GENEReviews

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Early-Onset Familial Alzheimer Disease

[*EOFAD. Includes: Alzheimer Disease Type 1 (AD1), Alzheimer Disease Type 3 (AD3), Alzheimer Disease Type 4 (AD4)*]

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Summary

Disease 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 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 disease-causing mutation 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 mutations in *APP* (10%-15% of EOFAD); Alzheimer disease type 3 (AD3), caused by mutations in *PSEN1,* (30%-70% of EOFAD); and Alzheimer disease type 4 (AD4), caused by mutations in *PSEN2* (<5% of EOFAD). Kindreds with autosomal dominant EOFAD with no identifiable mutations in *PSEN1, PSEN2,* or *APP* have been described; thus, it is likely that mutations in other genes are causative. Molecular genetic testing for *PSEN1*, *PSEN2*, and *APP* is available in clinical laboratories.

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 to therapy help manage activities of daily living. *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 mutation and developing EOFAD. Prenatal testing for pregnancies at increased risk for a *PSEN1* mutation is available. Prenatal testing for pregnancies at increased risk for a *PSEN2* or *APP*

mutation may be available through laboratories offering custom prenatal testing; however, prenatal testing for adult-onset disorders is unusual.

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 in Consensus Report 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

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. The following are the three genes known to be associated with early-onset familial Alzheimer disease:

PSEN1

- Mutations are associated with Alzheimer disease type 3 (AD3) [Larner & Doran 2005].
- AD3 accounts for 30%-70% of EOFAD [Cruts & Van Broeckhoven 1998, Campion et al 1999, Rogaeva et al 2001, Lleo et al 2002, Janssen et al 2003].

PSEN2

- Mutations are associated with Alzheimer disease type 4 (AD4).
- *PSEN2* 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, Lleo et al 2001].
- Mutations in *PSEN2* account for less than 5% of all EOFAD.

APP

- Mutations are associated with Alzheimer disease type 1 (AD1) [Van Broeckhoven 1995].
- AD1 accounts for no more than 10%-15% of EOFAD [Campion et al 1999].

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

Clinical testing

PSEN1

- **Targeted mutation analysis.** A mutation found in the Finnish population results in the deletion of exon 9 [Crook et al 1998, Verkkoniemi et al 2000]; this mutation is rarely observed in other populations.
- **Sequence analysis and mutation scanning** of the *PSEN1* gene are available on a clinical basis.

  Note: (1) Mutation detection frequency is low in persons with late-onset AD regardless of family history. Ninety percent of persons with *PSEN1* mutations have onset before age 60 years. (2) In one study [Lleo et al 2002] 1/16 (6.2%) of individuals with early-onset AD with no family history of AD had a *PSEN1* mutation. One individual with somatic mosaicism for a *PSEN1* mutation has been reported [Beck et al 2004].

PSEN2

- **Sequence analysis and mutation scanning** of the *PSEN2* gene are available on a clinical basis.

APP

- **Sequence analysis** for exons 16 and 17 of the *APP* gene is available clinically on a limited basis.

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Proportion of EOFAD Attributed to Mutations in This Gene	Mutation Detection Frequency [1]	Test Availability
Targeted mutation analysis	Deletion of exon 9 in *PSEN1*	30%-70% [2]	~2%	Clinical Testing
Sequence analysis and mutation scanning	*PSEN1* sequence variants		~98%	
	PSEN2 sequence variants	<5%	~100%	Clinical Testing
Sequence analysis	*APP* sequence variants in exons 16 and 17	10%-15%	~100%	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by test method and gene
2. The highest yield for identification of a mutation in the *PSEN1* gene 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, Lleo et al 2002, Janssen et al 2003, Tedde et al 2003]

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Establishing the diagnosis in a proband requires molecular genetic testing to identify a disease-causing mutation in one of the three genes known to be associated with EOFAD. *PSEN1* testing should be done first because it is the most common causative gene.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the disease-causing mutation in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

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

***APP*.** Another phenotype associated with mutations in *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 mutation.

Clinical Description

Natural History

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 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* mutations). 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, Menendez et al 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* mutations [Moonis et al 2005].

PET scans with PiB show early amyloid deposition in the striatum in persons with *PSEN1* mutations [Klunk et al 2007].

AD4 *(PSEN2* mutations). 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.

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

AD1 *(APP* mutations). The dementia observed in families with *APP* mutations 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).

Neuropathology. Mutations in *PSEN1* (AD1) or *PSEN2* (AD4) result 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].

Genotype-Phenotype Correlations

- The combination of cerebral hemorrhage and presenile dementia is caused by a p.Ala692Gly mutation in *APP* [Roks et al 2000].
- Mutations in transmembrane loops 2, 4, and 6 account for some differences in age of onset and duration between *PSEN1* and *PSEN2* mutations [Lippa et al 2000].
- A frontotemporal type of dementia with personality and behavioral changes has been associated with the p.Leu113Pro [Raux et al 2000] and p.Val89Leu [Queralt et al 2002] mutations in *PSEN1*.
- Psychiatric symptoms at onset have been described in families with the p.Leu392Pro and p.Met139Val mutations in *PSEN1* [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].
- Gomez-Isla et al (1999) have correlated the neuropathologic features of amyloid plaques and neurofibrillary tangle formation with various *PSEN1* mutations.
- Very early onset (mean age: 30 years) with additional Lewy body pathology has been associated with the p.Met233Val and p.Tyr256Ser mutations in *PSEN1* [Miklossy et al 2003].
- The p.Glu693Gly mutation (the "Arctic" mutation) in *APP*, present in a Swedish family, is associated with enhanced β amyloid protofibril formation [Nilsberth et al 2001].
- Two *PSEN1* mutations have been associated with pathologic changes of Pick's disease: p.Gly183Val and p.Met146Leu [Dermaut et al 2004, Halliday et al 2005].
- EOFAD has been associated with *APP* locus duplication [Rovelet-Lecrux et al 2006].
- Later-onset FAD (50s-70s) has been associated with the p.Ala79Val mutation in *PSEN1* [Brickell et al 2007, Kauwe et al 2007].
- Purkinje cell loss in the cerebellum has been reported with the p.Ser170Phe mutation in *PSEN1* [Piccini et al 2007].

Penetrance

AD3 *(PSEN1* mutations). Penetrance is complete by age 65 years.

AD4 *(PSEN2* mutations). Penetrance is approximately 95%. In rare instances, individuals with *PSEN2* mutations 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.
- EOFAD comprises less than 3% of all AD.
- Among families with EOFAD, 40%-80% have a mutation in the *APP*, *PSEN1*, or *PSEN2* gene *(PSEN1* being the most common) [Janssen et al 2003, Kowalska et al 2003, Tedde et al 2003]. The frequency of such mutations in simplex cases of early-onset AD (i.e., a single occurrence in a family) is not well documented, but is apparently low (<5%).

PSEN1 mutations 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 mutation p.Ala431Glu has been reported in Mexican families [Yescas et al 2006] and the founder mutation p.Glu280Ala in Columbian families [Pastor et al 2003].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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:

- History (especially first symptoms, duration, progression)
- Family history
- Examination (especially mental status)
- Neuroimaging
- Exclusion of other causes (e.g. metabolic, infectious, psychiatric)

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.

Testing 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.

Search Clinical Trials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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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. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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* gene mutation, 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 disease-causing mutation, the risk to sibs of having inherited the mutation 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* mutation. When neither parent of a proband with an autosomal dominant condition had the disease-causing mutation, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or maternity (i.e., 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 clinically available for *PSEN1* (presenilin-1), *PSEN2* (presenilin-2), and *APP* mutations. 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 disease-causing mutation 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 mutation.

Testing for the disease-causing mutation 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 about 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 FTDP-17, Steinbart et al (2001) reported that most individuals undergoing **presymptomatic** testing demonstrated effective coping skills, but long-term effects 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 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 (Genetic Testing; pdf).

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk for a *PSEN1* mutation is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

No laboratories listed in the GeneTests Laboratory Directory offer molecular genetic testing for prenatal diagnosis for *PSEN2* or *APP* mutations. However, prenatal testing may be available for families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see Testing.

Requests for prenatal testing for typically adult-onset conditions such as EOFAD are not common. 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. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD). Preimplantation diagnosis and embryo transfer have been successfully used to achieve a pregnancy in a 30-year-old asymptomatic woman with an *APP* disease-causing mutation, resulting in the birth of a healthy child who does not have the *APP* disease-causing mutation 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.

Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Alzheimer Disease, Early-Onset Familial

Gene Symbol	Chromosomal Locus	Protein Name
APP	21q21	Amyloid beta A4 protein
PSEN1	14q24.3	Presenilin-1
PSEN2	1q31-q42	Presenilin-2

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Alzheimer Disease, Early-Onset Familial

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

Table C. Genomic Databases for Alzheimer Disease, Early-Onset Familial

Gene Symbol	Locus Specific	Entrez Gene	HGMD
APP	APP	351 (MIM No. 104760)	APP
PSEN1	PSEN1	5663 (MIM No. 104311)	PSEN1
PSEN2	PSEN2	5664 (MIM No. 600759)	PSEN2

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

APP

Normal allelic variants: The *APP* gene 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. The A-beta peptide portion is encoded by parts of exons 16 and 17.

Pathologic allelic variants: The most common *APP* mutation is p.Val717Ile. Substitutions of phenylalanine and glycine may also occur at this codon. A two-nucleotide alternation in exon 16 (c.2010G>T and c.2011A>C) produces the so-called Swedish mutation. (See Table 2.)

Table 2. *APP* Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence [1]
c.2149G>A	p.Val717Ile	NM_000484.2 NP_000475.1
c.2010G>T	p.Lys670Asn	
c.2011A>C	p.Met671Leu	
c.2075C>G	p.Ala692Gly	
c.2078A>G	p.Glu693Gly	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Reference sequence (www.ncbi.nlm.nih.gov/Genbank/index.html)

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

Normal allelic variants: 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. The *PSEN1* and *PSEN2* genes are highly homologous.

Pathologic allelic variants: More than 40 mutations 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 2005]. All but one mutation are missense mutations. The single exception is a mutation 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. At least nine mutations occur in a cytosolic domain between transmembrane domains 6 and 7 and the rest of the mutations are within the other hydrophobic domains or immediately at the hydrophilic/hydrophobic junctions, especially of transmembrane domain 2. The relative frequency of mutations in the cytosolic domain that is encoded by the alternatively spliced exon 8 suggests that this region of the protein is functionally important. (See Table 3.)

Table 3. *PSEN1* Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence [1]
c.236C>T	p.Ala79Val	NM_000021.2 NP_000012.1
c.265G>T	p.Val89Leu	
c.338T>C	p.Leu113Pro	
c.415A>G	p.Met139Val	
c.436A>C	p.Met146Leu	
c.509C>T	p.Ser170Phe	
c.548G>T	p.Gly183Val	
c.697A>G	p.Met233Val	
c.767A>C	p.Tyr256Ser	
c.839A>C	p.Glu280Ala	
c.1175T>C	p.Leu392Pro	
c.1292C>A	p.Ala431Glu	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Reference sequence (www.ncbi.nlm.nih.gov/Genbank/index.html)

Normal gene product: The *PSEN1* gene 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: The *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 mutations may result in loss of function of presenilin-1 [Shen & Kelleher 2007].

PSEN2

Normal allelic variants: *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.

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

Table 4. PSEN2 Allelic Variants Discussed in This GeneReview

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence [1]
c.422A>T	p.Asn141Ile	NM_000447.1 NP_000438.1
c.717G>A	p.Met239Val	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Reference sequence (www.ncbi.nlm.nih.gov/Genbank/index.html)

Normal gene product: The *PSEN2* gene 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 result as noted for *PSEN1* mutations [Jankowsky et al 2004, Walker et al 2005]

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Alzheimer's Association National Headquarters
225 North Michigan Avenue Fl 17
Chicago IL 60601-7633
Phone: 800-272-3900; 312-335-8700
Fax: 312-335-1110
Email: info@alz.org
www.alz.org

Alzheimer's Disease Education and Referral Center
PO Box 8250

Silver Spring MD 20907-8250
Phone: 800-438-4380; 301-495-3334
Fax: 301-495-3334
Email: adear@alzheimers.org
www.alzheimers.org

NCBI Genes and Disease
Alzheimer Disease

National Institute on Aging
Building 31 Room 5C27
31 Center Drive MSC 2292
Bethesda MD 20892
Phone: 301-496-1752
Email: karpf@nia.nih.gov
www.nia.nih.gov

National Library of Medicine Genetics Home Reference
Alzheimer Disease

Teaching Case-Genetic Tools
Cases designed for teaching genetics in the primary care setting.
Case 15. Cognitive Difficulties in a 45-Year-Old Man

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

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Suggested Readings

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Chapter Notes

Revision History

- 2 October 2007 (me) Comprehensive update posted to live Web site
- 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 to live Web site
- 15 September 2003 (tb) Revision: clinical testing for *APP* available
- 7 August 2003 (me) Comprehensive update posted to live Web site
- 20 June 2001 (ca) Comprehensive update posted to live Web site
- 24 September 1999 (pb) Review posted to live Web site

- Spring 1996 (tb) Original submission