ability of the test method used to detect a variant that is present in the indicated gene
4. The highest yield for identification of a pathogenic variant in *PSEN1* is for persons with early-onset (age <60 years) AD who have another affected family member (especially a parent) with early-onset AD [Rogaeva et al 2001, Lleó et al 2002, Janssen et al 2003, Tedde et al 2003].
5. Finnish population; this variant is rarely observed in other populations.
6. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
7. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
8. Sequence analysis and scanning for pathogenic variants can have similar variant detection frequencies; however, variant detection frequencies for scanning may vary considerably among laboratories depending on the specific protocol used.

In one affected individual, a *PSEN1* pathogenic variant was identified in peripheral lymphocyte DNA; however, her clinical presentation was distinct from that of her affected deceased mother whose diagnosis was based on post-mortem neuropathology. Follow up studies demonstrated that the mother had somatic mosaicism for the *PSEN1* variant; using sequence analysis, the variant was detected in cerebral cortex DNA but not in peripheral lymphocyte DNA [Beck et al 2004].

Testing Strategy

Confirming/establishing the diagnosis in a proband requires molecular genetic testing to identify a pathogenic variant in one of the three genes known to be associated with EOFAD.

- When the family history is positive for early-onset AD:
  - First perform sequence analysis of *PSEN1*, the gene most commonly associated with EOFAD. If the affected individual is of Finnish ancestry, targeted analysis for pathogenic variants of *PSEN1* can be performed first.
  - If no pathogenic variant is identified, perform sequence analysis of exons 16 and 17 of *APP* and all of *PSEN2*.

    Note: Duplication analysis of APP and of PSEN1 need only be done if the goal is to test for even the rarest pathogenic variants.
- In simplex cases (i.e., a single occurrence in a family) the testing strategy is similar, but the likelihood of finding a pathogenic variant is relatively low (~6% in the study by Lleó et al [2002]). However, the likelihood of finding a pathogenic variant in a simplex case increases as age of onset decreases, especially in those with onset before age 50 years.

Note: Pathogenic variant detection frequency is low in persons with late-onset AD regardless of family history. Ninety percent of persons with *PSEN1* pathogenic variants have onset before age 60 years.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the pathogenic variant in the family.

Prenatal testing and preimplantation genetic testing for at-risk pregnancies require prior identification of the pathogenic variant in the family.

Clinical Characteristics

Clinical Description

Alzheimer disease (AD) typically begins with subtle and poorly recognized failure of memory [Godbolt et al 2004, Ringman et al 2005]. Slowly, over a period of years, the memory loss becomes more severe and is eventually incapacitating. Other common symptoms include confusion, poor judgment, language disturbance, agitation, withdrawal, and hallucinations. Some individuals may develop seizures, Parkinsonian features, increased muscle tone, myoclonus, incontinence, and mutism [Cummings et al 1998]. Death usually results from general inanition, malnutrition, and pneumonia.

AD3 (*PSEN1* pathogenic variants). Age of onset is usually in the 40s or early 50s. Onset in the 30s and early 60s has been reported. Onset after age 65 years is thought to be rare. Relatively rapid progression over six to seven years is common and the disease is often associated with seizures, myoclonus, and language deficits [Fox et al 1997, Gustafson et al 1998, Menéndez 2004]. Several families have had associated spastic paraplegia with "cotton wool" amyloid plaques [Crook et al 1998, Brooks et al 2003, Ataka et al 2004, Hattori et al 2004, Raman et al 2007].

The APOE e4 allele may influence age of onset [Wijsman et al 2005] (see Alzheimer Disease Overview).

CSF Aβ42 levels have been reported to be low in presymptomatic persons with *PSEN1* variants [Moonis et al 2005].

PET scans with Pittsburgh compound-B show early amyloid deposition in the striatum in persons with *PSEN1* variants [Klunk et al 2007].

AD4 (*PSEN2* pathogenic variants). AD4 has a wider range of onset age than either AD1 or AD3. The onset ranges from age 40 to 75 years with a few instances of non-penetrance after age 80 years [Bird et al 1996]. Mean duration of disease is 11 years. Jayadev et al [2010] have reviewed the clinical, pathologic, and genetic aspects of families with variants of *PSEN2*.

The APOE e4 allele influences age of onset (see Alzheimer Disease Overview) [Wijsman et al 2005].

AD1 (*APP* pathogenic variants). The dementia observed in families with *APP* variants is typical of AD. Age of onset is usually in the 40s and 50s (occasionally 60s). A few individuals have neuronal Lewy body inclusions in addition to plaques and tangles [Revesz et al 1997].

Homozygosity for the APOE e4 allele may be associated with younger age of onset (see Alzheimer Disease Overview).

Biomarkers. Bateman et al [2012] identified biomarker changes in individuals with a pathogenic variant in *APP*, *PSEN1*, or *PSEN2* ten to 20 years prior to the onset of symptoms including amyloid deposition on PET imaging, decreased CSF beta-amyloid and increased CSF tau.

Neuropathology. Mutation of *PSEN1* (AD1) or *PSEN2* (AD4) results in excessive brain deposition of amyloid-β [Mann et al 1997] associated with neurofibrillary tangles and amyloid angiopathy. Lewy body pathology is also common [Leverenz et al 2006]. A wide range in severity of AD pathology may be seen [Maarouf et al 2008, Jayadev et al 2010].

Genotype-Phenotype Correlations

PSEN1

- Pathogenic variants in transmembrane loops 2, 4, and 6 of *PSEN1* account for some differences in age of onset and duration between those with pathogenic variants of *PSEN1* and of *PSEN2* [Lippa et al 2000].
- A frontotemporal type of dementia with personality and behavioral changes has been associated with the pathogenic variants p.Leu113Pro [Raux et al 2000] and p.Val89Leu [Queralt et al 2002] PSEN1 proteins.
- Psychiatric symptoms at onset have been described in families with the pathogenic variants p.Leu392Pro and p.Met139Val PSEN1 proteins [Tedde et al 2000, Rippon et al 2003].
- Deletion of exon 9 in *PSEN1* is associated with early spastic paraparesis [Crook et al 1998, Verkkoniemi et al 2000, Brooks et al 2003].
- Gómez-Isla et al [1999] have correlated the neuropathologic features of amyloid plaques and neurofibrillary tangle formation with various *PSEN1* variants.
- Very early onset (mean age 30 years) with additional Lewy body pathology has been associated with the pathogenic variants p.Met233Val and p.Tyr256Ser PSEN1 proteins [Miklossy et al 2003].
- Two *PSEN1* variants have been associated with pathologic changes of Pick's disease: c.548G>T and c.436A>C [Dermaut et al 2004, Halliday et al 2005].
- Later-onset FAD (50s-70s) has been associated with the pathogenic variants p.Ala79Val and p.Arg269His PSEN1 proteins [Brickell et al 2007, Kauwe et al 2007, Larner et al 2007].
- Purkinje cell loss in the cerebellum has been reported with the p.Ser170Phe variant in *PSEN1* [Piccini et al 2007].

APP

- The combination of cerebral hemorrhage and presenile dementia is caused by the p.Ala692Gly variant in *APP* [Roks et al 2000].
- Di Fede et al [2009] reported that the p.Ala673Val variant in *APP* only causes disease in the homozygous state; therefore, inheritance is autosomal recessive. This variant is at the site where BACE1 cleaves the APP protein, part of the process that produces the β-amyloid peptide. Giaccone et al [2010] reported neuropathologic findings in a member of this family that included severe, typical plaque and tangle deposits of AD as well as β-amyloid deposition in the cerebellum.
- The p.Glu693Gly pathogenic variant (the "Arctic" variant) in *APP*, present in a Swedish family, is associated with enhanced β amyloid protofibril formation [Nilsberth et al 2001] and marked congophilic angiopathy [Basun et al 2008].
- EOFAD has been associated with *APP* locus duplication [Rovelet-Lecrux et al 2006]. Amyloid angiopathy [Sleegers et al 2006] and Lewy body pathology [Guyant-Marechal et al 2008] have been noted in single families with an *APP* duplication.

Penetrance

AD3 (*PSEN1* pathogenic variants). Penetrance is complete by age 65 years, except for occasional later onset associated with the variants p.Ala79Val and p.Arg269His [Brickell et al 2007, Kauwe et al 2007, Larner et al 2007].

AD4 (*PSEN2* pathogenic variants). Penetrance is approximately 95%. In rare instances, individuals with *PSEN2* variants who are older than age 80 years have no manifestations of AD.

Anticipation

Anticipation has not been documented.

Prevalence

Campion et al [1999] found a prevalence of early-onset AD of 41.2 per 100,000 for the population at risk (i.e., persons aged 40-59 years).

- Sixty-one percent of individuals with early-onset AD had a positive family history and 13% had affected individuals in three generations [Campion et al 1999].
- EOFAD comprises less than 3% of all AD.
- Some families with Volga German ancestry have a founder variant in *PSEN2* (c.422A>T) that has been reported in modern Germany [Nikisch et al 2008, Jayadev et al 2010, Yu et al 2010].
- Among families with EOFAD, 40%-80% have a pathogenic variant in *APP*, *PSEN1*, or *PSEN2* (*PSEN1* being the most common) [Janssen et al 2003, Kowalska et al 2003, Tedde et al 2003]. The frequency of such variants in simplex cases (i.e., a single occurrence in a family) of early-onset AD in the 50s is not well documented, but is apparently low (<5%); the frequency is higher in those with onset before age 50 years.
- *APP* duplication is quite rare, having been found in none of 141 persons with EOAD (75 familial) screened in Sweden and Finland [Blom et al 2008].
- *PSEN1* pathogenic variants have been reported in Japanese [Furuya et al 2003, Hattori et al 2004], African American [Rippon et al 2003], and Black African [Heckmann et al 2004] families. The founder variant p.Ala431Glu has been reported in Mexican families [Yescas et al 2006], the founder variant p.Glu280Ala in Colombian families [Pastor et al 2003], and the founder variant c.839A>C in Caribbean Hispanics [Athan et al 2001].

Genetically Related (Allelic) Disorders

***PSEN1* and *PSEN2*.** One study has found mutation of *PSEN1* and *PSEN2* in families with dilated cardiomyopathy only [Li et al 2006].

***APP*.** Another phenotype associated with mutation of *APP* is cerebral hemorrhagic amyloidosis of the Dutch type, a disorder in which dementia and brain amyloid plaques are uncommon. This disorder results from a p.Glu693Gly mutated protein.

Differential Diagnosis

Approximately 75% of individuals with Alzheimer disease (AD) have no family history of AD and approximately 25% of individuals with AD can be divided into several genetic subgroups. Familial cases appear to have the same phenotype as nonfamilial cases both clinically and pathologically and thus are distinguished only by a positive family history (see Alzheimer Disease Overview). Occasionally, cases of early-onset AD may occur in families with generally late-onset disease [Brickell et al 2006].

Other genetic causes of early-onset dementia include forms of frontotemporal dementia (e.g., frontotemporal dementia with parkinsonism-17 [FTDP-17], inclusion body myopathy with Paget disease of bone and/or frontotemporal dementia [IBMPFD], *PGRN*-related frontotemporal dementia, *CHMP2B*-related frontotemporal dementia, amyotrophic lateral sclerosis [ALS] with frontotemporal dementia [see ALS Overview]), Huntington disease, prion diseases, CADASIL, and other rare neurodegenerative disorders.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with early-onset familial Alzheimer disease (EOFAD), the following evaluations are recommended if they have not already been completed:

- History (especially first symptoms, duration, progression). In particular, onset before age 45 years may indicate more rapid progression.
- Examination (especially mental status)
- MRI, PET. Severe cortical atrophy on MRI or marked metabolic deficits on PET imaging suggest more advanced disease.

Treatment of Manifestations

The mainstay of treatment is supportive and each symptom is managed on an individual basis [Clare 2002]. In general, affected individuals eventually require assisted living arrangements or nursing home care.

Although the exact biochemical basis of Alzheimer disease is not well understood, it is known that deficiencies of the brain cholinergic system and of other neurotransmitters are present. Agents that increase cholinergic activity, such as tacrine cholinesterase inhibitors, are approved for treatment and show modest but variable benefit. Aricept® (donepezil), Exelon® (rivastigmine), and Reminyl® (galatamine) are such drugs [Rogers et al 1998, Farlow et al 2000, Raskind et al 2000, Feldman et al 2001, Mohs et al 2001, Seltzer et al 2004].

Memantine, an NMDA receptor antagonist, has also been approved for use in AD [Reisberg et al 2003].

Medical and behavioral management of depression, aggression, sleep disturbance, seizures, and hallucinations is required. Depression and seizures should be treated with appropriate medications.

Physical and occupational therapy can be helpful to manage problems with gait and activities of daily living.

Surveillance

Monthly surveillance to identify and manage secondary complications is indicated.

Agents/Circumstances to Avoid

Sudden changes in environment and over-sedation should be avoided.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Nonsteroidal anti-inflammatory drugs (NSAIDs), lipid-lowering agents, vitamin E, beta secretase inhibitors and β amyloid "vaccination" are being investigated as possible therapeutic agents for AD [Lahiri et al 2003]. None of these pharmacologic treatments has been systematically evaluated in individuals with EOFAD.

An amyloid vaccination immunization trial of Aβ42 in late-onset AD was stopped because encephalitis developed in 6% of the subjects [Holmes et al 2008].

A treatment trial of an anti-Aβ monoclonal antibody showed no significant differences when primary efficacy was analyzed [Salloway et al 2009].

A treatment trial with a gamma secretase inhibitor (tarenflurbil) showed no efficacy [Green et al 2009].

Retrospective studies of NSAIDs have been mixed, showing possible protective effects [Vlad et al 2008] and no protective effects [Breitner et al 2009].

Search Clinical Trials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

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.

Mode of Inheritance

Early-onset familial Alzheimer disease (EOFAD) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed as having 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 the disease, but a second-degree relative (e.g., an uncle, aunt, and/or grandparent) has or had EOFAD.
- A proband with EOFAD may have the disorder as the result of a *de novo* pathogenic variant, although this has not been documented.

Note: Although most individuals diagnosed with EOFAD have an affected parent, the family history 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 penetrance.

Sibs of a proband

- The risk to sibs depends on the genetic status of the parents.
- If a parent of the proband was affected or had a pathogenic variant, the risk to sibs of having inherited the variant is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.

Offspring of a proband. Offspring have a 50% chance of inheriting the altered gene.

Other family members of a proband. The risk to other family members depends on the genetic status of the proband's parents. If a parent was affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition had the pathogenic variant, it is likely that the proband has a *de novo* variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk of developing EOFAD.

Testing of at-risk asymptomatic adults. Testing of at-risk asymptomatic adults for EOFAD is possible for *PSEN1* (presenilin-1), *PSEN2* (presenilin-2), and *APP* pathogenic variants. Such testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. When testing at-risk individuals, an affected family member should be tested first to confirm the molecular diagnosis in the family. The identification of a pathogenic variant in an at-risk individual with equivocal symptoms does not prove or even imply that the questionable symptoms are related to the presence of the variant.

Testing for the pathogenic variant in the absence of definite symptoms of the disease is considered predictive testing.

At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Others may have different motivations including simply the "need to know." Testing of asymptomatic at-risk adult family members usually involves pre-test interviews in which the motives for requesting the test, the individual's knowledge of EOFAD, the possible impact of positive and negative test results, and neurologic status are assessed. Those seeking testing should be counseled regarding possible problems that they may encounter with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members. Informed consent for such testing is recommended and adequate procedures should be followed to safeguard confidentiality of test results and to ensure arrangements for long-term follow up and evaluations. In a study of 21 individuals at risk for EOFAD or *MAPT*-related disorders, Steinbart et al [2001] reported that most individuals undergoing **presymptomatic** testing demonstrated effective coping skills; long-term effects, however, are unknown.

Testing of at-risk individuals during childhood. Consensus holds that individuals at risk for adult-onset disorders should not have testing during childhood in the absence of symptoms. The principal arguments against testing asymptomatic individuals during childhood are that it removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it may have serious educational and career implications. See also 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic testing and embryo transfer have been successfully used to achieve a pregnancy in a 30-year-old asymptomatic woman with an *APP* pathogenic variant, resulting in the birth of a healthy child who does not have the *APP* pathogenic variant identified in the mother and her family [Verlinsky et al 2002]. Towner & Loewy [2002] and Spriggs [2002] identify some of the ethical issues arising from the decisions of parents and health care providers.

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

  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

  www.nia.nih.gov/alzheimers

- **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

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

  Alzheimer Disease

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Early-Onset Familial Alzheimer Disease : Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
APP	21q21.3	Amyloid-beta A4 protein	Alzheimer Disease & Frontotemporal Dementia Mutation Database (APP) APP database	APP	APP
PSEN1	14q24.2	Presenilin-1	alsod/PSEN1 genetic mutations Alzheimer Disease & Frontotemporal Dementia Mutation Database (PSEN1) PSEN1 database	PSEN1	PSEN1
PSEN2	1q42.13	Presenilin-2	Alzheimer Disease & Frontotemporal Dementia Mutation Database (PSEN2) PSEN2 database	PSEN2	PSEN2

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Early-Onset Familial Alzheimer Disease (View All in OMIM)

104300	ALZHEIMER DISEASE; AD
104311	PRESENILIN 1; PSEN1
104760	AMYLOID BETA A4 PRECURSOR PROTEIN; APP
600759	PRESENILIN 2; PSEN2
606889	ALZHEIMER DISEASE 4
607822	ALZHEIMER DISEASE 3; AD

APP

Gene structure. *APP* has 19 exons and encodes a large precursor protein of 695-770 amino acids that is proteolytically cleaved to form A-beta peptide. Alternative *APP* transcripts are often designated by the number of amino acids they encode, e.g., APP770 transcript or NM_000484.2. The A-beta peptide portion is encoded by parts of exons 16 and 17; these exons encode codons 655-737. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. The most common *APP* pathogenic variant is p.Val717Ile. Substitutions of phenylalanine and glycine may also occur at this codon. A two-nucleotide indel (insertion and deletion) in exon 16 (c.2010_2011delinsTC) produces the so-called Swedish variant (see Table 2).

APP duplication has been reported in a few families (see Genotype-Phenotype Correlations).

Table 2. Selected *APP* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.2149G>A	p.Val717Ile	NM_000484.2 NP_000475.1
c.2010_2011delinsTC	p.Lys670_Met671delinsAsnLeu	
c.2075C>G	p.Ala692Gly [1]	
c.2018C>T	p.Ala673Val [1]	
c.2078A>G [2]	p.Glu693Gly [1, 2]	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Genotype-Phenotype Correlations.
2. Pathogenic variant associated with cerebral hemorrhagic amyloidosis of the Dutch type

Normal gene product. The protein encoded for by *APP*, amyloid-β A4 protein, contains 695 to 770 amino acids and undergoes alternative splicing. A 57-amino-acid portion is homologous to Kunitz-type protease inhibitors. The major transcripts in peripheral tissues are the APP751 and APP770 variants. The A-beta peptide contains 38 to 42 amino acids and resides in the transmembrane domain of the protein. Amyloid-β A4 protein may be cleaved by an alpha secretase within the amyloid-β peptide sequence, thus eliminating the possibility of amyloid-β accumulation. However, amyloid-β A4 may also be cleaved by beta and gamma secretases that result in the accumulation of amyloid-β peptide.

Abnormal gene product. Imbalance in cleavage produces excess of longer amyloid beta peptide isoforms that are neurotoxic and prone to self-aggregation.

PSEN1

Gene structure. The coding region is composed of ten exons numbered 3 through 12. Exon 8 and part of exon 3 are alternatively spliced, so shorter isoforms of the protein are predicted to exist. Alternative splicing may also introduce a new exon between exons 10 and 11. *PSEN1* and *PSEN2* are highly homologous. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 40 pathogenic variants that result in EOFAD have been described in more than 50 families [Cruts et al 1998, Cruts & Van Broeckhoven 1998, Poorkaj et al 1998, Larner & Doran 2006]. The majority are missense variants. One exception is a variant eliminating a splice site in which exon 9 is lost but the reading frame is unaltered and the protein is predicted to be 29 amino acids shorter. A genomic deletion spanning exon 9 is also found in the Finnish population. At least nine pathogenic variants occur in a cytosolic domain between transmembrane domains 6 and 7 and the rest of the variants are within the other hydrophobic domains or immediately at the hydrophilic/hydrophobic junctions, especially of transmembrane domain 2. The relative frequency of pathogenic variants in the cytosolic domain encoded by the alternatively spliced exon 8 suggests that this region of the protein is functionally important (see Table 3).

Table 3. Selected *PSEN1* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.236C>T	p.Ala79Val [1]	NM_000021.3 NP_000012.1
c.265G>T	p.Val89Leu [1]	
c.338T>C	p.Leu113Pro [1]	
c.415A>G	p.Met139Val [1]	
c.436A>C	p.Met146Leu	

Table 3. continued from previous page.

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.509C>T	p.Ser170Phe [1]	
c.548G>T	p.Gly183Val	
c.697A>G	p.Met233Val [1]	
c.767A>C	p.Tyr256Ser [1]	
c.806G>A	p.Arg269His [1]	
c.839A>C	p.Glu280Ala [2]	
c.1175T>C	p.Leu392Pro [1]	
c.1292C>A	p.Ala431Glu	
4,555-bp deletion of exon 9	See footnotes 1 and 3	

Note on variant classification: Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Genotype-Phenotype Correlations.
2. See Prevalence.
3. Prihar et al [1999]

Normal gene product. *PSEN1* is predicted to encode a 467-amino acid protein with between seven and ten (probably eight) hydrophobic transmembrane domains. The presenilin-1 protein is highly homologous to the presenilin-2 protein; the regions of greatest divergence are between the two large hydrophilic loops, one at the amino terminal end and the other in the cytosolic domain between the sixth and seventh transmembrane domains [Tandon & Fraser 2002]. This cytosolic domain contains a proteolytic cleavage site [Podlisny et al 1997]. The protein is a functional homolog of SEL-12, a *C elegans* protein that facilitates signaling mediated by the Notch/LIN-12 receptor family [Wong et al 1997]. The protein acts as part of the gamma secretase cleavage system for amyloid-β A4 protein. *PS1* knockout mice die in utero and have severe skeletal abnormalities [Shen et al 1997]. The presenilins cleave other proteins in addition to amyloid-β A4 protein [Thinakaran & Parent 2004].

Abnormal gene product. Abnormal *PSEN1* results in increased production of the longer isoforms of amyloid-β peptide, which are neurotoxic and prone to self-aggregation [Jankowsky et al 2004]. Some pathogenic variants may result in loss of the gamma secretase function of presenilin-1 [De Strooper 2007, Shen & Kelleher 2007].

PSEN2

Gene structure. *PSEN2* is highly homologous to *PSEN1*. It includes 12 exons with ten coding exons in a genomic region spanning 23,737 bp. The first two exons encode the 5' untranslated region. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. A single variant (p.Asn141Ile) has been found in several Volga German FAD pedigrees, confirming the founder effect in this population. Another pathogenic variant (p.Met239Val) has been reported in an Italian kindred with FAD [Rogaev et al 1995, Marcon et al 2004] (see Table 4). A few additional and possibly pathogenic variants have been reported [Beyer et al 1998, Cruts & Van Broeckhoven 1998, Tedde et al 2003, Zekanowski et al 2003].

Table 4. Selected *PSEN2* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.422A>T	p.Asn141Ile [1]	NM_000447.2 NP_000438.2
c.717G>A	p.Met239Val	

Note on variant classification: Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Prevalence.

Normal gene product. *PSEN2* is predicted to encode a 448-amino acid protein that is highly homologous to the presenilin-1 protein. The presenilin-2 protein is also thought to contain eight transmembrane domains. The regions of greatest divergence between the two proteins are at the amino terminal end and in the cytosolic domain between the sixth and seventh transmembrane domains [Uemura et al 2003, Thinakaran & Parent 2004].

Abnormal gene product. Presumably similar to that noted for *PSEN1* pathogenic variants [Jankowsky et al 2004, Walker et al 2005, De Strooper 2007]

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Suggested Reading

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Chapter Notes

Revision History

- 13 September 2018 (ma) Chapter retired: covered in Alzheimer Disease Overview
- 18 October 2012 (tb) Revision: changes in biomarkers identified in individuals with mutations associated with EOFAD
- 2 August 2012 (tb) Revision: additional information about *APP* mutation p.Ala673Val
- 23 December 2010 (me) Comprehensive update posted live

- 28 April 2009 (tb) Revision: FISH testing available clinically for duplications in *APP*
- 2 October 2007 (me) Comprehensive update posted live
- 26 April 2007 (tb) Revision: sequence analysis for AD1 (APP mutations) clinically available
- 12 February 2007 (tb) Revision: clinical testing for APP mutations no longer available
- 19 September 2005 (me) Comprehensive update posted live
- 15 September 2003 (tb) Revision: clinical testing for APP available
- 7 August 2003 (me) Comprehensive update posted live
- 20 June 2001 (ca) Comprehensive update posted live
- 24 September 1999 (pb) Review posted live
- Spring 1996 (tb) Original submission

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