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Ataxia with Oculomotor Apraxia Type 2

Synonym: AOA2

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Summary

Clinical characteristics

Ataxia with oculomotor apraxia type 2 (AOA2) is characterized by onset of ataxia between age three and 30 years after initial normal development, axonal sensorimotor neuropathy, oculomotor apraxia, cerebellar atrophy, and elevated serum concentration of alpha-fetoprotein (AFP).

Diagnosis/testing

The diagnosis of AOA2 is based on clinical, laboratory, and radiographic features; family history; and exclusion of the diagnosis of ataxia-telangiectasia, AOA1, and AOA4. Identification of biallelic pathogenic variants in *SETX* by molecular genetic testing confirms the diagnosis.

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).

Preventions of secondary complications: A low-cholesterol diet is advised.

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. Carrier testing for at-risk family members and prenatal diagnosis for pregnancies at increased risk are possible if the pathogenic variants in the family have been identified.

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Diagnosis

Suggestive Findings

Ataxia with oculomotor apraxia type 2 (AOA2) **should be suspected** in individuals with the following clinical, laboratory, and radiographic features.

Clinical features

- Cerebellar ataxia
- Absent or diminished tendon reflexes and later a peripheral axonal sensorimotor neuropathy (>90% of individuals)
- Oculomotor apraxia (~51% of individuals)
- Pyramidal signs (Plantar response is either flexor or neutral.)
- Dystonic posture of the hands, choreic movements, head or postural tremor
- Onset between age three and 30 years
- Slow progression
- Absence of cardiac involvement, cancer predisposition, and immunodeficiency; rare or absent telangiectasia
- Absence of severe intellectual disability / cognitive regression
- Family history consistent with autosomal recessive inheritance

Laboratory features

- **Serum alpha-fetoprotein (AFP) concentration** >20 ng/mL (normal 0-20 ng/mL) in >95% of affected individuals

  Note: Normal serum AFP concentration is highly variable, varies over time, and in individuals with AOA2 is lower than that usually observed in individuals with ataxia-telangiectasia [Mariani et al 2017].

- **Increased serum total cholesterol concentration** >5.6 mmol/L (normal value: 3.5-5.8 mmol/L) in ~50% of affected individuals [Le Ber et al 2004]

- Increased serum creatine kinase (CK) concentration in some affected individuals

- **Elevated immunoglobulin levels (IgG and IgA)** reported in several families [Gazulla et al 2010]

Radiographic features. Brain MRI examination shows marked cerebellar atrophy (including cerebellar hemispheres and vermis) with relative sparing of the brain stem.

Other

- **EMG** shows signs of axonal neuropathy in 90%-100% of individuals with AOA2 [Bohlega et al 2011, H'mida-Ben Brahim et al 2011].
- **Neuropathology.** Nerve biopsy confirms axonal neuropathy.
- **Post-mortem brain examination** showed marked loss of Purkinje cells as well as mild fibrous gliosis that was more severe in the vermis than in the hemispheres [Criscuolo et al 2006].

Establishing the Diagnosis

The diagnosis of AOA2 **is established** in a proband with the above clinical, laboratory, and radiographic features. Identification of biallelic pathogenic (or likely pathogenic) variants in *SETX* by molecular genetic testing (see Table 1) confirms the diagnosis.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *SETX* variants of uncertain significance (or of one known *SETX* pathogenic variant and one *SETX* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing, exome array) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of AOA2 is broad, individuals with the distinctive features described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with ataxia are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of AOA2 molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SETX* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications (see Table 1).
- **An ataxia multigene panel** that includes *SETX* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by ataxia, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if exome sequencing is not diagnostic.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

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

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
SETX	Sequence analysis [3]	~80%-92% [4]
	Gene-targeted deletion/duplication analysis [5]	~8%-20% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Moreira et al [2004], Duquette et al [2005], Asaka et al [2006], Criscuolo et al [2006], Fogel & Perlman [2006], Lynch et al [2007], Zühlke et al [2007], Anheim et al [2008], Nicolaou et al [2008], Schöls et al [2008], Anheim et al [2009], Fogel et al [2009], Nakamura et al [2009], Bohlega et al [2011], Hammer et al [2012], Davis et al [2013], Nanetti et al [2013], Roda et al [2014], Newrick et al [2015], Pera et al [2015], Lu et al [2016]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Detailed in Molecular Genetics, **Pathogenic variants**

Clinical Characteristics

Clinical Description

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.

Cerebellar ataxia. All affected individuals, after initial normal development, show cerebellar ataxia, with slowly progressive gait imbalance. The first symptoms are recognized between age seven and 25 years (mean 14.6 years) [Anheim et al 2009, Hammer et al 2012]. In a 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 individuals with AOA2 have sensorimotor neuropathy (i.e., absent or diminished tendon reflexes and sensorimotor deficit).

Oculomotor apraxia. Oculomotor apraxia is present in about 51% of individuals [Anheim et al 2009]. 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 an Italian cohort, this feature was present in only 20% of individuals [Criscuolo et al 2006], while in a study of 19 affected Algerian individuals oculomotor apraxia was present in 32% [Tazir et al 2009]. A study of five individuals with AOA2, without head thrusts, revealed that hypometric saccades with a staircase pattern could be a more reliable sign of oculomotor apraxia than head thrust movements [Panouillères et al 2013].

Saccadic pursuit, gaze-evoked nystagmus, poor horizontal optokinetic nystagmus, and square-wave jerks have also been observed in several individuals [Al-Kaabi et al 2011].

In an Algerian study, 37% of affected individuals presented with convergent strabismus [Tazir et al 2009] and in a study of 90 affected individuals worldwide, strabismus was found in 12.3% [Anheim et al 2009]. Unilateral strabismus combined with nystagmus was found in an affected Algerian individual [H'mida-Ben Brahim et al 2011].

Movement disorders. Dystonic posture of the hands, choreic movements, and head or postural tremor are observed in about 14% of individuals [Anheim et al 2009, Tazir et al 2009]. The severity of the movement disorders persists in individuals with AOA2 in contrast to the movement disorder in individuals with ataxia with oculomotor apraxia type 1 (AOA1; OMIM 208920), in which chorea tends to disappear with time [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].

Rarely, involuntary movements have been reported as a prominent presenting sign of AOA2, although they are accompanied by ataxia in almost all individuals. Two individuals had upper limb dystonia as an initial sign. Two sibs presented with prominent chorea of the trunk and face. One individual had isolated head tremor as the initial sign at age nine years [Pearson 2016].

Pyramidal signs were found in 20.5% of individuals with AOA2 [Anheim et al 2009]. Plantar response was either flexor or neutral [Koenig & Moreira 2007]

Intellect. Mild cognitive impairment is present in some individuals [Le Ber et al 2004]; none have had severe intellectual disability or dementia, even after long disease duration [Le Ber et al 2004]. In the Criscuolo et al [2006] study, three of ten persons presented with mild intellectual impairment with onset around age 50 years. A study of the neuropsychological profile of an individual age 45 years with AOA2 indicated that the pathogenesis of the cerebrocerebellar circuit in AOA2 was responsible for the weaker coordination of complex cognitive functions such as working memory, executive functions, speech, and sequence learning [Klivényi et al 2012].

Other. Deep sensory loss [Le Ber et al 2004, Fogel et al 2009, H'mida-Ben Brahim et al 2011], extensor plantar reflexes, swallowing difficulties, and sphincter disturbances are observed in some individuals [Le Ber et al 2004]. Various signs of extraneurologic involvement including early-onset menopause [Criscuolo et al 2006], ovarian failure [Gazulla et al 2009], dermatofibrosarcoma protuberans [Schöls et al 2008], polycystic ovarian syndrome [Fogel et al 2009], and amenorrhea secondary to hypogonadotropic hypogonadism [Anheim et al 2009] have been reported.

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

Neuropathology. Chronic axonal neuropathy with preferential loss of large (and to a lesser degree small) myelinated fibers is detected in sural nerve biopsies [Al-Kaabi et al 2011].

Postmortem brain examination in an Italian individual age 79 years 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. A study of 3 Tesla (3T) brain MRI examinations of five individuals with AOA2 revealed significant atrophy of all cerebellar lobules. The degree of atrophy was highest in the vermis, consistent with the oculomotor presentation, and the anterior lobe, consistent with kinetic limb ataxia. An absence of hypointensity of the iron signal on susceptibility-weighted imaging (SWI) was seen in the dentate nucleus of all affected individuals [Frismand et al 2013].

Neurochemical patterns. Short-echo, single-voxel proton ((1)H) magnetic resonance spectroscopy performed in nine individuals with AOA2 showed total N-acetylaspartate levels in the cerebellum strongly correlated with the Friedreich Ataxia Rating Scale (FARS), which may be used as a measure of impairment in those with ataxia [Iltis et al 2010].

Genotype-Phenotype Correlations

A study of 90 individuals with AOA2 found that pathogenic missense variants in the helicase domain caused less severe AOA2 phenotypes than missense variants outside of this domain, or deletions, or truncating variants of *SETX*. However, individuals with pathogenic truncating or missense variants outside of the helicase domain had a lower frequency of pyramidal signs – a finding that may reflect masking of the pyramidal signs by severe motor neuropathy [Anheim et al 2009].

Nomenclature

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

Prevalence

The prevalence of p.Leu1976Arg and p.Glu65Lys pathogenic variants 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 p.Leu1976Arg common French-Canadian variant and none was a carrier of the rarer p.Glu65Lys variant. According to these results, the carrier rate for the p.Leu1976Arg variant is estimated to be 3.5% (1:28) for Québécois of Anglo-Norman origin and 2.1% (1:47) for the French-Canadian population of Gaspésie. No individuals homozygous for the pathogenic variants p.Leu1976Arg or p.Glu65Lys were identified.

A study of 102 individuals with suspected autosomal recessive cerebellar ataxia from Eastern Europe (95 from Alsace, in eastern France) reported seven individuals with AOA2 (6.9%). AOA2 prevalence in Alsace was inferred to be slightly less than 1:400,000 [Anheim et al 2010].

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 variants (p.Thr3Ile, p.Leu389Ser, and p.Arg2136His) 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 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.

An autosomal dominant form of ataxia appears to be associated with two *SETX* missense variants in *cis* configuration p.[Asn603Asp;Gln653Lys] 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 serum concentration of alpha-fetoprotein and creatine kinase were within normal range.

Differential Diagnosis

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

- Ataxia with oculomotor apraxia type 1 (AOA1; OMIM 208920) is a progressive cerebellar ataxia characterized by childhood onset 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. After a long disease duration (>10-15 years), low serum concentration of albumin and high serum concentration of total cholesterol are observed. AOA1 is caused by pathogenic variants in *APTX*, the gene encoding aprataxin.
- Ataxia with oculomotor apraxia type 4 (AOA4) (OMIM 616267) a form of recessive ataxia characterized by mean age at onset of 4.3 years, marked extrapyramidal manifestations, rapid progression, low or normal albumin levels, normal or high cholesterol levels, and elevated alpha-fetoprotein in some individuals. AOA4 is caused by pathogenic variants in *PNKP*.
- When oculomotor apraxia and/or high serum concentrations of alpha-fetoprotein are present, ataxia-telangiectasia (caused by pathogenic variants in *ATM*) and ataxia-telangiectasia-like disorder (caused by pathogenic variants in *MRE11*; OMIM 604391) 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 *FRDA* can detect pathogenic variants in virtually 100% of affected individuals.
- Ataxia with vitamin E deficiency (AVED) and primary coenzyme Q_{10} deficiency should be considered because they are treatable disorders.

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 *SCA2*.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with oculomotor apraxia type 2 (AOA2), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Neurologic examination including assessment of cranial nerve function, gait and limb ataxia, coordination, tone, strength, reflexes, and sensory perception
- Ophthalmologic examination
- Physical therapy and occupational therapy assessment of strength and balance
- Assessment of cognitive function
- Serum cholesterol

- Consultation with a clinical geneticist and/or genetic counselor
- Serum alpha-fetoprotein (AFP) concentration, if not evaluated previously

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 (e.g., 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 to reduce the risk of adverse health effects of hypercholesterolemia

Surveillance

Routine visits to the attending neurologist are indicated.

Ophthalmologic surveillance is recommended.

Cholesterol level should be monitored regularly.

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

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 (i.e., carriers of one *SETX* 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Individuals with AOA2 are not known to reproduce.

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SETX* pathogenic variants in the family.

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 carriers or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *SETX* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

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.

- **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 2: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SETX	9q34.13	Probable helicase senataxin	SETX database SETX homepage - Leiden Muscular Dystrophy pages	SETX	SETX

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 2 (View All in OMIM)

606002	SPINOCEREBELLAR ATAXIA, AUTOSOMAL RECESSIVE, WITH AXONAL NEUROPATHY 2; SCAN2
608465	SENATAXIN; SETX

Gene structure. *SETX* is composed of 24 coding and two noncoding exons (NM_015046.6). Multiple transcript variants and isoforms are described; for a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 100 pathogenic variants have been found in families worldwide. The majority are nonsense, missense, and splice site variants and small deletions and insertions. There have also been multiple reports of gross deletions, insertions, duplications, and even a complex allele [Criscuolo et al 2006, Arning et al 2008, Anheim et al 2009, Bernard et al 2009, Nanetti et al 2013] (see also Table A, **Locus-Specific Databases** and **HGMD**]. Such rearrangements accounted for 8%-20% of variants in different studies, with the largest study having 8% (4/51) [Bernard et al 2009].

Table 2. *SETX* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.193G>A	p.Glu65Lys	NM_015046.6 NP_055861.3
c.5927T>G	p.Leu1976Arg	

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.

Normal gene product. Probable helicase senataxin is a ubiquitously expressed 2,677 amino-acid enzyme encoded by *SETX*. Senataxin is strongly conserved throughout evolution and has been implicated in a large variety of biologic processes, including transcription, meiosis completion, neurogenesis, antiviral response, and maintenance of genomic integrity. In general, senataxin, likely complexed with other proteins, has a critical role in RNA metabolism to maintain genome stability in both proliferating cells and post-mitotic cells.

Because investigating the roles of senataxin in human and model organisms is an active area of research, the authors direct the reader to both recent reviews [Lavin et al 2013, Bennett & La Spada 2015, Groh et al 2017] and

a limited selection of publications of primary data [Miller et al 2015, Sariki et al 2016, Bennett et al 2018, Cohen et al 2018, Grunseich et al 2018].

Abnormal gene product. Importantly, the pathogenic missense variants to date cluster within the N-terminus and helicase domains marking these regions as being functionally important. The *SETX* deletions, insertions, and duplications in affected individuals indicate that loss of senataxin function is the cause of AOA2.

Chapter Notes

Acknowledgments

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Revision History

- 12 July 2018 (sw) Comprehensive update posted live
- 8 December 2011 (me) Comprehensive update posted live
- 24 March 2009 (cd) Revision: deletion/duplication analysis available clinically for *SETX*
- 5 March 2007 (me) Comprehensive update posted live
- 31 May 2005 (mcm) Revision: Sequence analysis clinically available
- 15 November 2004 (me) Review posted live
- 23 June 2004 (mcm) Original submission

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