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Ataxia with Oculomotor Apraxia Type 2

[*AOA2*]

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Summary

Disease characteristics. Ataxia with oculomotor apraxia type 2 (AOA2) 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).

Diagnosis/testing. The diagnosis of AOA2 is based on clinical and biochemical findings, family history, and exclusion of the diagnosis of ataxia-telangiectasia and AOA1. AOA2 is associated with mutations in the gene *SETX*, which encodes the protein senataxin. Molecular genetic testing is available on a clinical basis.

Management. *Treatment of manifestations:* physical therapy for disabilities resulting from peripheral neuropathy; wheelchair for mobility as needed; educational support (e.g., computer with speech recognition and special keyboard for typing) to compensate for difficulties in reading (caused by oculomotor apraxia) and in writing (caused by upper-limb ataxia). *Surveillance:* routine follow-up with a neurologist.

Genetic counseling. AOA2 is inherited in an autosomal recessive manner. 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. No laboratories offering prenatal testing are listed in the GeneTests Laboratory Directory; however, such testing may be available through laboratories offering custom prenatal diagnosis.

Diagnosis

Clinical Diagnosis

Ataxia with oculomotor apraxia type 2 (AOA2) is suspected in individuals with the following findings [Moreira et al 2004]:

- Cerebellar ataxia
- Oculomotor apraxia (in <47% of individuals)

- Areflexia and later a peripheral axonal sensorimotor neuropathy (>90% of individuals)
- Onset between age three and 30 years
- Slow progression
- Absence of cardiac involvement, cancer predisposition, or immunodeficiency, and rare or absent telangiectasia
- Family history consistent with autosomal recessive inheritance

MRI. Marked cerebellar atrophy on MRI was detected in all individuals undergoing this examination [Moreira et al 2004, Duquette et al 2005, Asaka et al 2006, Criscuolo et al 2006, Fogel & Perlman 2006]. In the case described by Chen et al (2006), MRI at age 40 years showed mild cerebellar hemispheric and moderate vermian hypoplasia/atrophy.

EMG. Signs of axonal neuropathy are found in 90%-100% of individuals with AOA2 [Moreira et al 2004, Duquette et al 2005, Asaka et al 2006, Criscuolo et al 2006].

Testing

Laboratory findings that can be used to establish the diagnosis of AOA2 in a symptomatic individual include the following:

- **Serum alpha-fetoprotein (AFP) concentration** greater than 20 ng/mL (in >90% of affected individuals) [Moreira et al 2004, Duquette et al 2005, Asaka et al 2006, Chen et al 2006, Criscuolo et al 2006, Fogel & Perlman 2006]. Although normal laboratory values for serum AFP concentration are highly variable, the majority range between 0 and 20 ng/mL. Serum AFP concentration varies over time and is lower than that usually observed in ataxia-telangiectasia [Le Ber et al 2004].
- **Serum total cholesterol concentration** greater than 5.6 mmol/L (in ~50% of affected individuals) [Le Ber et al 2004]. Normal value: 3.5-5.8 mmol/L.
- **Serum creatine kinase (CK) concentration** is increased in some affected individuals and elevated immunoglobulin levels (IgG and A) have been found in several families [Watanabe et al 1998, Le Ber et al 2004].

Neuropathology. Nerve biopsy confirms axonal neuropathy.

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.

Molecular Genetic Testing—Gene. *SETX* is the only gene currently known to be associated with AOA2 [Moreira et al 2004].

Clinical uses

- Confirmatory diagnostic testing
- Carrier testing
- Prenatal diagnosis

Clinical testing

- **Sequence analysis.** Direct sequencing of the *SETX* coding sequence, intronic flanking sequences, and a part of 5' and 3' UTRs identified mutations in families from Algeria, Canada, Cape Verde, France, Italy, Japan, Pakistan, Portugal, Spain, Tunisia, Turkey, United Kingdom, United State, and Vietnam [Moreira et al 2004, Duquette et al 2005, Asaka et al 2006, Criscuolo et al 2006, Fogel & Perlman 2006]. Mutation detection rates have not yet been reported.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Ataxia with Oculomotor Apraxia Type 2

Test Method	Mutations Detected	Mutation Detection Frequency [1]	Test Availability
Sequence analysis	*SETX* sequence alterations	Unknown	Clinical Testing

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, and/or test method

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

Testing Strategy

When the clinical findings are characteristic of AOA2, sequence analysis of the *SETX* full coding sequence, intronic flanking sequences, and a part of 5' and 3' UTRs is performed.

Genetically Related (Allelic) Disorders

Juvenile amyotrophic lateral sclerosis (ALS4) (also known as distal hereditary motor neuronopathy with pyramidal features, or dHMN) is associated with three different missense mutations (T3I, L389S, and R2136H) in *SETX* [Chen et al 2004]. ALS4 is a rare autosomal dominant form of amyotrophic lateral sclerosis (ALS) characterized by severe distal muscle weakness and atrophy, normal sensation, and pyramidal signs associated with degeneration of motor neurons in the brain and spinal cord. Individuals affected with ALS4 usually have onset before age 25 years, a slow rate of progression, sparing of bulbar and respiratory muscles, and a normal life span [Chance et al 1998, Rabin et al 1999, De Jonghe et al 2002, Chen et al 2004].

An autosomal dominant form of ataxia appears to be associated with two *SETX* missense mutations (N603D-Q653K) shared in *cis* configuration by a mother and daughter [Bassuk et al 2007]. Both had cerebellar ataxia with atrophy of the cerebellum, dysarthria, oculomotor defects (saccadic pursuits and gaze-evoked nystagmus), and tremor. The mother had onset of cerebellar ataxia at age 13 years, the daughter at age three years. Mental status, reflexes, sensation, muscle tone, and levels of alpha-fetoprotein and serum creatine kinase were within normal range.

Clinical Description

Natural History

Ataxia is the first sign of ataxia with oculomotor apraxia type 2 (AOA2) and is the major cause of disability early in the disease course. Later, peripheral sensorimotor neuropathy, particularly of the lower limbs, plays a significant role in disease progression.

Findings by Le Ber et al (2004), Moreira et al (2004), Duquette et al (2005), Asaka et al (2006), Chen et al (2006), Criscuolo et al (2006), Fogel & Perlman (2006) showed the following:

Cerebellar ataxia. All affected individuals, after initial normal development, show cerebellar ataxia, with slowly progressive gait imbalance [Watanabe et al 1998, Nemeth et al 2000]. The first symptoms are recognized between age ten and 23 years (mean 15.0 years). In a recent study of ten affected individuals from Italy, age at onset ranged between three and 30 years (mean 20.3 years) [Criscuolo et al 2006].

Neuropathy. Ninety percent to 100% of the individuals with AOA2 have sensorimotor neuropathy (i.e., absent or diminished tendon reflexes and sensorimotor deficit).

Oculomotor apraxia. Oculomotor apraxia is present in about 50% of individuals. It is characterized by a dissociation of eye-head movements in the "head-free" condition, in which the head reaches the lateral target before the eyes. In the Italian cohort, this feature was present in only 20% of individuals [Criscuolo et al 2006]. Saccadic pursuit and gaze-evoked nystagmus have also been observed in several individuals [Nemeth et al 2000].

Movement disorders. Dystonic posture of the hands, choreic movements, and head or postural tremor are observed in about 20% of individuals [Nemeth et al 2000, Le Ber et al 2004]. The severity of the movement disorders persists in individuals with AOA2 in contrast to the movement disorder in individuals with AOA1, in which chorea tends to disappear with time [Le Ber et al 2003, Le Ber et al 2004]. In the Italian study, extrapyramidal symptoms (including choreiform head movements, truncal dystonia, and head tremor) were reported in 20% of individuals; however, they rapidly disappeared as the disease progressed [Criscuolo et al 2006]. In the French-Canadian group of individuals tremor was an inconsistent feature present in 57% [Duquette et al 2005].

Intellect. Mild cognitive impairment is present in some individuals [Le Ber et al 2004], but none have had severe mental retardation or dementia, even after long disease duration [Le Ber et al 2004]. In the Criscuolo et al (2006) study, three out of ten persons presented with mild mental impairment with onset around age 50 years.

Other. Deep sensory loss, extensor plantar reflexes, swallowing difficulties, and sphincter disturbances are observed in some individuals [Le Ber et al 2004]. No signs of extraneurologic involvement, other than early-onset menopause [Le Ber et al 2004, Criscuolo et al 2006], are evident.

Neuropathology. Chronic axonal neuropathy with preferential loss of large myelinated fibers and to a lesser degree small myelinated fibers is detected in sural nerve biopsies [Duquette et al 2005, Criscuolo et al 2006].

Postmortem brain examination in a 79-year-old Italian who died of heart failure revealed reduction in the overall size of the brain, including atrophy of the cerebellar folia and marked widening of the sulci [Criscuolo et al 2006]. Cerebellar atrophy was most evident at the level of the vermis and the anterior lobe. The brain stem and spinal cord were slightly reduced in size without other anomalies. The substantia nigra appeared normally pigmented. Atheromatous plaques were present in all the arteries of the circle of Willis. Histologic examination showed normal cortical neurons (both in number and shape), marked loss of Purkinje cells in the cerebellar cortex, and mild fibrous gliosis that was more severe in the vermis than in the hemispheres. No inclusions or torpedos were found. The neurons of the dentate nuclei were slightly reduced in number. Chromatolysis of the oculomotor and raphe nuclei was observed in the brain stem. The inferior and accessory olives appeared relatively spared. In the spinal cord severe demyelination of the gracilis and cuneatus funiculi and degeneration of Clarke's columns with gliosis were observed.

Life span. In individuals studied to date, disease duration ranged between age two and 53 years, corresponding to the maximum age of last examination (79 years).

Genotype-Phenotype Correlations

No obvious genotype-phenotype correlations have been established.

Nomenclature

AOA2 was first known as "ataxia with later onset and high level of alpha-fetoprotein."

Prevalence

The prevalence of L1976R and E65K mutations was studied by genotyping 154 samples from the Gaspésie region, including 82 French-Canadian and 72 Anglo-Norman control samples [Duquette et al 2005]. In this study, five individuals (3 of Anglo-Norman and 2 of French-Canadian backgrounds) were carriers of the L1976R common French-Canadian mutation and none was a carrier of the rarer E65K mutation. According to these results, the carrier rate for the L1976R mutation is estimated to be 3.5% (1:28) for Quebecois of Anglo-Norman origin and 2.1% (1:47) for the French-Canadian population of Gaspésie. No individuals homozygous for the mutations L1976R and E65K were identified.

Differential Diagnosis

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

Childhood. The diagnosis of ataxia with oculomotor apraxia type 2 (AOA2) can be difficult to establish in young children because all features of the disease are not present or apparent. AOA2 in childhood needs to be distinguished from the following disorders:

- AOA1 is a progressive cerebellar ataxia characterized by childhood onset (age 2-15 years [Moreira et al 2004]), followed by oculomotor apraxia, which is usually noticed a few years after the onset of ataxia, and progressing to external ophthalmoplegia. The majority of individuals with AOA1 have generalized areflexia followed by a peripheral neuropathy and quadriplegia with loss of ambulation about seven to ten years after onset [Tachi et al 2000, Barbot et al 2001, Le Ber et al 2003, Tranchant et al 2003]. Cognitive impairment in different degrees is observed in individuals of different ethnic origins, while in others, intellect remains normal [Tachi et al 2000; Moreira, Barbot, Tachi, Kozuka, Mendonca et al 2001; Shimazaki et al 2002; Le Ber et al 2003; Sekijima et al 2003]. After a long disease duration (>15 years), low serum concentration of albumin and high serum concentration of total cholesterol are observed [Tachi et al 2000; Moreira, Barbot, Tachi, Kozuka, Uchida et al 2001]. AOA1 is caused by mutations in *APTX*, the gene encoding aprataxin [Date et al 2001; Moreira, Barbot, Tachi, Kozuka, Uchida et al 2001].
- When oculomotor apraxia and/or high serum concentrations of alpha-fetoprotein are present, ataxia-telangiectasia (caused by mutations in *ATM*) and ataxia-telangiectasia-like disorder (caused by mutations in *MRE11A*) should also be considered.

Adolescence

- Friedreich ataxia (FRDA) can be excluded on clinical grounds, as oculomotor apraxia is not observed in FRDA and cerebellar atrophy is not observed on MRI in FRDA early in the disease course. Molecular genetic testing of the gene *FRDA* can detect mutations in virtually 100% of affected individuals.

- Ataxia with vitamin E deficiency (AVED) and Q10 deficiency [Musumeci et al 2001] should be considered because they are treatable.

Adulthood. In simplex cases (i.e., a single occurrence in a family), the possibility of spinocerebellar ataxia type 2 (SCA2) (a dominant form of ataxia which also associates cerebellar ataxia with slow eye movements) can be excluded by molecular genetic testing of the *SCA2* gene [Pulst et al 1996].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with oculomotor apraxia type 2 (AOA2):

- Assessment of cognitive function
- Examination of cranial nerve function
- Neurologic examination including assessment of gait and limb ataxia, coordination, tone, strength, reflexes, and sensory perception
- Oculomotor examination

Treatment of Manifestations

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

A wheelchair is usually necessary for mobility by age 30 years.

Educational support (such as use of a computer with speech recognition and special keyboard for typing) should be provided to compensate for difficulties in reading (caused by oculomotor apraxia) and in writing (caused by upper-limb ataxia).

Prevention of Secondary Complications

A low-cholesterol diet is advised.

Surveillance

Routine visits to the attending neurologist are indicated.

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

Genetics clinics are a source of 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 (below) may include disease-specific and/or umbrella support organizations.

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

Ataxia with oculomotor apraxia type 2 (AOA2) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

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 is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. No individuals with AOA2 have been known to reproduce.

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

Carrier Detection

Carrier testing for at-risk family members is available on a clinical basis once the mutations have been identified in the proband.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk and clarification of carrier status is before pregnancy.

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 DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Both disease-causing

alleles of an affected family member must be identified or linkage established in the family 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.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member. 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 Ataxia with Oculomotor Apraxia Type 2

Gene Symbol	Chromosomal Locus	Protein Name
SETX	9q34	Probable helicase senataxin

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 Ataxia with Oculomotor Apraxia Type 2

606002	SPINOCEREBELLAR ATAXIA, AUTOSOMAL RECESSIVE 1; SCAR1
608465	SENATAXIN

Table C. Genomic Databases for Ataxia with Oculomotor Apraxia Type 2

Gene Symbol	Entrez Gene	HGMD	GeneCards	GenAtlas
SETX	23064 (MIM No. 608465)	SETX	*SETX*	SETX

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

Normal allelic variants: *SETX* is composed of 24 coding and two none-coding exons. To date, eight different polymorphisms have been identified, all located in exon 8: 3147C>T, 3455G>T, 3576T>G, 3754G>A, 4156G>A [Moreira et al 2004], 4755T>G, 2975A>G, and 4755T>G [Fogel & Perlman 2006].

Pathologic allelic variants: To date, 27 mutations have been found in 32 families from 14 countries (Table 2, pdf). Also see Genomic Databases table.

Normal gene product: *SETX* encodes the newly identified and ubiquitously expressed 2,677 amino-acid protein, probable helicase senataxin. Senataxin is composed of four regions: an N-terminal region that shares homologies with the fungal Sen1p proteins; a second region that is not conserved; a third region that contains a classic seven-motif domain found in the superfamily 1 of helicases; and a C-terminal region that is not conserved [Moreira et al 2004].

Saccharomyces cerevisiae Sen1p is involved in splicing and termination of tRNA and small nuclear and nucleolar RNAs, and has RNA helicase activity encoded by its C-terminal domain [Ursic et al 1997, Rasmussen & Culbertson 1998, Kim et al 1999]. The first reported *Schizosaccharomyces pombe* Sen1p encoded by chromosome 1 (*S. pombe* has two *Sen1* genes) has both RNA and DNA helicase activities [Kim et al 1999]. The helicase domain of senataxin and the Sen1p proteins share significant similarity with two other members of the DExxQ-box family of helicases [Moreira et al 2004]: RENT1/Upf1, involved in nonsense-mediated RNA

decay [Wang et al 2001] and IGHMBP2, defective in spinal muscular atrophy with respiratory distress (SMARD1) [Grohmann et al 2001] and in mouse neuromuscular degeneration [Cox et al 1998]. SMARD1 is a human disease characterized by dysfunction and progressive loss of alpha-motor neurons in the anterior horn of the spinal cord, leading to neurogenic muscular atrophy with subsequent symmetric muscle weakness of the trunk and limbs [Grohmann et al 2001]. Life-threatening respiratory distress with clinical and radiologic evidence of unilateral or bilateral paralysis of the diaphragm is the most important presenting symptom of this disease.

Upf1 proteins have RNA helicase activity, but IGHMBP2 was initially identified as a DNA-binding protein with transcriptional transactivating properties. It is therefore possible that, like *S. pombe* Sen1p-1, senataxin has both RNA and DNA helicase activities and that senataxin acts in a DNA repair pathway, like several other proteins mutated in autosomal recessive cerebellar ataxias, for example, ataxia-telangiectasia [Shiloh 2003], ataxia with oculomotor apraxia type 1 [Moreira, Barbot, Tachi, Kozuka, Uchida et al 2001], ataxia-telangiectasia-like disorder [Stewart et al 1999], and spinocerebellar ataxia with peripheral neuropathy 1 [Takashima et al 2002]. The results also suggest that senataxin might be a nuclear RNA helicase with a role in the splicing machinery and that the molecular pathology of AOA2 may share features with spinal muscular atrophy and spinal muscular atrophy with respiratory distress.

The first data on senataxin characterization and localization showed that in murine brain, senataxin concentrates in several regions (including cerebellum, hippocampus, and olfactory bulb) with a general neuronal expression profile, colocalizing with NeuN (a protein present in neuronal nuclei). In cultured cells, *SETX* was found to be cytoplasmically diffuse, but in the nucleus, senataxin was punctuated, colocalizing with fibrillarin, a marker of the nucleolus. In differentiated non-cycling cells, nuclear senataxin was not restricted to the nucleolus but was diffuse within the nucleoplasm, suggesting cell cycle-dependent localization [Chen et al 2006].

Abnormal gene product: An important part of the missense mutations so far reported cluster within the N-terminus and helicase domains. Flag tagging at the N-terminus caused protein mislocation to the nucleoplasm and failure to export to the cytoplasm, suggesting that the N-terminus may be essential for correct senataxin localization [Chen et al 2006].

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.

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www.euro-ataxia.org

International Network of Ataxia Friends (INTERNAF)
www.internaf.org

National Ataxia Foundation
2600 Fernbrook Lane Suite 119
Minneapolis MN 55447
Phone: 763-553-0020
Fax: 763-553-0167
Email: naf@ataxia.org
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WE MOVE (Worldwide Education and Awareness for Movement Disorders)
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www.wemove.org

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

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Suggested Readings

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Author Information

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Revision History

- 5 March 2007 (me) Comprehensive update posted to live Web site
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- 15 November 2004 (me) Review posted to live Web site
- 23 June 2004 (mcm) Original submission