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Ataxia with Oculomotor Apraxia Type 1

Synonym: AOA1

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Summary

Clinical characteristics

Ataxia with oculomotor apraxia type 1 (AOA1) is characterized by childhood onset of slowly progressive cerebellar ataxia, followed by oculomotor apraxia and a severe primary motor peripheral axonal motor neuropathy. The first manifestation is progressive gait imbalance (mean age of onset: 4.3 years; range: 2-10 years), followed by dysarthria, then upper-limb dysmetria with mild intention tremor. Oculomotor apraxia, usually noticed a few years after the onset of ataxia, progresses to external ophthalmoplegia. All affected individuals have generalized areflexia followed by a peripheral neuropathy and quadriplegia with loss of ambulation about seven to ten years after onset. Hands and feet are short and atrophic. Chorea and upper-limb dystonia are common. Intellect remains normal in some individuals; in others, different degrees of cognitive impairment have been observed.

Diagnosis/testing

The diagnosis of AOA1 is based on clinical findings (including family history) and exclusion of the diagnosis of ataxia-telangiectasia. Cerebellar atrophy is visible on MRI in all affected individuals. EMG reveals axonal neuropathy in 100% of individuals with AOA1. *APTX* is the only gene known to be associated with AOA1.

Management

Treatment of manifestations: May include physical therapy, particularly for disabilities resulting from peripheral neuropathy; a wheelchair for mobility, usually by age 15-20 years; educational support for difficulties with speaking, reading, and writing.

Prevention of secondary complications: High-protein diet to prevent edema by restoring serum albumin concentration; low-cholesterol diet.

Surveillance: Routine follow up with a neurologist.

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Genetic counseling

AOA1 is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being neither affected nor a carrier. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible if both pathogenic variants in a family have been identified.

Diagnosis

Suggestive Findings

Diagnosis of ataxia with oculomotor apraxia type 1 (AOA1) should be suspected in individuals with the following combination of clinical features and test results.

Clinical features

- Cerebellar ataxia, oculomotor apraxia, and areflexia followed by signs of severe peripheral neuropathy
- Childhood onset
- Slow progression leading to severe motor handicap
- Long survival [Barbot et al 2001]
- Absence of extraneurologic findings common in ataxia-telangiectasia (telangiectasias and immunodeficiency).
- Family history consistent with autosomal recessive inheritance

Test results

- **MRI.** Cerebellar atrophy is present in all affected individuals. A very few individuals also have brain stem atrophy.
- **EMG.** Signs of axonal neuropathy are found in 100% of individuals with AOA1. Note: Normal EMG results may be observed only in those investigated in the very early stages of the disease.
- **Laboratory findings** that can be used to confirm the diagnosis of AOA1 in a symptomatic person include [Barbot et al 2001, Le Ber et al 2003]:
  - **Serum concentration of albumin.** Serum concentration of albumin is decreased (<3.8 g/L) in 83% of individuals with disease duration of more than ten to 15 years.
  - **Serum concentration of total cholesterol.** Serum concentration of total cholesterol is increased (>5.6 mmol) in 68% of individuals with disease duration of more than ten to 15 years.
  - **Normal serum concentration of alpha-fetoprotein**
  - **Neuropathology.** Nerve biopsy confirms axonal neuropathy.

Establishing the Diagnosis

The diagnosis of AOA1 is established in a proband with the detection of biallelic pathogenic variants in *APTX* (see Table 1).

One genetic testing strategy is sequence analysis of *APTX*. If only one or no pathogenic variant is found, perform deletion/duplication analysis.

An alternative genetic testing strategy is use of a multigene panel that includes *APTX* and other genes of interest (see Differential Diagnosis). 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*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most

reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (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.

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

Table 1. Molecular Genetic Testing Used in AOA1

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant Detectable by Method
APTX	Sequence analysis [2]	Unknown [3]
	Deletion/duplication analysis [4]	Unknown [5]
Unknown [6]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein. See Molecular Genetics for information on allelic variants.
2. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or 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.
3. All Portuguese families with AOA1 share the same pathogenic variant (p.Trp279Ter), while Japanese families first described by Uekawa et al [1992] shared another pathogenic variant (c.689dupT).
4. Testing that identifies exon or whole-gene deletions/duplications not detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
5. Deletion of the entire gene *APTX* has been reported [Amouri et al 2004]. The frequency of alleles with partial- or whole-gene deletions is not known.
6. Scanning for pathogenic variants identified variants diagnostic for either AOA1 or AOA2 in only 20 of the 43 (46.5%) individuals with the ataxia with oculomotor apraxia phenotype. In other words, almost half of Portuguese families with AOA do not appear to have AOA1 or AOA2 using scanning for pathogenic variants; thus, pathogenic variants in other genes or pathogenic variants not detectable by this test method (e.g., exon or whole-gene deletions) may be causative [Bras et al 2015].

Clinical Characteristics

Clinical Description

Ataxia is the main cause of disability in ataxia with oculomotor apraxia type 1 in the first stages of the disease. Later, peripheral axonal motor neuropathy dominates the clinical picture.

Cerebellar ataxia. Symptoms are first noticed between ages two and ten years (mean: 4.3 years). In about 50% of affected individuals, onset is before age seven years. Two Italian adults with cerebellar ataxia were reported having disease onset at ages 28 and 29 years [Criscuolo et al 2004].

After initial normal motor development, all individuals develop cerebellar ataxia. The first manifestations of AOA1 are slowly progressive gait imbalance followed by dysarthria, then upper-limb dysmetria with mild intention tremor.

Oculomotor apraxia. Oculomotor apraxia is present in all individuals with AOA1. It is usually noticed a few years after the onset of ataxia. Oculomotor apraxia is the most striking feature in this disorder, but can be missed on routine neurologic examination. Individuals with oculomotor apraxia do not fixate normally on objects. When asked to look to one side, they turn their heads first, with eye contraversion, after which their eyes follow to the same side in several slow saccades with head thrusts.

Blinking is exaggerated in most individuals.

Ocular movements on command are usually slightly limited; the eyes stop before reaching extreme positions of gaze. These slow eye movements appear equally on lateral and vertical gaze.

When the head is immobilized, movement of the eyes is impossible.

Oculocephalic reflexes are spared until advanced stages of the disease. When standing and turning their heads, affected individuals lose their balance and tend to move the whole body to compensate.

Ocular pursuit movements remain normal during the first years after the appearance of oculomotor apraxia. Later, oculomotor apraxia is followed by progressive external ophthalmoplegia (beginning with upward gaze).

Neuropathy. All individuals with AOA1 have an axonal peripheral neuropathy, with early areflexia that dominates the clinical picture in advanced phases of the disease and is the major cause of motor disability with severe weakness and wasting. Loss of independent walking happens about seven to ten years after onset; most individuals become wheelchair bound by adolescence.

Hands and feet are short and atrophic. *Pes cavus* is present in 30% of individuals and scoliosis in a few.

Vibration and postural sense are impaired only in older individuals with very long disease duration. Pain and light touch sensation are preserved.

Chorea. About 45% of affected individuals have chorea even after a long disease duration (≤51 years) [Shimazaki et al 2002, Le Ber et al 2003, Sekijima et al 2003, Tranchant et al 2003, Criscuolo et al 2004, Habeck et al 2004]. At onset, the percentage may be as high as 80%, but in almost 50% of affected individuals, chorea disappears over the course of the disease [Le Ber et al 2003].

Dystonia. Upper-limb dystonia occurs in about 50% of individuals and may in some cases be sufficiently pronounced to justify diagnostic consideration of extrapyramidal disorders.

Intellect. Different degrees of cognitive impairment are observed, largely independent of ethnic origin [Tachi et al 2000, Moreira et al 2001a, Shimazaki et al 2002, Le Ber et al 2003, Sekijima et al 2003, Criscuolo et al 2004, Quinzii et al 2005]. Severe cognitive disability was reported in a single family [Moreira et al 2001b].

Life span. In the Portuguese kindreds, the age at last examination ranged from 17 to 68 years, corresponding to a disease duration of 12 to 58 years (mean: 27.5 years); two individuals died, one of an unknown cause and the other, a girl age 11 years with AOA1 who had been symptomatic for eight years, from a thalamic tumor. One Japanese individual died at age 71 years. In the cohort reported by Le Ber et al [2003], disease duration was 51 years.

Other. No signs of extraneurologic involvement are evident.

Genotype-Phenotype Correlations

APTX pathogenic missense variants may be associated with a later onset (age ~9 years). All other individuals with AOA1 with homozygous truncating variants (nonsense or frameshift) had onset ranging between ages two and 12 years (mean: 4.6 years) [Moreira et al 2001b, Shimazaki et al 2002, Le Ber et al 2003, Sekijima et al 2003, Amouri et al 2004, Habeck et al 2004, Quinzii et al 2005].

Cognitive impairment was reported in several families of different ethnic origins who had a range of variant types, including nonsense, frameshift, splice site, and missense [Tachi et al 2000, Barbot et al 2001, Moreira et al 2001a, Shimazaki et al 2002, Le Ber et al 2003, Sekijima et al 2003, Criscuolo et al 2004, Quinzii et al 2005].

- The p.Trp279Ter nonsense variant can be associated with cognitive impairment [Le Ber et al 2003] or normal cognitive development [Moreira et al 2001a, Le Ber et al 2003, Tranchant et al 2003].

- The presence of severe cognitive impairment in p.[Glu232GlyfsTer38]+[Pro206Leu] compound heterozygotes and the presence of mild cognitive impairment/borderline intelligence in the respective homozygotes is unexplained.

Two compound heterozygotes for the p.Arg199His missense variant and an unidentified second pathogenic variant had an atypical presentation with marked dystonia and mask-like faces in addition to the AOA1 clinical picture.

The pathogenic variant p.Ala198Val is associated with predominant, more severe and persistent chorea [Le Ber et al 2003].

In two Italian adults, homozygous p.Pro206Leu and p.His201Gln pathogenic variants were associated with late-onset AOA1 (ages 28 and 29 years). In contrast, in Japanese individuals with AOA1, the p.Pro206Leu pathogenic variant is associated with earlier onset (age 10 years).

The pathogenic missense variant p.Pro206Leu is associated with a later onset [Date et al 2001] and the pathogenic variants p.Val263Gly and p.Lys197Gln with even later onset: age 15 years [Tranchant et al 2003] and 25 years [Date et al 2001] respectively.

To the authors' knowledge, no correlation exists between a specific pathogenic variant and the affected individual's survival.

Nomenclature

In Japan, AOA1 is called early-onset ataxia with oculomotor apraxia and hypoalbuminemia [Date et al 2001, Shimazaki et al 2002, Sekijima et al 2003].

Prevalence

Through a systematic population-based survey of hereditary ataxias being conducted in Portugal since 1993 [Silva et al 1997], Friedreich ataxia (as expected) was found to be the most frequent autosomal recessive ataxia (32.8%), followed by AOA (12.6%). In Portugal there are now 42 individuals with AOA in 20 different families (AOA1= 3.6% of all autosomal recessive ataxias; AOA2= 3.3%). AOA prevalence in Portugal is estimated at 0.41 per 100,000 inhabitants. However, 20 of these individuals with AOA from 13 different families do not have either AOA1 or AOA2, illustrating AOA genetic heterogeneity [Bras et al 2015].

In Japan, AOA1 appears to be the most frequent cause of autosomal recessive ataxia [Uekawa et al 1992, Fukuhara et al 1995, Hanihara et al 1995, Kubota et al 1995, Sekijima et al 1998, Tachi et al 2000, Moreira et al 2001a, Shimazaki et al 2002, Sekijima et al 2003]. In the entire cohort studied by Le Ber et al [2003] mostly individuals of French origin with progressive cerebellar ataxia in whom Friedreich ataxia had been excluded — the frequency of AOA1 was 5.7%; among the subset of individuals with onset before age 25 years, the frequency of AOA1 was 9.1%.

Affected individuals with pathogenic variants in *APTX* have been identified worldwide: thirteen individuals from three unrelated Tunisian families [Amouri et al 2004]; two unrelated individuals from Germany [Habeck et al 2004]; three unrelated Italian individuals [Criscuolo et al 2004]; two American children [Tsao & Paulson 2005]; and four individuals of northern European heritage with ataxia and CoQ_{10} deficiency [Quinzii et al 2005].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *APTX*.

Differential Diagnosis

The diagnosis of AOA1 is ruled out whenever the clinical picture includes non-progressive ataxia, microcephaly, or seizures. The differential diagnosis varies by age group.

Ataxia with oculomotor apraxia type 2 (AOA2), the disorder most likely to be confused with AOA1, is characterized by onset between age three and 30 years, cerebellar atrophy, axonal sensorimotor neuropathy, oculomotor apraxia, and elevated serum concentration of alpha-fetoprotein (AFP). See Table 2.

AOA2 is associated with pathogenic variants of *SETX*, the gene that encodes the protein senataxin [Moreira et al 2004]. In one study, AOA2 accounted for 8% of all autosomal recessive cerebellar ataxia, making it second only to Friedreich ataxia in prevalence among adults with autosomal recessive ataxia [Le Ber et al 2004].

Ataxia with oculomotor apraxia type 3 (AOA3) (OMIM 615217) was described in a Saudi family in association with a pathogenic missense variant in *PIK3R5*. The disorder is most likely to be clinically and biochemically confused with AOA2 [Al Tassan et al 2012].

Ataxia with oculomotor apraxia type 4 (AOA4) was recently described in a cohort of nine Portuguese families associated with pathogenic variants in *PNKP*. Age of onset and clinical presentation, with marked extrapyramidal manifestations and rapid progression resembles AOA1 except for cognitive impairment. AOA4 is the most frequent form of AOA in the Portuguese population [Bras et al 2015].

Table 2. Comparison of AOA1, AOA2, AOA3 and AOA4

AOA Type	AOA1	AOA2	AOA3	AOA4
Mean age at onset (range)	4.3 yrs (2-10)	13 yrs (10-14)	15.6 yrs (14-18)	4.3 yrs (1-9)
Evolution	More severe	More benign	More benign	More severe
Oculomotor apraxia	Early & severe	Mild to moderate	Late & severe	Early & severe
Dystonia	Marked, early in the disease, disappearing w/age	Less marked	Not mentioned	Marked, early in the disease
Neuropathy	Early & severe	Less severe & beginning later in the disease	Severe	Early & severe
Cognitive impairment	Not present	Not present	Not mentioned	Often present
Biochemical findings	Late-onset low serum albumin & high cholesterol; normal alpha-fetoprotein at all stages	Early elevation of alpha-fetoprotein	Early elevation of alpha-fetoprotein	Variable levels of serum albumin, cholesterol, & alpha-fetoprotein

Early childhood. The diagnosis of AOA1 can be difficult to establish in very young children because all features of the disorder are not yet apparent.

- When oculomotor apraxia is present, ataxia-telangiectasia can be excluded.
- Joubert syndrome is a rare, autosomal recessive disorder that affects the cerebellum and brain stem. It is characterized by the presence of a distinct respiratory pattern and profound tachypnea in the newborn period. Nonspecific features such as hypotonia, ataxia, developmental delay, and oculomotor apraxia can occur. The diagnosis of Joubert syndrome is based on the presence of these characteristic clinical features and is confirmed with cranial magnetic resonance imaging (MRI), which reveals the "molar tooth sign" resulting from hypoplasia of the cerebellar vermis and accompanying brain stem abnormalities [Maria et al 1999, Merritt 2003].

Adolescence

- Friedreich ataxia (FRDA) can be excluded on clinical grounds. In FRDA, oculomotor apraxia is not observed and the cerebellum is normal on MRI. Molecular genetic testing of *FRDA* detects pathogenic variants in almost 100% of affected individuals.
- Ataxia with vitamin E deficiency (AVED) and coenzyme Q_{10} deficiency should be considered because they are treatable disorders [Musumeci et al 2001, Quinzii et al 2005].
- Peripheral neuropathy with areflexia and *pes cavus* may be confused with Charcot-Marie-Tooth syndrome. See Charcot-Marie-Tooth Hereditary Neuropathy Overview.

Adulthood. In apparent simplex cases (individuals with no family history of AOA1), SCA2, which also associates cerebellar ataxia with slow eye movements, can be excluded by molecular genetic testing of *ATXN2,* the gene in which mutation causes SCA2 [Pulst et al 1996].

See also Ataxia Overview.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with ataxia with oculomotor apraxia type 1 (AOA1), the following evaluations are recommended:

- Examination of cognitive function
- Examination of cranial nerve function
- Extended neurologic examination of the limbs: initial inspection, tone, strength testing, reflexes, coordination, sensory testing
- Ophthalmologic examination
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Physical therapy may be helpful, particularly for disabilities resulting from peripheral neuropathy.

A wheelchair is usually necessary for mobility by age 15-20 years.

Educational support should be provided to compensate for difficulties in speaking (dysarthria), in reading (oculomotor apraxia), and in writing (upper-limb ataxia and weakness).

Prevention of Secondary Complications

High-protein diet to restore serum albumin concentration is indicated to prevent edema secondary to hypoalbuminemia.

Low-cholesterol diet is advised.

Surveillance

Routine visits to the neurologist are appropriate.

Evaluation of Relatives at Risk

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

Therapies Under Investigation

Search ClinicalTrials.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. Note: There may not be clinical trials for this disorder.

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

AOA1 is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- Both parents of an affected indiviudal are obligate heterozygotes (i.e., carriers of one *APTX* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier of an *APTX* pathogenic variant is 2/3.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. All the offspring of an individual with AOA1 are obligate heterozygotes (carriers) for a pathogenic variant in *APTX*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *APTX* pathogenic variant.

Carrier Detection

Carrier testing for at-risk family members is possible if the pathogenic variants in the family have been identified.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is 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, are carriers, or are at risk of being carriers.

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 *APTX* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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.

- **Associação Portuguesa de Ataxias Hereditárias (APAHE)**
  Rua 25 de Abril n.º 82
  Castro Marim 8950-122
  Portugal
  Email: apaheportugal@gmail.com
  www.apahe.pt
- **euro-ATAXIA (European Federation of Hereditary Ataxias)**
  United Kingdom
  Email: lporter@ataxia.org.uk
  www.euroataxia.org
- **National Ataxia Foundation**
  Phone: 763-553-0020
  Fax: 763-553-0167
  Email: naf@ataxia.org
  www.ataxia.org
- **CoRDS Registry**
  Sanford Research
  Phone: 605-312-6300
  CoRDS Registry

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. Ataxia with Oculomotor Apraxia Type 1: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
APTX	9p21.1	Aprataxin	APTX database	APTX	APTX

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 Ataxia with Oculomotor Apraxia Type 1 (View All in OMIM)

208920	ATAXIA, EARLY-ONSET, WITH OCULOMOTOR APRAXIA AND HYPOALBUMINEMIA; EAOH

Table B. continued from previous page.

606350	APRATAXIN; APTX

Molecular Pathogenesis

APTX is the only gene known to be associated with AOA1 [Date et al 2001, Moreira et al 2001b]. It encodes the protein aprataxin, which plays a role in DNA-single-strand break repair [Hirano et al 2007] and double-strand break repair machinery [Clements et al 2004].

Gene structure. *APTX* consists of seven exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Benign variants have been reported (see Table 3).

Pathogenic variants. To date, 16 different pathogenic variants have been found in 37 families from different countries on three continents (Table 3).

Table 3. Selected *APTX* Variants

Variant Classification	Exon / Intron	DNA Nucleotide Change (Alias [1])	Predicted Protein Change [2]	Predicted Effect on Aprataxin	Reference
Benign	Intron 1	c.134-12A>C	---	None	--
	Exon 3	c.431C>A	p.Ser144Tyr		--
Pathogenic	Exon 5	c.589A>C	p.Lys197Gln	Missense; aberrant processing	Tranchant et al [2003]
		c.593C>T	p.Ala198Val		Le Ber et al [2003], Criscuolo et al [2004]
		c.596G>A	p.Arg199His		Moreira et al [2001b]
		c.602A>G	p.His201Arg		Shimazaki et al [2002]
		c.603T>A	p.His201Gln		Criscuolo et al [2004]
		c.617C>T	p.Pro206Leu		Date et al [2001], Moreira et al [2001b], Shimazaki et al [2002], Criscuolo et al [2004]
		c.689dupT (689insT) (689-690insT)	p.Glu232GlyfsTer38	Frameshift; truncation	Date et al [2001], Moreira et al [2001b], Shimazaki et al [2002], Sekijima et al [2003]
		c.739 C>T	p.Arg247Ter	Stop; truncation	Mosesso et al [2005]
		c.770+1G>A	--	Splice; truncation	Le Ber et al [2003]
	Exon 6	c.788T>G	p.Val263Gly	Missense; aberrant processing	Date et al [2001]
		c.800A>G	p.Asp267Gly		Le Ber et al [2003]
		c.835T>C	p.Trp279Arg		
		c.837G>A	p.Trp279Ter	Stop; truncation	Moreira et al [2001b], Le Ber et al [2003], Tranchant et al [2003], Habeck et al [2004], Quinzii et al [2005]
		c.841delT	p.Ser281LeufsTer8	Frameshift; truncation	Date et al [2001]

Table 3. continued from previous page.

Variant Classification	Exon / Intron	DNA Nucleotide Change (Alias [1])	Predicted Protein Change [2]	Predicted Effect on Aprataxin	Reference
	Exon 7	c.875-1G>A	--	Splice; truncation	Amouri et al [2004]
		Total deletion of gene	--	No product	

Variants listed in the table have been provided by the authors. *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. Variant designation that does not conform to current naming conventions
2. Reference sequences are those of the long isoform: NP_778243.1 and NM_175073.1

Normal gene product. *APTX* encodes a ubiquitously expressed protein, aprataxin. Alternative splicing on exon 3 generates two distinct isoforms. The longer transcript (NM_175073.1) is the major form found in human cell lines, with the shorter, frame-shifted form being present in lower amount [Date et al 2001, Moreira et al 2001b]. The longer transcript codes for a 342-amino acid protein (NP_778243.1), while the shorter one encodes a 168-amino acid protein. The longer transcript is composed of three domains:

- The PANT domain (PNKP-AOA1 N-terminal domain), also known as putative forkhead-associated (FHA) domain [Caldecott 2003] corresponding to the N-terminal region of aprataxin that shares 41% identity only with the N-terminus of animal polynucleotide kinase 3' phosphatase (PNKP) [Jilani et al 1999, Karimi-Busheri et al 1999, Moreira et al 2001b]. This domain facilitates binding to phosphorylated proteins [Kijas et al 2006]. The PNKP (dual 5' kinase 3' phosphatase) interacts with DNA polymerase b, DNA ligase III, and XRCC1 protein, forming the single-strand break repair (SSBR) complex, following exposure to ionizing radiation and reactive oxygen species [Whitehouse et al 2001].
- The HIT domain (middle domain), defined by the HIT motif, for nucleotide binding and hydrolysis. Members of the HIT super family (histidine triad) of nucleotide hydrolases/transferases [Brenner 2002] can be divided into two main groups:
  - The Hint (histidine triad nucleotide binding)-related proteins, binding nucleotides and displaying adenosine 5'-monophosphoramidase activity [Brenner et al 1997]
  - The Fhit (fragile histidine triad)-related proteins, cleaving diadenosine tetraphosphate (Ap_4A), which is potentially produced during activation of the SSBR complex [McLennan 2000]
- The C-terminal domain, containing a divergent zinc-finger motif [Moreira et al 2001b], which could allow binding to DNA and/or RNA [Kijas et al 2006]

The presence of these three domains has suggested that aprataxin is a nuclear protein with a role in DNA repair, reminiscent of the function of the protein defective in ataxia-telangiectasia, which would cause a phenotype restricted to neurologic signs when mutated. Subcellular localization studies showed that aprataxin is a nuclear protein, present in both the nucleoplasm and the nucleolus [Gueven et al 2004, Sano et al 2004]. Recent experimental studies indicate that aprataxin has dual DNA binding and nucleotide hydrolase activities. Aprataxin binds to double-stranded DNA with high affinity but is also capable of binding to double-stranded RNA and to single-stranded DNA, with increased affinity for hairpin structures. Aprataxin also hydrolyses, with similar efficiency, the model histidine triad nucleotide-binding protein substrate ($AMPNH_2$) and the fragile histidine triad protein substrate (Ap_4A) [Kijas et al 2006].

Several in vitro and in vivo studies have shown that aprataxin (long isoform) interacts with *XRCC1* [Caldecott 2003, Clements et al 2004, Gueven et al 2004, Sano et al 2004] and *XRCC4* [Clements et al 2004], proteins implicated in single-strand and double-strand repair mechanisms, respectively. The interaction with C-terminal region of *XRCC1* is made through the 20 N-terminal amino acids of aprataxin FHA domain [Date et al 2004].

This interaction is important in maintaining the steady-state protein level of *XRCC1* [Luo et al 2004]. Interaction with another single-strand break repair protein, PARP-1, was also reported [Date et al 2004].

Abnormal gene product. Gueven et al [2004] demonstrated that pathogenic variants (even missense ones) in *APTX* destabilize aprataxin and that cells from individuals with AOA1 are characterized by enhanced sensitivity to agents that cause single-strand breaks in DNA; however, no gross defect in single-strand break repair is apparent, even though the long isoform of aprataxin interacts with XRCC1 [Caldecott 2003, Clements et al 2004, Gueven et al 2004, Sano et al 2004].

Even when in vitro and in vivo studies show that aprataxin interacts with XRCC4, AOA1 cell lines exhibit neither radio-resistant DNA synthesis nor a reduced ability to phosphorylate downstream targets of ATM following DNA damage, suggesting that AOA1 lacks the cell cycle checkpoint defects that are characteristic of ataxia-telangiectasia [Clements et al 2004]. Recently, cells of an individual with AOA1 homozygous for a stop variant showed marked, dose-related increases in induced chromosomal aberrations but did not show hypersensitivity to ionizing radiation, indicating direct involvement of aprataxin in the DNA single-strand break repair mechanisms [Mosesso et al 2005].

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Chapter Notes

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