

Hereditary ataxias: overview

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The hereditary ataxias are a highly heterogeneous group of disorders phenotypically characterized by gait ataxia, incoordination of eye movements, speech, and hand movements, and usually associated with atrophy of the cerebellum. There are more than 35 autosomal dominant types frequently termed spinocerebellar ataxia and typically having adult onset. The most common subtypes are spinocerebellar ataxia 1, 2, 3, 6, and 7, all of which are nucleotide repeat expansion disorders. Autosomal recessive ataxias usually have onset in childhood; the most common subtypes are Friedreich, ataxia-telangiectasia, ataxia with oculomotor apraxia type 1, and ataxia with oculomotor apraxia type 2. Four autosomal recessive types have dietary or biochemical treatment modalities

(ataxia with vitamin E deficiency, cerebrotendinous xanthomatosis, Refsum, and coenzyme Q10 deficiency), whereas there are no specific treatments for other ataxias. Diagnostic genetic testing is complicated because of the large number of relatively uncommon subtypes with extensive phenotypic overlap. However, the best testing strategy is based on assessing relative frequencies, ethnic predilections, and recognition of associated phenotypic features such as seizures, visual loss, or associated movement abnormalities.

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HEREDITARY ATAXIA

The hereditary ataxias are a clinically and genetically heterogeneous group of disorders characterized by slowly progressive incoordination of gait and often associated with poor coordination of hands, speech, and eye movements. Frequently, atrophy of the cerebellum occurs (**Figure 1**). In this review, the hereditary ataxias are categorized by mode of inheritance and gene in which causative mutations occur, or chromosomal locus. The hereditary ataxias can be inherited in an autosomal dominant, autosomal recessive, X-linked manner or through maternal inheritance if part of a mitochondrial genetic syndrome. The genetic forms of ataxia are diagnosed by family history, physical examination, neuroimaging, and molecular genetic testing. The clinical manifestations may result from one or a combination of dysfunction of the cerebellar systems, lesions in the spinal cord, and peripheral sensory loss.

Clinical manifestations

The clinical manifestations of the hereditary ataxias are progressive incoordination of movement and speech, and a wide-based, uncoordinated, unsteady gait. In addition, patients may develop ophthalmoplegia (limitations of eye movement), spasticity, neuropathy, and cognitive/behavioral difficulties. Particular signs beyond ataxia may guide the clinician in pursuit of directed genetic testing when investigating the cause of ataxia. For instance, cone-rod retinal dystrophy in conjunction with familial ataxia may suggest spinocerebellar ataxia (SCA)7; Native American origin or co-occurrence of epilepsy would raise the possibility of SCA10.

Establishing the diagnosis

Establishing the diagnosis of hereditary ataxia requires:

1. Detection on neurological examination of typical clinical signs including poorly coordinated gait and finger/hand movements, dysarthria (incoordination of speech), and eye movement abnormalities such as nystagmus, abnormal saccade movements, and ophthalmoplegia.
2. Exclusion of nongenetic causes of ataxia (see Differential Diagnosis below).
3. Documentation of the hereditary nature of the disease by finding a positive family history of ataxia, identifying an ataxia-causing mutation, or recognizing a clinical phenotype characteristic of a genetic form of ataxia.

Differential diagnosis

Differential diagnosis of hereditary ataxia includes acquired, nongenetic causes of ataxia, such as alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, primary or metastatic tumors, and paraneoplastic diseases associated with occult carcinoma of the ovary, breast, or lung, and the idiopathic degenerative disease multiple system atrophy (spinal muscular atrophy). The possibility of an acquired cause of ataxia needs to be considered in each individual with ataxia because a specific treatment may be available.

TYPES OF HEREDITARY ATAXIA

As discussed above, the hereditary ataxias can be subdivided by mode of inheritance, (i.e., autosomal dominant, autosomal

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recessive, X-linked, and mitochondrial), gene in which causative mutations occur, or chromosomal locus.^{1–3}

Autosomal dominant cerebellar ataxias

Synonyms for autosomal dominant cerebellar ataxias (ADCAs) used prior to the identification of the molecular genetic basis of these disorders were Marie's ataxia, inherited olivopontocerebellar atrophy, cerebello-olivary atrophy, or the more generic term, spinocerebellar degeneration.

Clinical features of ADCA. The age of onset and physical findings in the autosomal dominant ataxias overlap. **Table 1** indicates a few distinguishing clinical features for each type.^{4–8} Scales for rating symptoms and signs of ataxia have been published.⁹ Often the autosomal dominant ataxias cannot be differentiated by clinical or neuroimaging studies; they are usually slowly progressive and often associated with cerebellar atrophy, as seen from brain imaging studies (**Figure 1**). The frequency of the occurrence of each disease within the autosomal dominant cerebellar ataxia (ADCA) population is noted in **Table 1**. Pyramidal signs (hyperreflexia and spasticity) are commonly found in patients with SCA1 and SCA3; cognitive impairment has been reported in association with SCA2, SCA12, SCA13, SCA17; chorea may manifest in patients with SCA17 or dentatorubral-pallidoluysian atrophy (DRPLA). Many of the ADCAs in addition to limb and truncal ataxia cause dysarthria, dysphagia, and neuropathy. The clinical syndrome associated with SCA2 may include parkinsonism or motor neuron disease (amyotrophic lateral sclerosis)^{10,11} Age of onset is quite variable and usually in adulthood. Disease course

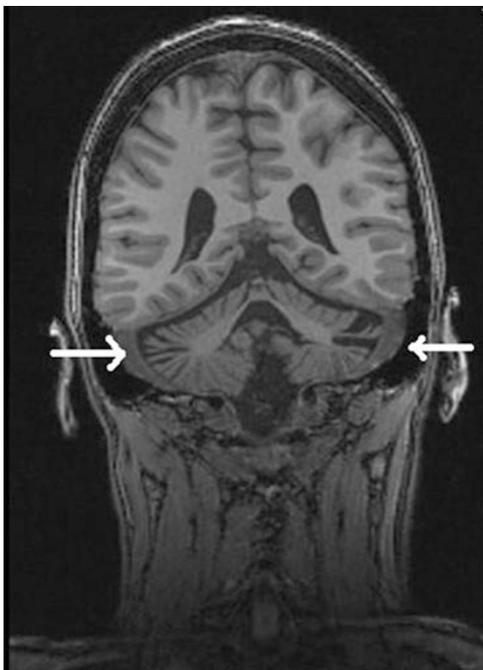


Figure 1 Coronal brain MRI showing atrophy of both cerebellar hemispheres (arrows) in a 28-year-old woman with SCA2. MRI, magnetic resonance imaging; SCA, spinocerebellar ataxia.

is also variable, although generally the disease progresses over decades. Life span may be shortened in SCA1, -2, -3, and -7 or normal in SCA5, -6, and -14.⁵ The most common form of episodic ataxia is EA2, caused by a variety of point mutations in the same calcium channel gene (*CACNA1A*) associated with SCA6 and familial hemiplegic migraine.¹²

Genetics. The ADCAs for which specific genetic information is available are summarized in **Table 1**. Most are SCAs; one is a complex form with additional phenotypic features in addition to ataxia; four are episodic ataxias; and one is a spastic ataxia. In addition to ADCAs described in **Table 1**, ADCAs include:

1. Ataxia with early sensory/motor neuropathy (linked to 7q22–q32); caused by mutations in *IFRD1*.^{13,14}
2. Cerebellar ataxia, deafness, narcolepsy, and optic atrophy (linked to 6p21–p23 in one family).¹⁵
3. Ataxia, cerebellar atrophy, intellectual disability, and possible attention deficit/hyperactivity disorder (associated with a heterozygous mutation in *SCN8A*, encoding a sodium channel).¹⁶
4. Late-onset (40s–60s) cerebellar ataxia preceded by many years of spasmodic coughing. One individual had calcification of the dentate nuclei on magnetic resonance imaging (MRI).¹⁷

Molecular genetic testing. Mutations associated with the ADCAs include nucleotide expansions occurring in either expressed or nonexpression regions of the gene, point mutations, duplications, and deletions.

Some of the earliest identified and most common ADCAs result from CAG trinucleotide expansions. SCA1, SCA2, SCA3, SCA6, SCA7, SCA12, SCA17, and DRPLA are all caused by CAG repeats within the coding region of the respective genes translating into an elongated polyglutamine tract in the protein. Molecular genetic testing for CAG repeat length is a highly specific and sensitive diagnostic test. The sizes of the normal CAG repeat allele and of the full-penetrance disease-causing CAG expansion vary among the disorders (for individual reviews of each disorder see GeneReviews.org).

Although ordering molecular testing for the polyglutamine ataxia disorders listed above is straightforward and tests are commercially available, there are two notes of caution in the interpretation of results:

1. Some disorders are associated with alleles for which overlap exists between the upper range of normal and the lower range of abnormal CAG repeat size. Typically, such alleles are categorized as mutable normal or reduced penetrance. Mutable normal alleles (previously referred to as intermediate alleles) do not cause disease in the individual but can expand on transmission to a reduced or fully penetrant allele. Therefore, children of an individual carrying a mutable normal allele are at increased risk of inheriting a disease-causing allele. In addition,

there are reduced-penetrance alleles that may or may not cause the disease in an individual; the probability of disease in persons with such alleles is typically unknown. Interpretation of test results in which the CAG repeat length is at the interface between the allele categories mutable normal/reduced penetrance and reduced penetrance/disease-causing can be difficult. In such cases, a consultation with the testing laboratory may be helpful to determine the precision of the CAG repeat length measurement.

2. In some instances, SCA2, SCA7, SCA8, and SCA10 result from extremely large CAG expansions in length that may be detected only by Southern blot analysis. For these disorders, a test result of apparent homozygosity (detection of a single allele by PCR analysis) must be interpreted in the context of multiple factors including clinical findings, family history, and age of onset of symptoms to determine whether Southern blot analysis to test for the presence of a large CAG expansion mutation is appropriate.

Other repeat expansions. SCA8 has a CTG trinucleotide repeat expansion in *ATXN8OS*.¹⁸ Extremely large repeats (~800) in *ATXN8OS* may be associated with an absence of clinical symptoms.¹⁹ The pathogenesis of the SCA8 phenotype is complex and also involves a (CAG)ⁿ repeat in a second overlapping gene, *ATXN8*.

SCA10 has a large expansion of an ATTCT pentanucleotide repeat in *ATXN10*, with the abnormal expansion range being much larger than that seen in the CAG repeat disorders.²⁰

Anticipation. Anticipation is observed in the autosomal dominant ataxias in which CAG trinucleotide repeats occur. Anticipation refers to earlier onset of an increasing severity of disease in subsequent generations of a family. In the trinucleotide repeat diseases, anticipation results from expansion in the number of CAG repeats that occurs with transmission of the gene to the next generation. *ATN1* (DRPLA) and *ATXN7* (SCA7) have particularly unstable CAG repeats.²¹ In SCA7, anticipation may be so extreme that children with early-onset, severe disease die of the disorder long before the affected parent or grandparent is symptomatic.

Anticipation is a significant issue in the genetic counseling of asymptomatic at-risk family members and in prenatal testing. Although general correlations exist between earlier age of onset and more severe disease with increasing number of CAG repeats, the age of onset, severity of disease, specific symptoms, and rate of disease progression are variable and cannot be accurately predicted by the family history or molecular genetic testing. Attention has been focused on the phenomena of anticipation and trinucleotide repeat expansion, but it is important to note that the number of trinucleotide repeats can also remain stable or even contract on transmission to subsequent generations.

In the CAG repeat disorders, expansion of the repeat is more likely to occur with paternal than with maternal transmission of

the expanded allele. By contrast, in SCA8, the majority of expansions of the CTG repeat occur during maternal transmission.

Prevalence. The prevalence of these rare diseases is not widely known. The prevalence of the ADCAs in the Netherlands is estimated to be at least 3:100,000.²² The prevalence of individual subtypes of ADCA may vary from region to region, frequently because of founder effects. For example, DRPLA is more common in Japan and SCA3 in Portugal; SCA2 is common in Korea and SCA3 is much more common in Japan and Germany than in the United Kingdom.^{23–25} SCA3 was originally described in Portuguese families from the Azores and called Machado-Joseph disease. DRPLA is rare in North America and common in Japan. A recent study found evidence of frequency variation between different regions in Japan.²⁶ Data are based on a comprehensive study in the United States by Moseley et al.²⁷

Autosomal recessive hereditary ataxias

Numerous recent reviews have detailed the clinical findings, genetics, and pathogenesis of the autosomal recessive ataxias.²⁸ The autosomal recessive ataxias may present with additional extra-central nervous system signs and symptoms. **Table 2** summarizes information for 13 typical autosomal recessive disorders in which ataxia is a prominent feature. The disorders are selected to indicate the range of genetic understanding that currently exists regarding recessive causes of ataxia.

Friedreich ataxia (FRDA) is the most common autosomal recessive ataxia, with a population frequency of 1–2:50,000. FRDA is characterized by slowly progressive ataxia with onset usually before 25 years of age and is typically associated with depressed tendon reflexes, dysarthria, Babinski responses, and loss of position and vibration senses.²⁹ About 25% of affected individuals have an “atypical” presentation with later onset (age >25 years), retained tendon reflexes, or unusually slow progression of disease. The vast majority of individuals have a GAA triplet-repeat expansion in *FXN*. Unlike the ADCAs caused by CAG trinucleotide repeats, FRDA is not associated with anticipation.

Ataxia-telangiectasia (A-T) is characterized by progressive cerebellar ataxia beginning between 1 and 4 years of age, oculomotor apraxia, frequent infections, choreoathetosis, telangiectasias of the conjunctivae, immunodeficiency, and an increased risk for malignancy, particularly leukemia and lymphoma. Testing that supports the diagnosis of individuals with A-T is identification of a 7;14 chromosome translocation on routine karyotype of peripheral blood, the presence of immunodeficiency and elevated serum α -fetoprotein, and *in vitro* radio-sensitivity assay. Molecular genetic testing of A-T is available clinically.

Ataxia with vitamin E deficiency (AVED) generally manifests in late childhood or early teens with dysarthria, poor balance when walking (especially in the dark), and progressive clumsiness resulting from early loss of proprioception. Some individuals experience dystonia, psychotic episodes (paranoia), pigmentary retinopathy, and/or intellectual decline. Most

Table 1 Autosomal dominant hereditary ataxias

Disease Name ^a	Gene	Average onset (range in years)	Average duration (range in years)	Distinguishing features ^b
SCA1	<i>ATXN1</i>	3rd–4th decade (<10 to >60)	15 years (10–28)	Pyramidal signs, peripheral neuropathy
SCA2	<i>ATXN2</i>	3rd–4th decade (<10 to >60)	10 years (1–30)	Slow saccadic eye movements, peripheral neuropathy, decreased DTRs, dementia
SCA3	<i>ATXN3</i>	4th decade (10–70)	10 years (1–20)	Pyramidal and extrapyramidal signs; lid retraction, nystagmus, decreased saccade velocity; amyotrophy fasciculations, sensory loss
SCA4	16q22.1	4th–7th decade (19–72)	Decades	Sensory axonal neuropathy, deafness; may be allelic with 16q22-linked SCA
SCA5	<i>SPTBN2</i>	3rd–4th decade (10–68)	>25 years	Early onset, slow course; first reported in descendants of Abraham Lincoln
SCA6	<i>CACNA1A</i>	5th–6th decade (19–71)	>25 years	Sometimes episodic ataxia, very slow progression
SCA7	<i>ATXN7</i>	3rd–4th decade (0.5–60)	20 years (1–45; early onset correlates with shorter duration)	Visual loss with retinopathy
SCA8	<i>ATXN8/ATXN8OS</i>	4th decade (1–65)	Normal life span	Slowly progressive, sometimes brisk DTRs, decreased vibration sense; rarely, cognitive impairment
SCA10	<i>ATXN10</i>	4th decade (12–48)	9 years	Occasional seizures; most families are of Native American background
SCA11	<i>TTBK2</i>	Age 30 years (15–70)	Normal life span	Mild, remain ambulatory
SCA12	<i>PPP2R2B</i>	4th decade (8–62)		Slowly progressive ataxia; action tremor in the 30s; hyperreflexia; subtle Parkinsonism possible; cognitive/psychiatric disorders including dementia
SCA13	<i>KCNC3</i>	Childhood or adulthood	Unknown	Mild intellectual disability, short stature
SCA14	<i>PRKCG</i>	3rd–4th decade (3–70)	Decades (1–30)	Early axial myoclonus
SCA15	<i>ITPR1</i>	4th decade (7–66)	Decades	Pure ataxia, very slow progression
SCA16	<i>SCA16</i>	Age 39 years (20–66)	1–40 years	Head tremor; one Japanese family
SCA17	<i>TBP</i>	4th decade (3–55)	>8 years	Mental deterioration; occasional chorea, dystonia, myoclonus, epilepsy; Purkinje cell loss, intranuclear inclusions with expanded polyglutamine
SCA18	7q22–q32	Adolescence (12–25)	Decades	Ataxia with early sensory/motor neuropathy, nystagmus, dysarthria, decreased tendon reflexes, muscle weakness, atrophy, fasciculations, Babinski responses
SCA19/22	<i>KCND3</i>	4th decade (10–51)	Decades	Slowly progressive, rare cognitive impairment, myoclonus, hyperreflexia
SCA20	11q12.2–11q12.3	5th decade (19–64)	Decades	Early dysarthria, spasmodic dysphonia, hyperreflexia, bradykinesia; calcification of the dentate nucleus
SCA21	<i>SCA21</i>	6–30	Decades	Mild cognitive impairment
SCA23	<i>PDYN</i>	5th–6th decade	>10 years	Dysarthria, abnormal eye movements, reduced vibration and position sense; one Dutch family; neuropathology ^c
SCA25	<i>SCA25</i>	(1.5–39)	Unknown	Sensory neuropathy; one French family
SCA26	<i>EEF2</i>	(26–60)	Unknown	Dysarthria, irregular visual pursuits; one Norwegian-American family; MRI: cerebellar atrophy
SCA27	<i>FGF14</i>	Age 11 years (7–20)	Decades	Early-onset tremor; dyskinesia, cognitive deficits; one Dutch family
SCA28	<i>AFG3L2</i>	Age 19.5 years (12–36)	Decades	Nystagmus, ophthalmoparesis, ptosis, increased tendon reflexes; two Italian families
SCA29	3p26	Early childhood	Lifelong	Learning deficits
SCA30	4q34.3–q35.1	(45–76)	Lifelong	Hyperreflexia

ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; DRPLA, dentatorubral-pallidoluysian atrophy; DTR, deep tendon reflex; EA, episodic ataxia; MRI, magnetic resonance imaging; SCA, spinocerebellar ataxia; SPAX1, autosomal dominant spastic ataxia 1.

^aSCA9 has not been assigned. ^bAll have gait ataxia. ^cPurkinje cell loss, demyelination of the posterior and lateral columns of the spinal cord, and neuronal intranuclear inclusions in the substantia nigra.

Table 1 Continued on next page

Table 1 Continued

Disease Name ^a	Gene	Average onset (range in years)	Average duration (range in years)	Distinguishing features ^b
SCA31	<i>BEAN1</i>	5th–6th decade	Lifelong	Normal sensation
SCA35	<i>TGM6</i>	43.7 ± 2.9 (40–48) years	15.9 ± 8.8 (5–31) years	Hyperreflexia, Babinski responses; spasmodic torticollis
SCA36	<i>NOP56</i>	52.8 ± 4.3 years	Decades	Muscle fasciculations, tongue atrophy, hyperreflexia
DRPLA	<i>ATN1</i>	3rd–4th decade (8–20 or 40–60s)	Early onset correlates with shorter duration	Chorea, seizures, dementia, myoclonus; often confused with Huntington disease
EA1	<i>KCNA1</i>	1st–2nd decade (2–15)	Attenuates after 20 years	Myokymia; attacks lasting seconds to minutes; startle or exercise induced; no vertigo
EA2	<i>CACNA1A</i> ; <i>CACNB4</i>	2–32	Lifelong	Nystagmus; attacks lasting minutes to hours; posture-change induced; vertigo; later, permanent ataxia
EA5	<i>CACNB4</i>	20–30	Lifelong	Nystagmus; acetazolamide helpful
EA6	<i>SLC1A3</i>	Childhood	Lifelong	Headache; nausea; photophobia; rare alternating hemiplegia/seizures
SPAX1	<i>VAMP1</i>	10–20	Normal life span	Initial progressive leg spasticity; similar to ARSACS

ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; DRPLA, dentatorubral-pallidoluysian atrophy; DTR, deep tendon reflex; EA, episodic ataxia; MRI, magnetic resonance imaging; SCA, spinocerebellar ataxia; SPAX1, autosomal dominant spastic ataxia 1.

^aSCA9 has not been assigned. ^bAll have gait ataxia. ^cPurkinje cell loss, demyelination of the posterior and lateral columns of the spinal cord, and neuronal intranuclear inclusions in the substantia nigra.

individuals become wheelchair bound as a result of ataxia and/or leg weakness between the ages 11 and 50 years. Although phenotypically similar to FRDA, AVED is more likely to be associated with head titubation or dystonia, and less likely to be associated with cardiomyopathy. It is important to consider the diagnosis of AVED (which can be made by measuring serum concentration of vitamin E) because it is treatable with vitamin E supplementation.^{30,31}

A different autosomal recessive ataxia occurring on Grand Cayman Island is caused by mutations in *ATCAY*, the gene encoding the protein CRAL-TRIO, which may also be involved in vitamin E metabolism.³²

Ataxia with oculomotor apraxia type 1 (AOA1) is characterized by childhood onset of slowly progressive cerebellar ataxia (mean onset age ~7 years), followed in a few years by oculomotor apraxia that progresses to external ophthalmoplegia. All affected individuals have a severe primary motor peripheral neuropathy leading to quadriplegia with loss of ambulation about 7–10 years after onset. Intellect remains normal in affected individuals of Portuguese ancestry, but mental deterioration has been seen in affected individuals of Japanese ancestry. The diagnosis of AOA1 is based on clinical findings and confirmed by molecular genetic testing.^{33–35}

Ataxia with oculomotor apraxia type 2 (AOA2) is characterized by onset between ages 10 and 22 years, cerebellar atrophy, axonal sensorimotor neuropathy, oculomotor apraxia, and elevated serum concentration of α -fetoprotein.^{36,37} The diagnosis of AOA2 is based on clinical and biochemical findings, family history, and exclusion of the diagnoses of A-T and AOA1; it is confirmed by molecular genetic testing.

Infantile-onset SCA is a rare disorder reported in Finland with degeneration of the cerebellum, spinal cord, and brain stem, and sensory axonal neuropathy.³⁸

Marinesco–Sjögren syndrome is a rare disorder in which ataxia is associated with intellectual disability, cataract, short stature, and hypotonia.^{39,40}

Polymerase γ -1-associated hereditary ataxias. Mutations in mitochondrial genes can result in an ataxia phenotype (see below). In addition, nuclear genes regulating mitochondrial processes can also result in a hereditary ataxia. Autosomal recessive mutations in polymerase γ -1 are associated with a broad spectrum of central nervous system and systemic phenotypes, but two in particular manifest with ataxia as a prominent feature.

1. Mitochondrial recessive ataxic syndrome: This is caused by autosomal recessive mutations in polymerase γ -1 and is characterized by cerebellar ataxia, nystagmus, dysarthria ophthalmoplegia, and frequently epilepsy; it is relatively common in Scandinavia. Age of onset ranges from childhood to mid-adulthood. Brain MRI may reveal cerebellar atrophy.⁴¹
2. Sensory ataxia, neuropathy, dysarthria, and ophthalmoplegia: As the name implies, a sensory neuropathy contributes to the ataxia observed in patients with sensory ataxia, neuropathy, dysarthria, and ophthalmoplegia. In addition, affected individuals may have eye movement abnormalities (ophthalmoplegia) and dysarthria.⁴² Epilepsy, myopathy, MRI abnormalities, and ragged red fibers have all been reported in association with sensory ataxia, neuropathy, dysarthria, and ophthalmoplegia.

Autosomal recessive spastic ataxia of Charlevoix-Saguenay is characterized by early onset (age 12–18 months) difficulty in walking and gait unsteadiness. Ataxia, dysarthria, spasticity,

Table 2 Autosomal recessive ataxias

Disease name	Gene symbol/ protein name	Population frequency	Onset (range in years)	Duration in years	Distinguishing features
Friedreich ataxia (FRDA)	<i>FXN</i> /frataxin	1–2:50,000	1st–2nd decade (4–40)	10–30	Hyporeflexia, Babinski responses, sensory loss, cardiomyopathy
Ataxia-telangiectasia	<i>ATM</i>	1:40,000 to 1:100,000	1st decade	10–20	Telangiectasia, immune deficiency, cancer, chromosomal instability, increased α -fetoprotein
Ataxia with vitamin E deficiency	<i>TTPA</i>	Rare	Age 2–52 years, usually <20	Decades	Similar to FRDA, head titubation (28%)
Ataxia with oculomotor apraxia type 1	<i>APTX</i> / aprataxin	Unknown	Childhood	Decades	Oculomotor apraxia, choreoathetosis, mild intellectual disability, hypoalbuminemia
Ataxia with oculomotor apraxia type 2	<i>SETX</i>	Unknown	Age 10–22 years	Decades	Cerebellar atrophy, axonal sensorimotor neuropathy, oculomotor apraxia
IOSCA	<i>C10orf2</i> / twinkle	Rare (Finland)	Infancy	Decades or less	Peripheral neuropathy, athetosis, optic atrophy, deafness, ophthalmoplegia, seizures
Marinesco–Sjögren syndrome	<i>SIL1</i>	Rare	Infancy	Decades	Intellectual disability, cataract, hypotonia, myopathy
Autosomal recessive spastic ataxia of Charlevoix-Saguenay	<i>SACS</i> /sacsin	Rare	Childhood	Decades	Spasticity, peripheral neuropathy, retinal striation
Refsum disease	<i>PHYH</i> ; <i>PEX7</i>	Rare	1st–6th decade	Decades	Neuropathy, deafness, ichthyosis, retinopathy
CoQ10 deficiency	<i>CABC1</i> ; <i>COQ2</i> ; <i>COQ9</i> ; <i>PDSS1</i> ; <i>PDSS2</i>	Rare	Childhood	Decades	Seizures, cognitive decline, pyramidal signs, myopathy
MIRAS	<i>POLG1</i>	Rare (Finland and Norway)	Childhood to young adulthood	Decades	Nystagmus, dysarthria, epilepsy, cerebellar atrophy on MRI
SANDO	<i>POLG1</i>	Rare	Childhood to young adulthood	Decades	Abnormal eye movements, ragged red fibers, myopathy, dysphagia, neuropathy, myopathy
Cerebrotendinous xanthomatosis	<i>CYP27A1</i>	1:50,000	Childhood to young adulthood	Decades	Thick tendons, cognitive decline, dystonia, white matter disease, cataract

CoQ10, coenzyme Q10; IOSCA, infantile-onset spinocerebellar ataxia; MIRAS, mitochondrial recessive ataxia syndrome; MRI, magnetic resonance imaging; SANDO, sensory ataxia, neuropathy, dysarthria and ophthalmoplegia.

extensor plantar reflexes, distal muscle wasting, a distal sensorimotor neuropathy predominantly in the legs, and horizontal gaze nystagmus constitute the major neurologic signs, which are most often progressive. Yellow streaks of hypermyelinated fibers radiate from the edges of the optic fundi in the retina of Quebec-born individuals with autosomal recessive spastic ataxia of Charlevoix-Saguenay,⁴³ whereas the retinal changes are uncommon in French, Tunisian, and Turkish individuals with the condition.^{44,45} Individuals with autosomal recessive spastic ataxia of Charlevoix-Saguenay become wheelchair bound at the average age of 41 years; cognitive skills are preserved long term, and individuals are able to accomplish activities of daily living late into adulthood. Death commonly occurs in the sixth decade.

Refsum disease generally presents in childhood or young adulthood; in addition to ataxia, there may be peripheral neuropathy, deafness, ichthyosis, or retinitis pigmentosa.⁴⁶

Polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC), a syndrome similar to Refsum disease, is caused by mutations in *ABHD12*.⁴⁷

Coenzyme Q10 (CoQ10) deficiency is often associated with seizures, cognitive decline, pyramidal track signs, and myopathy but may also include prominent cerebellar ataxia.^{48,49} The symptoms may respond to CoQ10 treatment.

Cerebrotendinous xanthomatosis has characteristic thickening of tendons often associated with cognitive decline, dystonia, cataract, and white matter changes on brain MRI.

Other autosomal recessive ataxias

1. Members of a family from Saudi Arabia have cerebellar atrophy, ataxia, and axonal sensorimotor neuropathy (linked to chromosome 14q31–q32; associated with mutations in *TDPI*, encoding a topoisomerase 1-dependent DNA damage repair enzyme, SCAN1).^{50,51}
2. Ataxia with hypogonadotropic hypogonadism. A similar sibship has shown a deficiency of CoQ10.⁵²
3. A single Slovenian family in which 5 of 14 siblings have ataxia with saccadic intrusions, sensory neuropathy, and myoclonus.⁵³

4. A large consanguineous Norwegian family with infantile-onset nonprogressive ataxia (linked to 20q11–q13).⁵⁴
5. A large consanguineous Saudi Arabian family has childhood-onset ataxia sometimes associated with epilepsy and cognitive deficits with a frameshift mutation in K1AA0226, which encodes rundataxin.⁵⁵
6. Mutations in *VLDLR*, encoding the very low-density lipoprotein receptor, in Hutterite families with nonprogressive cerebellar ataxia and intellectual disability with inferior cerebellar hypoplasia and mild cerebral gyral simplification.⁵⁶
7. Several French Canadian families in the Beauce region of Quebec with a late-onset cerebellar ataxia associated with mutations in *SYNE1*.^{57,58}
8. Disorders associated with congenital cerebellar agenesis or hypoplasia of varying degrees:
 - Joubert syndrome with pontine molar-tooth sign on MRI.^{59,60}
 - Cerebellar agenesis with neonatal diabetes mellitus.⁶¹
 - Very low-density lipoprotein receptor-associated cerebellar hypoplasia.
 - Congenital disorders of glycosylation.⁶²
 - Pontocerebellar hypoplasia.^{63,64}
9. Doi et al. (2011)⁶⁵ have reported a single consanguineous Japanese sibship with childhood-onset psychomotor retardation followed by adult-onset gait ataxia associated with cerebellar vermis atrophy on MRI and a homozygous missense mutation in *SYT14*, the gene encoding synaptotagmin-14.

X-linked hereditary ataxias

X-linked sideroblastic anemia and ataxia are characterized by early-onset ataxia, dysmetria, and dysdiadochokinesis. The ataxia is either nonprogressive or slowly progressive. Upper motor neuron signs (brisk deep tendon reflexes, unsustained ankle clonus, and equivocal or extensor plantar responses) are present in some males. Mild learning disability is seen. Anemia is mild without symptoms. Carrier females have a normal neurologic examination. Causative mutations are present in *ABC7*, encoding a protein involved with mitochondrial iron transport, suggesting a common pathogenesis with FRDA.⁶⁶

Adult-onset ataxia, especially in men, may be part of the fragile X-associated tremor/ataxia syndrome.^{67,68}

Ataxias with mitochondrial gene mutations

A progressive ataxia is sometimes associated with mitochondrial disorders including myoclonic epilepsy with ragged red fibers; neuropathy, ataxia, and retinitis pigmentosa;¹ and Kearns–Sayre syndrome. Mitochondrial disorders are often associated with additional clinical manifestations, such as seizures, deafness, diabetes mellitus, cardiomyopathy, retinopathy, and short stature.⁶⁹ Pfeiffer et al.⁷⁰ report that missense mutations in *MTATP6* can cause both childhood- and adult-onset cerebellar ataxia sometimes associated with abnormal eye movements, dysarthria, weakness, axonal neuropathy, and hyperreflexia.

EVALUATION STRATEGY

Once a hereditary ataxia is considered in an individual, the following approach can be used to determine the specific cause to aid in discussions of prognosis and genetic counseling. Establishing the specific cause of hereditary ataxia for a given individual usually involves a medical history, physical examination, neurologic examination, neuroimaging, detailed family history, and molecular genetic testing.

Because of extensive clinical overlap among all of the forms of hereditary ataxia, it is difficult in any given individual with ataxia and a family history consistent with autosomal dominant inheritance to establish a diagnosis without molecular genetic testing. Clinical findings may help distinguish among some of the autosomal recessive ataxias.

A three-generation family history with attention to other relatives with neurologic signs and symptoms should be obtained. Documentation of relevant findings in relatives can be accomplished either through direct examination of those individuals or review of their medical records, including the results of molecular genetic testing, neuroimaging studies, and autopsy examinations.

NonDNA testing. Plasma clinical tests are available that suggest the presence of five autosomal recessive hereditary ataxias: elevated α -fetoprotein in A-T and AOA2, low serum vitamin E in AVED, elevated cholestanol in cerebrotendinous xanthomatosis, and hypoalbuminemia in AOA1. Normal values of these tests may sometimes represent false negatives and do not exclude a specific type of ataxia.

Testing strategy when family history suggests autosomal dominant inheritance. There has been much progress in our ability to identify causative genes for a significant proportion of autosomal dominantly inherited ataxias. An estimated 50–60% of the dominant hereditary ataxias (see **Table 1**) can be identified with highly accurate and specific molecular genetic testing for SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA12, SCA17, and DRPLA; all have nucleotide repeat expansions in the pertinent genes. Of note, the interpretation of test results can be complex because (i) the exact range for the abnormal repeat expansion has not been fully established for many of these disorders; and (ii) only a few families have been reported with SCA8 and thus penetrance and gender effects have not been completely resolved.⁷¹ Thus, diagnosis and genetic counseling of individuals undergoing such testing require the support of an experienced laboratory, medical geneticist, and genetic counselor.

Because of the broad clinical overlap, most laboratories that test for the hereditary ataxias have a battery of tests including testing for SCA1, SCA2, SCA3, SCA6, SCA7, SCA10, SCA12, SCA14, and SCA17. Many laboratories offer them as two groups in stepwise fashion based on population frequency, testing first for the more common ataxias, SCA1, SCA2, SCA3, SCA6, and SCA7. Although pursuing multiple genes simultaneously may seem less optimal than serial genetic testing, it is important

to recognize that the cost of the battery of ataxia tests often is equivalent to that of an MRI. Positive results from the molecular genetic testing are more specific than MRI findings in the hereditary ataxias. Guidelines for genetic testing of hereditary ataxia have been published.⁷²

Testing is also available for some autosomal dominant forms of SCA that are not associated with repeat expansions, namely SCA5, SCA13, SCA14, SCA15, SCA27, SCA28, and 16q22-linked SCA.

Testing for the less common hereditary ataxias should be individualized and may depend on factors such as ethnic background (SCA3 in the Portuguese, SCA10 in the Native American population with some exceptions⁷³); seizures (SCA10); presence of tremor (SCA12, fragile X-associated tremor/ataxia syndrome); presence of psychiatric disease or chorea (SCA17); or uncomplicated ataxia with long duration (SCA6, SCA8, and SCA14). Dysphonia and palatal myoclonus are associated with calcification of the dentate nucleus of cerebellum (SCA20).

If a strong clinical indication of a specific diagnosis exists based on the affected individual's examination (e.g., the presence of retinopathy, which suggests SCA7) or if family history is positive for a known type, testing can be performed for a single disease.

Testing strategy when the family history suggests autosomal recessive inheritance. A family history in which only sibs are affected and/or when the parents are consanguineous suggests autosomal recessive inheritance. Because of their frequency and/or treatment potential, FRDA, A-T, AOA1, AOA2, AVED, and metabolic or lipid storage disorders such as Refsum disease and mitochondrial diseases should be considered.

Testing simplex cases. A simplex case is a single occurrence of a disorder in a family, sometimes incorrectly referred to as a "sporadic" case. If no acquired cause of the ataxia is identified, the probability is ~13% that the affected individual has SCA1, SCA2, SCA3, SCA6, SCA8, SCA17, or FRDA,⁷⁴ and mutations in rare ataxia genes are even less common.⁷⁵ Other possibilities to consider are a *de novo* mutation in a different autosomal dominant ataxia, decreased penetrance, alternative paternity, or a single occurrence of an autosomal recessive or X-linked disorder in a family such as fragile X-associated tremor/ataxia syndrome. Although the probability of a positive result from molecular genetic testing is low in an individual with ataxia who has no family history of ataxia, such testing is usually justified to establish a specific diagnosis for the individual's medical evaluation and for genetic counseling. Always consider a possible nongenetic cause such as multiple system atrophy, cerebellar type in simplex cases.⁷⁶

GENETIC COUNSELING

Risk to family members: autosomal dominant hereditary ataxia

Most individuals diagnosed as having autosomal dominant ataxia have an affected parent, although occasionally the family

history is negative. For instance, family history may not be obvious because of early death of a parent, failure to recognize autosomal dominant ataxia in family members, late onset in a parent, reduced penetrance of the mutant allele in an asymptomatic parent, or a *de novo* mutation. The risk to siblings depends on the genetic status of the proband's parents. If one of the proband's parents has a mutant allele, the risk to the sibs of inheriting the mutant allele is 50%. Individuals with autosomal dominant ataxia have a 50% chance of transmitting the mutant allele to each child.

Risk to family members: autosomal recessive hereditary ataxia

The parents of an individual affected with an autosomal recessive ataxia are obligate heterozygotes and therefore carry a single copy of a disease-causing mutation. In general, the heterozygotes are asymptomatic. Siblings of a proband have a 25% chance of being affected, a 50% chance of being a heterozygote carrier, and a 25% chance of being unaffected and not a carrier. Once it is established that an at-risk sib is unaffected, the chance of his/her being a carrier is two-thirds. All offspring of affected patients are obligate carriers.

Risk to family members: X-linked hereditary ataxia

The father of an affected male will not have the disease nor will he be a carrier of the mutation. However, women with an affected son and another affected male relative are obligate heterozygotes. The risk to siblings depends on the carrier status of the mother. If the mother of the proband has a disease-causing mutation, the chance of transmitting it in each pregnancy is 50%. Male siblings who inherit the mutation will be affected whereas female siblings inheriting the mutation will be carriers and usually not affected. If the proband with an X-linked disease represents a simplex (single occurrence in the family) and if the disease-causing mutation cannot be detected in the leukocyte DNA of the mother, the risk to siblings is low but greater than that of the general population because of the possibility of maternal germline mosaicism. The daughters of an affected male are all carriers whereas none of his sons will be affected or be carriers.

Related genetic counseling issues

Testing of at-risk asymptomatic adult relatives of individuals with autosomal dominant cerebellar ataxia is possible after molecular genetic testing has identified the specific disorder and mutation in the family. Such testing should be performed in the context of formal genetic counseling. This testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. Testing of asymptomatic at-risk individuals with nonspecific or equivocal symptoms is predictive testing, not diagnostic testing. When testing at-risk individuals, an affected family member should be tested first to confirm that the mutation is identifiable by currently available techniques. Results of testing of 29 asymptomatic persons at risk for autosomal dominant ataxias have been reported.⁷⁷

Molecular genetic testing of asymptomatic individuals younger than 18 years who are at risk for adult-onset disorders for which no treatment exists is not considered appropriate, primarily because it negates the autonomy of the child with no compelling benefit. Furthermore, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.

For more information, 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.

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.

Prenatal testing. Prenatal diagnosis for some of the hereditary ataxias is possible by analyzing fetal DNA (extracted from cells obtained by chorionic villus sampling at about 10–12 weeks' gestation or amniocentesis, usually performed at about 15–18 weeks' gestation) for disease-causing mutations. The disease-causing allele(s) of an affected family member must be identified before prenatal testing can be performed.

Requests for prenatal testing for (typically) adult-onset diseases 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, discussion of these issues is appropriate.

Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified.

MANAGEMENT

Treatment of manifestations

Management of ataxias is usually directed at providing assistance for coordination problems through established methods of rehabilitation medicine and occupational and physical therapy. Patients can be evaluated for mobility-assist devices such as canes, walkers, and wheelchairs, which are useful for gait ataxia. Similarly, special devices are available to assist with handwriting, buttoning, and use of eating utensils.

Speech therapy may benefit persons with dysarthria. Computer devices are available to assist persons with severe speech deficits.

Parkinsonian features may respond to L-Dopa, and spasticity may respond to Baclofen or tizanidine.

Prevention of primary manifestations

Treatments are available for a few autosomal recessive ataxias: Vitamin E therapy for AVED, chenodeoxycholic acid for cerebrotendinous xanthomatosis, CoQ10 for CoQ10 deficiency, and dietary restriction of phytanic acid for Refsum disease. Idebenone may ameliorate the cardiac and neurologic manifestations of FRDA.⁷⁸ No other specific treatments exist for hereditary ataxias.

Therapies under investigation

Underwood and Rubinsztein⁷⁹ review potential strategies for treating ataxias associated with trinucleotide repeat expansions. RNA interference strategies have been suggested for some autosomal dominant SCAs.⁸⁰ For further and up-to-date information, readers may search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Resource

National Ataxia Foundation, 2600 Fernbrook Lane Suite 119, Minneapolis, MN 55447; Phone: 763.553.0020; <http://www.ataxia.org>.

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DISCLOSURE

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