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Hereditary Ataxia Overview

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Summary

The purpose of this overview on hereditary ataxia is to increase the awareness of clinicians regarding the causes of hereditary ataxia, related genetic counseling issues, and management.

Goal 1

Briefly describe the clinical characteristics of hereditary ataxias (sometimes referred to as "primary hereditary ataxias") for which an adult with ataxia or the caregivers of a child with ataxia would seek diagnosis and management from a neurologist as part of a multidisciplinary team.

Goal 2

Review common and notable genetic causes of hereditary ataxia.

Goal 3

Provide an evaluation strategy to identify the genetic cause of hereditary ataxia in a proband.

Goal 4

Inform genetic counseling of family members of an individual with hereditary ataxia.

Goal 5

Review management of hereditary ataxia.

1. Clinical Characteristics of Primary Hereditary Ataxia

For the purposes of this chapter, which deals exclusively with hereditary ataxias, the term "primary hereditary ataxia" has been used to designate hereditary ataxias for which an adult with ataxia or the caregivers of a child with ataxia would seek diagnosis and management from a neurologist as part of a multidisciplinary team.

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Use of the term "primary hereditary ataxia" is intended to exclude hereditary multisystem disorders in which ataxia may be observed, but is usually not the primary presenting manifestation.

Excluded Categories

For the purposes of this overview the following categories of hereditary disorders in which ataxia may occur are not considered primary hereditary ataxias:

- Infantile-onset multisystem disorder
- Epileptic encephalopathy
- Presence of distinctive MRI findings:
 - Brain malformation (e.g., cerebellar hypoplasia, cerebellar vermis hypoplasia as in [Joubert syndrome](#) and related disorders)
 - Leukodystrophy
- Developmental delay / intellectual disability
- An inborn error of metabolism (e.g., [peroxisomal biogenesis disorders](#), [Zellweger spectrum disorders](#), disorders of glycosylation)
- Primary mitochondrial disorders (See [Primary Mitochondrial Disorders Overview](#).)
- Other complex multisystem disorders such as [Niemann-Pick disease type C](#) and late-onset Tay-Sachs disease (see [HEXA Disorders](#)), which can on occasion present with ataxia

Manifestations

The manifestations of many of the more common primary hereditary ataxias discussed in Section 2 of this overview become evident between ages 30 and 50 years, although manifestations of other ataxias are evident before age 25 years (e.g., ataxia with oculomotor apraxia, [Friedreich ataxia](#)) or before age five years (e.g., [ataxia-telangiectasia](#)).

The **first manifestation** of ataxia can include:

- Most commonly, a slowly progressive gait disorder that appears unsteady and predisposes to unexpected falls;
- Disequilibrium ("dizziness"), which may lead to an evaluation for peripheral vestibular dysfunction;
- Hand and finger clumsiness or tremor, which may raise the possibility of essential tremor or even parkinsonism;
- Slurring of speech or unexpected choking, which could lead to an evaluation for [amyotrophic lateral sclerosis](#) (ALS);
- Rarely, double vision, which could lead to an evaluation by an optometrist or ophthalmologist.

At disease onset, these manifestations may be intermittent or evident only at certain times (e.g., later in the day, when tired, after consuming alcohol). The manifestations typically become constant and slowly worsen.

Typical **cerebellar features** on neurologic examination include:

- Wide-based, staggering walk with difficulty performing tandem gait;
- Truncal instability when sitting unsupported;
- Difficulty with target maneuvers of the upper extremities (dysmetria, terminal tremor);
- Slowed rapid alternating movements (dysdiadochokinesis);
- Dysarthria (slowed or slurred articulation, variable pitch and loudness, monotonous or "scanning" speech);
- Abnormal eye movements (saccade intrusions in primary gaze, nystagmus in horizontal or vertical gaze, saccade hypermetria).

Non-cerebellar findings that can mimic or exacerbate the cerebellar ataxia (which can be identified by examination or testing) include:

- Alterations in descending frontal or parietal motor pathways (e.g., in normal pressure hydrocephalus);
- Brain stem changes that disrupt cerebellar pathways (e.g., in central vestibular dysfunction);
- Sensory pathway dysfunctions that alter input to the cerebellum (visual, peripheral vestibular, posterior column, peripheral sensory);
- Other sources of motor change, especially as they affect gait (weakness, rigidity, spasticity);
- Non-neurologic disorders (e.g., joint disease).

Brain imaging (MRI, MRS, PET) confirms the presence of cerebellar atrophy or hypoplasia.

Electronystagmography can document dysfunction in cerebellar, vestibular, or oculomotor pathways.

Progression of a hereditary ataxia usually leads to:

- Use of assistive devices for ambulation five to ten years after onset and ultimately to wheelchair dependence;
- Choking or falls resulting in, for example, head injury or hip fracture, which are common causes of morbidity and mortality;
- Infection and sepsis (from aspiration or other pneumonia, urinary tract infection, decubiti), especially prominent in the later stages of disease;
- Decline in self-care ability, increasing risk of falls, dependence on a feeding tube, and/or incontinence;
- The family or caregiver's need to consider more in-home care assistance or out-of-home placement.

Affected individuals do not usually live longer than 25 years after manifestations emerge.

See Figure 1 for worldwide distribution of the most common primary hereditary ataxias.

2. Causes of Hereditary Ataxia

Note: Up to 40% of adults with late-onset cerebellar ataxia and no family history of ataxia will not have an identified genetic cause despite a comprehensive evaluation (see Section 3).

The causes of primary hereditary ataxia included in this overview are separated into nucleotide repeat disorders (Table 1 and Table 2), other common hereditary ataxias (Table 3), and potentially treatable causes of hereditary ataxia (Table 4 and Table 5).

Nucleotide Repeat Disorders

The nucleotide repeat disorders (see Table 1), the most common cause of hereditary ataxia, are discussed separately because of their unique molecular mechanism and inheritance issues.

Molecular Mechanism

In nucleotide repeat disorders, a sequence of nucleotides is repeated a number of times in tandem within a gene (in an exon or intron) or near a [gene](#). For a given gene, the size of the nucleotide repeats varies: smaller numbers of repeats are common and not associated with phenotypic abnormalities, whereas abnormally large numbers of repeats (uninterrupted or interrupted) may be associated with phenotypic abnormalities.

Inheritance Issues

All three modes of inheritance can be observed in nucleotide repeat disorders: autosomal dominant, autosomal recessive, and X-linked.

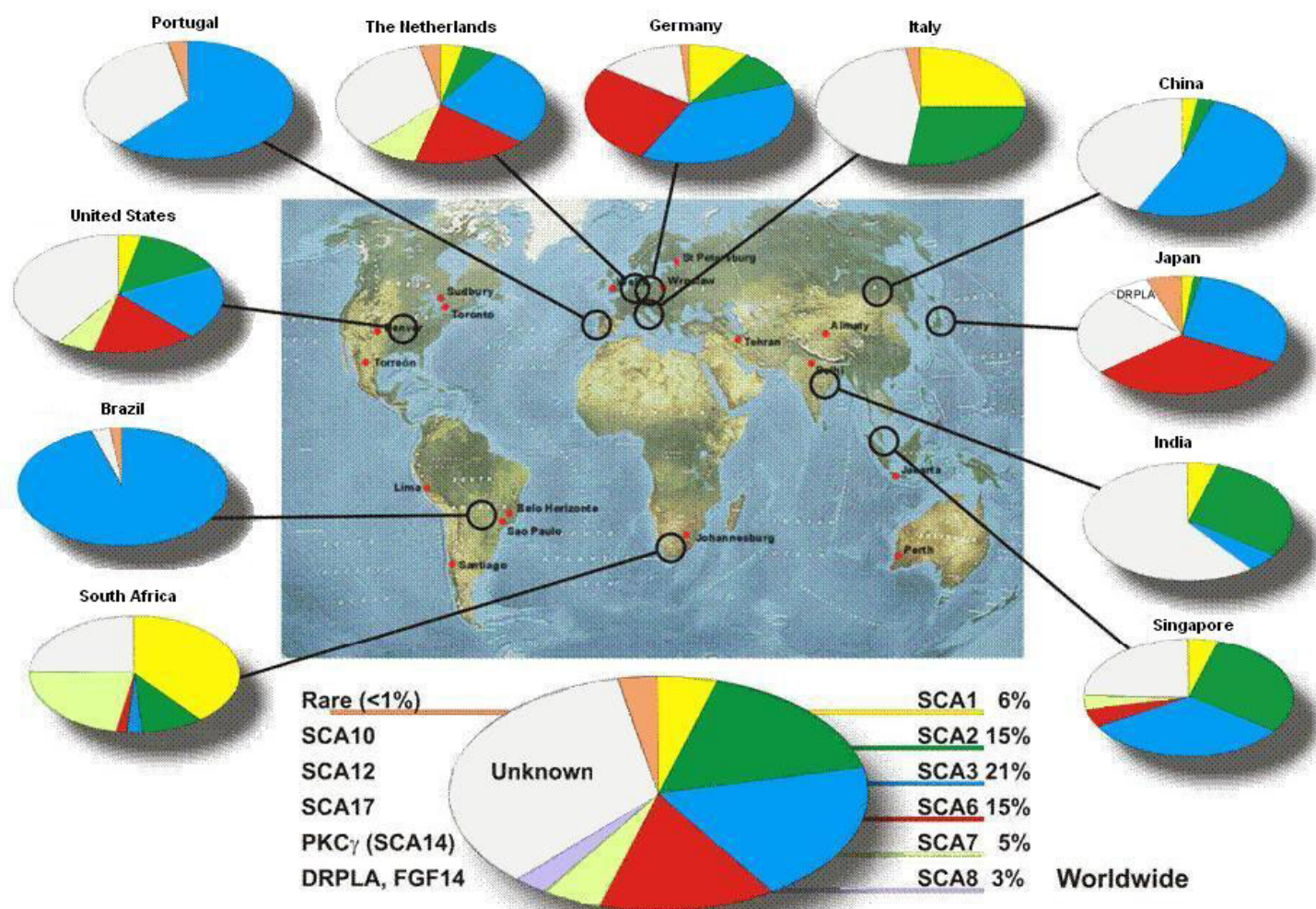


Figure 1. Worldwide distribution of SCA subtypes[Schöls et al 1997, Moseley et al 1998, Saleem et al 2000, Storey et al 2000, Tang et al 2000, Maruyama et al 2002, Silveira et al 2002, van de Warrenburg et al 2002, Dryer et al 2003, Brusco et al 2004, Schöls et al 2004, Shimizu et al 2004, Zortea et al 2004, Jiang et al 2005, Jiang et al 2013]

Note: The data in Figure 1 was gathered before the use of multigene panels and exome/genome sequencing. The data are still appropriate for nucleotide repeat disorders; new SCAs found by exome/genome sequencing represent a very small percentage. There have been no recent regional updates to SCA subtype distribution in Australia or sub-Saharan Africa.

(For a pdf version click [here](#).)

Figure published courtesy of L Schöls, P Bauer, T Schmidt, T Schulte, O Reiss of University of Tübingen and Ruhr-University Bochum, Germany

Autosomal dominant inheritance. A unique aspect of autosomal dominant inheritance of nucleotide repeat disorders is anticipation, the earlier onset and increasing severity of disease in subsequent generations as a result of expansion in the repeat size during transmission. In some disorders, anticipation may be so extreme that children with early-onset, severe, and usually phenotypically different disease die of disease complications long before the affected parent or grandparent is symptomatic.

X-linked inheritance. A unique aspect of [fragile X tremor/ataxia syndrome](#), the most common X-linked ataxia, is its occurrence in males and females with repeat sizes in the premutation range (see Table 2).

Table 1. Hereditary Ataxias Caused by Nucleotide Repeat Expansions: Clinical Findings

Gene ¹	Disorder ²	MOI	Distinguishing Non-Ataxic Clinical Features	Comment
Most commonly involved genes ³				
<i>ATN1</i>	DRPLA	AD	Chorea, dementia, myoclonus, seizures; mimics Huntington disease.	<ul style="list-style-type: none"> Anticipation is prominent. More common in Japan
<i>ATXN1</i>	SCA1	AD	Peripheral neuropathy, pyramidal signs; early bulbar features; occasional cognitive decline	Anticipation is more likely w/paternal transmission.
<i>ATXN2</i>	SCA2	AD	↓ DTRs, dementia, peripheral neuropathy, slow saccadic eye movements	<ul style="list-style-type: none"> Anticipation is more likely w/ paternal transmission. Large Cuban founder population
<i>ATXN3</i>	SCA3	AD	Amyotrophy, fasciculations, sensory loss; lid retraction, nystagmus, & ↓ saccade velocity; pyramidal & extrapyramidal signs; shortened life span	<ul style="list-style-type: none"> Anticipation may be more likely w/paternal transmission. Large Portuguese founder population Also known as Machado-Joseph disease
<i>ATXN7</i>	SCA7	AD	Visual loss w/retinopathy; often rapidly progressive; shortened life span	Anticipation is prominent w/more marked repeat expansions w/paternal transmission.
<i>ATXN8</i> <i>ATXN8OS</i>	SCA8	AD	Slowly progressive, sometimes brisk DTRs, ↓ vibration sense; rarely, cognitive impairment in persons w/earlier onset	Anticipation is more likely w/maternal transmission.
<i>ATXN10</i>	SCA10	AD	Seizures in certain families	<ul style="list-style-type: none"> Anticipation can occur w/paternal transmission. Large Mexican founder population
<i>CACNA1A</i>	SCA6	AD	May begin w/episodic ataxia, very slow progression; onset often after age 50 yrs; normal life span	<ul style="list-style-type: none"> Anticipation is not seen. See Table 3 for ataxia caused by missense variants.
<i>FXN</i>	Friedreich ataxia	AR	Generally childhood onset w/slowly progressive ataxia, absent tendon reflexes, Babinski responses, posterior column sensory loss, cardiomyopathy, scoliosis, pes cavus, & diabetes; in some: onset ≥25 yrs, slower progression, & retained reflexes	Anticipation is not seen.
<i>RFC1</i>	RFC1 CANVAS / spectrum disorder	AR	Spectrum ranges from typical cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS), to cerebellar, sensory, & vestibular impairment, to more limited phenotypes involving predominantly or exclusively 1 of the systems involved in balance control.	Anticipation is not seen.
<i>TBP</i>	SCA17	AD	Mental deterioration; occasional chorea, dystonia, myoclonus, epilepsy	Anticipation is infrequently observed.
Less commonly involved genes				
<i>BEAN1</i> ^{3, 4}	SCA31 (OMIM 117210)	AD	Normal sensation	Common in Japan

Table 1. continued from previous page.

Gene ¹	Disorder ²	MOI	Distinguishing Non-Ataxic Clinical Features	Comment
<i>FMR1</i>	Fragile X-associated tremor/ataxia syndrome (FXTAS) (See FMR1 Disorders .)	XL		<ul style="list-style-type: none"> Anticipation occurs almost exclusively w/maternal transmission. Most common X-linked ataxia; occurs in male & female premutation carriers
<i>NOP56</i> ^{3, 4}	SCA36	AD	Hyperreflexia, muscle fasciculations, tongue atrophy	Insufficient evidence for anticipation
<i>PPP2R2B</i> ^{3, 4}	SCA12 (OMIM 604326)	AD	Action tremor in the 4th decade, cognitive/psychiatric disorders incl dementia, hyperreflexia, slowly progressive ataxia, subtle parkinsonism possible	Insufficient evidence for anticipation

DRPLA = dentatorubral-pallidoluysian atrophy; DTR = deep tendon reflex; SCA = spinocerebellar ataxia

1. Genes are listed in alphabetic order within prevalence categories.

2. For more information see hyperlinked *GeneReview*. An OMIM phenotype entry is provided if a *GeneReview* is not available.

3. Dürr [2010]

4. Nucleotide repeat expansions in *BEAN1*, *NOP56*, and *PPP2R2B* represent relatively rare causes of hereditary ataxia.

Table 2. Hereditary Ataxias Caused by Nucleotide Repeat Expansions: Molecular Genetics

Gene ¹	% of Pathogenic Variants	Nucleotide Repeat (Amino Acid)	Repeat Location	Normal Repeat Number	Full-Penetrance Pathogenic Repeat Number	Comment
<i>ATN1</i>	100	CAG (Gln)	Exon 5	6-35	≥48	
<i>ATXN1</i>	100	CAG (Gln)	Exon 8	6-35	≥39	
<i>ATXN2</i>	100	CAG (Gln)	Exon 1	≤31	≥33	
<i>ATXN3</i>	100	CAG (Gln)	Exon 8	12-44	60-87	
<i>ATXN7</i>	100	CAG (Gln)	Exon 1	4-19	≥36	
<i>ATXN8</i>	100	CAG (Gln)	Exon 1	~80	Unknown	
<i>ATXN8OS</i>	100	CTG	3' UTR	15-50 CTA/CTG	≥71-1300 CTA/CTG ²	Penetrance is <100%. ²
<i>ATXN10</i>	100	ATTCT	Intron 9	10-32	≥800	Repeat interruptions are assoc w/presence of seizures.
<i>BEAN1</i>	100	TGGAA	Intron 6	0	2.5- to 3.8-kb insertion	
<i>CACNA1A</i> ³	>99	CAG (Gln)	Exon 7	≤18	20-33	See Table 3 for phenotype assoc w/ variants that are not nucleotide repeat disorders.
<i>FMR1</i>	>99	CGG	5' UTR	5-44	≥200	Premutation alleles: 55-200 CGG repeats

Table 2. continued from previous page.

Gene ¹	% of Pathogenic Variants	Nucleotide Repeat (Amino Acid)	Repeat Location	Normal Repeat Number	Full-Penetrance Pathogenic Repeat Number	Comment
<i>FXN</i>	~98	GAA	Intron 1	5-33	≥66	In about 5% of affected persons 1 <i>FXN</i> allele is an expanded GAA repeat & 1 is a pathogenic missense variant.
<i>NOP56</i>	100	GGCCTG	Intron 1	3-14	≥650	
<i>PPP2R2B</i>	100	CAG	Promoter	7-31	51-78	
<i>RFC1</i>	100	AAGGG ⁴	Intron 2	Unknown	~400~2000	ACAGG repeat expansion has been reported in 3 persons from Asian & Asian Pacific populations. ⁴
<i>TBP</i>	100	CAG or CAA (Gln)	Exon 3	25-40	≥49	

Based on [Resources for Genetics Professionals — Genetic Disorders Caused by Nucleotide Repeat Expansions and Contractions](#)

1. Genes are listed in alphabetic order.

2. While penetrance less than 100% has been reported at all repeat sizes, higher penetrance is reported for CTA/CTG repeat sizes of 80-250 [Ranum et al 1999].

3. The majority of *CACNA1A* pathogenic variants are CAG repeat expansions associated with spinocerebellar ataxia type 6. Heterozygous *CACNA1A* missense, nonsense, splice site, frameshift, and exon/multiexon deletions have been reported in individuals with episodic ataxia type 2 and progressive cerebellar ataxia.

4. *RFC1* intron 2 contains a microsatellite region with variable **benign AAAAG** repeats (range: 11-200 repeats) and/or **benign AAAGG** repeats (range: 40-1000 repeats). Interruption of the benign AAAAG/AAAGG repeated units with **biallelic pathogenic AAGGG** expansions has been identified in individuals with [RFC1 CANVAS / spectrum disorder](#) [Cortese et al 2019].

Other Common Hereditary Ataxias

Table 3. Most Common Hereditary Ataxias (Excluding Nucleotide Repeat Disorders)

Gene ¹	MOI	Phenotype		Other Phenotypic Features / Comments	Designation / <i>GeneReview</i> / OMIM
		Ataxia	Spasticity		
<i>AFG3L2</i>	AD	+	+	Ophthalmoparesis, slow saccades, ptosis ³	SCA28 (OMIM 610246)
	AR				SCAR5 (OMIM 614487)
<i>ANO10</i>	AR	+	+	Downbeat nystagmus, fasciculations	SCAR10 (OMIM 613728)
<i>APTX</i>	AR	+		Early-onset ataxia, oculomotor apraxia, extrapyramidal features, sensorimotor neuropathy, hypoalbuminemia; secondary coenzyme Q ₁₀ deficiency (See Primary Coenzyme Q₁₀ Deficiency .)	Ataxia with Oculomotor Apraxia Type 1
<i>ATM</i>	AR	+		Early-onset ataxia, oculomotor apraxia, extrapyramidal features, immunodeficiency, cancer risk, ↑ alpha-fetoprotein	Ataxia-Telangiectasia
<i>CACNA1A</i> ²	AD	+			Episodic ataxia type 2 (OMIM 108500)

Table 3. continued from previous page.

Gene ¹	MOI	Phenotype		Other Phenotypic Features / Comments	Designation / <i>GeneReview</i> / OMIM
		Ataxia	Spasticity		
<i>ITPR1</i>	AD	+		Adult onset, slowly progressive	SCA15/16 (OMIM 606658)
	AD ³	+		Congenital, non-progressive	SCA29 (OMIM 117360)
<i>KCNC3</i>	AD ³	+		Adult onset, slowly progressive	SCA13
				Congenital, non-progressive	
<i>KCND3</i> ⁴	AD	+			SCA19/22 (OMIM 605411)
<i>PRKCG</i>	AD	+			SCA14
<i>SACS</i>	AR	+	+	Early-onset ataxia w/spastic paraparesis & axonal-demyelinating sensorimotor neuropathy; hypointense pontine stripes on T ₂ -weighted MRI ⁵	ARSACS (SPAX6)
<i>SETX</i> ⁶	AR	+	+	Early-onset ataxia, oculomotor apraxia w/↑ alpha-fetoprotein ⁵	Ataxia with Oculomotor Apraxia Type 2 (SCAR1)
<i>SPG7</i>	AR	+	+	Variable spasticity & cerebellar ataxia ⁵	Spastic Paraplegia 7
<i>SPTBN2</i>	AD	+			SCA5 (OMIM 600224)
	AR				SCAR14 (OMIM 615386)
<i>SYNE1</i> ⁷	AR	+	+	Cerebellar ataxia, variable spasticity, & further multisystemic neurologic damage ⁵	ARCA1 (SCAR8) (See SYNE1 Deficiency .)

Based on Synofzik & Schüle [2017] and Galatolo et al [2018]

AD = autosomal dominant; ARCA = autosomal recessive cerebellar ataxia; MOI = mode of inheritance; SCA = spinocerebellar ataxia; SCAR = spinocerebellar ataxia, autosomal recessive; SPAX = spastic ataxia, autosomal recessive

1. Genes are listed in alphabetic order.

2. Allelic disorders include [familial hemiplegic migraine](#) and [spinocerebellar ataxia type 6](#).

3. The disorder may occur as the result of a *de novo* pathogenic variant.

4. Allelic disorder: [Brugada syndrome](#)

5. Synofzik & Schüle [2017]

6. Allelic disorder: [amyotrophic lateral sclerosis](#)

7. Allelic phenotype: arthrogryposis multiplex congenita (See [SYNE1 Deficiency](#).)

Potentially Treatable Hereditary Ataxias

Table 4. Genetic Causes of Vitamin E Deficiency (Treatable with Vitamin E Replacement)

Gene ¹	MOI	Phenotypic Features in Addition to Ataxia / Comments	Designation / <i>GeneReview</i> / OMIM
<i>ANGPTL3</i>	AR	Neuropathy, retinopathy, acanthocytosis	Familial combined hypolipidemia
<i>APOB</i>	AR ³		APOB-Related Familial Hypobetalipoproteinemia
<i>MTTP</i>	AR	Large fiber sensory neuropathy, retinopathy, acanthocytosis	Abetalipoproteinemia (Bassen-Kornzweig disease)

Table 4. continued from previous page.

Gene ¹	MOI	Phenotypic Features in Addition to Ataxia / Comments	Designation / <i>GeneReview</i> / OMIM
<i>TTPA</i>	AR	Proprioceptive sensory loss, absent DTR	Ataxia w/Vitamin E Deficiency

Based on Synofzik & Schüle [2017]

AR = autosomal recessive; DTR = deep tendon reflex; MOI = mode of inheritance

1. Genes are listed in alphabetic order.

2. Burnett & Hooper [2015]

3. *APOB*-related familial hypobetalipoproteinemia caused by homozygous (or compound heterozygous) pathogenic variants in *APOB* is inherited in an autosomal recessive manner.

Table 5. Primary Coenzyme Q₁₀ (CoQ₁₀) Deficiency (Possibly Responsive to CoQ₁₀ Replacement)

Gene ¹	MOI	Other Phenotypic Features / Comments	Designation / <i>GeneReview</i> / OMIM
<i>COQ2</i>	AR	SRNS, retinitis pigmentosa, SNHL, hypertrophic cardiomyopathy, ragged red muscle changes, seizures, lactic acidemia ²	COQ10D1; Primary CoQ₁₀ Deficiency
	AD AR	A small number of persons of Japanese ancestry w/multiple system atrophy type C have biallelic or heterozygous <i>COQ2</i> pathogenic variants.	OMIM 146500
<i>COQ4</i>	AR	Similar to <i>COQ2</i> -related CoQ ₁₀ deficiency ²	COQ10D7; Primary CoQ₁₀ Deficiency
<i>COQ6</i>	AR	Similar to <i>COQ2</i> -related CoQ ₁₀ deficiency; SRNS, SNHL ²	COQ10D6; Primary CoQ₁₀ Deficiency
<i>COQ8A</i>	AR	Seizures ²	COQ10D4; Primary CoQ₁₀ Deficiency ; SCAR9 (OMIM 612016)
<i>PDSS1</i>	AR	Similar to <i>COQ2</i> -related CoQ ₁₀ deficiency ²	COQ10D2; Primary CoQ₁₀ Deficiency

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; SNHL = sensorineural hearing loss; SRNS = steroid-resistant nephrotic syndrome

1. Genes are listed in alphabetic order.

2. Onset usually in infancy or early childhood

3. Evaluation Strategies to Identify the Genetic Cause of Hereditary Ataxia in a Proband

Establishing a specific genetic cause of primary hereditary ataxia (as defined in this chapter):

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, family history, and genomic/genetic testing.

Medical History

Most of the common primary hereditary ataxias start similarly with an unsteady gait, imbalance or "dizziness," unexpected falls, clumsiness, and tremors.

Distinctive features of the medical history that could suggest a specific diagnosis (see Table 1 and Table 3) include the following:

- Age of onset:
 - After age 50 years: SCA6
 - Before age 20 years: Friedreich ataxia, ataxia with oculomotor apraxia types 1 and 2
 - Before age five years: ataxia-telangiectasia

- Infantile: SCA2, SCA7
- Onset with episodic features: SCA6, the episodic ataxias
- Associated with:
 - Retinopathy: SCA7
 - Seizure disorder: SCA10, infantile-onset SCA7, DRPLA
 - Dementia: SCA2, SCA17, DRPLA
 - Severe dizziness or vertigo: SCA3, SCA6, *RFC1* CANVAS / spectrum disorder
 - Muscle cramping: SCA2, SCA3
 - Scoliosis, pes cavus, cardiomyopathy: Friedreich ataxia
 - Immunodeficiency or cancer: ataxia-telangiectasia

Physical Examination

All the primary hereditary ataxias have cerebellar features, but some have specific cerebellar or extracerebellar changes on examination that can suggest a specific diagnosis (see Table 1 and Table 3). In addition to the information provided in the medical history above, the following may be observed:

- Early presence of slowed oculomotor saccades: SCA2, SCA7
- Ophthalmoplegia: SCA1, SCA2, SCA3
- Oculomotor apraxia: ataxia-telangiectasia, ataxia with oculomotor apraxia types 1 and 2
- Fixation instability (saccade intrusions) in primary gaze: Friedreich ataxia
- Ocular conjunctival and skin telangiectases: ataxia-telangiectasia
- Downbeat nystagmus: SCA6 and episodic ataxia type 2
- Central or peripheral vestibular involvement: SCA3, SCA6, *RFC1* CANVAS / spectrum disorder
- Motor unit fasciculations: SCA2, SCA3
- Peripheral neuropathy: SCA3, *RFC1* CANVAS / spectrum disorder
- Spasticity: SCA1, SCA3, SCA7
- Extrapyrimal signs: SCA1, SCA2, SCA3, SCA17, DRPLA
- Absent deep tendon reflexes and upgoing toes: Friedreich ataxia

Family History

A three-generation family history should be taken with attention to relatives with manifestations of hereditary ataxia and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing, neuroimaging studies, and autopsy examinations. Findings in the family that may assist in narrowing the scope of relevant hereditary ataxias include the following:

- Earlier onset and increasing severity of disease in subsequent generations suggest an autosomal dominant nucleotide repeat disorder associated with anticipation (see Table 1).
- An affected parent or grandparent suggests autosomal dominant inheritance.
- No male-to-male transmission of the disorder suggests X-linked inheritance.
- Affected sibs or consanguinity suggests autosomal recessive inheritance. Note: In communities with a high prevalence of an autosomal recessive ataxia (e.g., the [ARSACS](#) carrier frequency in the Saguenay–Lac-Saint-Jean region of Quebec is 1:21), affected individuals in two or more generations may be observed.
- Late-onset cerebellar ataxia in a grandfather who has a grandson with intellectual disability suggests [fragile X-associated tremor/ataxia syndrome](#) in the grandfather.
- Note: In the absence of a molecularly confirmed ataxia, reports of balance problems in a grandparent, parent, or sib do not necessarily indicate a shared genetic cause. Multifactorial and acquired cerebellar disorders, which are four to five times more common than inherited ataxias, can confuse a family history.

Molecular Genetic Testing

Nucleotide repeat disorders. Establishing the diagnosis in an individual with one of the nucleotide repeat disorders (see Table 1) requires identification of an expanded nucleotide repeat and determination of the nucleotide repeat size for each disorder (see Table 2).

Note that commercially available multigene panels that rely on sequence analysis alone will not identify these nucleotide repeat expansions; thus, specific assays are required to analyze the nucleotide repeat in each gene of interest. Options offered by some laboratories:

- A multigene "repeat expansion" panel to specifically identify nucleotide repeat expansions
- A multigene ataxia panel that combines both repeat expansion testing and sequence-based testing analysis

Non-nucleotide repeat disorders. Establishing the diagnosis of one of the disorders listed in Table 3 requires detection of a sequence variant. Molecular genetic testing approaches can include a combination of gene-targeted testing (multigene panel) and comprehensive genomic testing (exome sequencing, genome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

- A **"sequence-based" ataxia multigene panel** is most likely 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) 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. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. (4) Sequencing-based tests including exome sequencing do not readily detect nucleotide repeat expansions.

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

- **Comprehensive genomic testing** is an option that does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. Note that sequencing-based tests including exome sequencing do not readily detect nucleotide repeat expansions.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

4. Genetic Counseling of Family Members of an Individual with Hereditary Ataxia

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

The hereditary ataxias included in this overview can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. Genetic counseling and risk assessment depend on determination of the specific cause of an inherited ataxia in an individual.

For hereditary ataxias that are nucleotide repeat disorders, select the relevant link to the *GeneReview* chapter (if available) in Table 1 for genetic counseling issues.

The genetic counseling issues for the other common hereditary ataxias (see Table 3) are discussed below.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with autosomal dominant hereditary ataxia have an affected parent.
- Some individuals diagnosed with hereditary ataxia have the disorder as the result of a *de novo* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
 - The proband has a *de novo* pathogenic variant.
 - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- The family history of some individuals diagnosed with autosomal dominant hereditary ataxia may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to sibs is 50%.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. (Note: Parental mosaicism has been reported in SCA29 [Ngo et al 2019] and other rarer ataxias.)
- If the parents have not been tested for the pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for hereditary ataxia because of the possibility of age-related penetrance in a heterozygous parent or the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with autosomal dominant hereditary ataxia has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an individual diagnosed with autosomal recessive hereditary ataxia are presumed to be heterozygous for a pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
 - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
 - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are not at risk of developing autosomal recessive hereditary ataxia. (Note: Individuals who are heterozygous for an *ATM* pathogenic variant are at increased risk for cancer and coronary artery disease; see [Ataxia-Telangiectasia](#).)

Sibs of a proband

- If both parents are known to be heterozygous for a pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygotes (carriers) are not at risk of developing autosomal recessive hereditary ataxia. (Note: Individuals who are heterozygous for an *ATM* pathogenic variant are at increased risk for cancer and coronary artery disease; see [Ataxia-Telangiectasia](#).)

Offspring of a proband. The offspring of an individual with autosomal recessive hereditary ataxia are obligate heterozygotes (carriers) for a pathogenic variant.

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

Carrier detection. Carrier testing for at-risk relatives requires prior identification of the ataxia-related pathogenic variants in the family.

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](#).

- **Ataxia UK**
United Kingdom
Phone: 0800 995 6037; +44 (0) 20 7582 1444 (from abroad)
Email: help@ataxia.org.uk
www.ataxia.org.uk
- **National Ataxia Foundation**

Phone: 763-553-0020

Fax: 763-553-0167

Email: naf@ataxia.org

www.ataxia.org

- **Spanish Ataxia Federation (FEDAES)**

Spain

Phone: 34 983 278 029; 34 985 097 152; 34 634 597 503

Email: sede.valladolid@fedaes.org; sede.gijon@fedaes.org; sede.bilbao@fedaes.org

fedaes.org

- **Associazione Italiana per la lotta alle Sindromi Atassiche (AISA)**

Via Sara 12

16039

Italy

Phone: 39 342 9124574

Email: nazionale@atassia.it

www.atassia.it

- **A-T Children's Project**

Ataxia-Telangiectasia Children's Project

Phone: 800.5.HELP.A-T (800.543.5728); 954-481-6611

www.atcp.org

- **euro-ATAXIA (European Federation of Hereditary Ataxias)**

United Kingdom

Email: lporter@ataxia.org.uk

www.euroataxia.org

- **Friedreich's Ataxia Research Alliance (FARA)**

Phone: 484-879-6160

Fax: 484-872-1402

Email: info@CureFA.org

CureFA.org

- **NCBI Genes and Disease**

[Spinocerebellar ataxia](#)

5. Management of Hereditary Ataxia

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with a hereditary ataxia, the evaluations summarized in Table 6 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 6. Recommended Evaluations Following Initial Diagnosis in Individuals with a Hereditary Ataxia

System	Evaluation	Comment
Neurologic	Assessment by neurologist for: <ul style="list-style-type: none"> Cerebellar motor dysfunction (gait & postural ataxia, dysmetria, dysdiadochokinesis, tremor, dysarthria, nystagmus, saccades, & smooth pursuit) UMN &/or LMN dysfunction (weakness, spasticity, Babinski signs, hyperreflexia, amyotrophy, fasciculations) Vibration loss or polyneuropathy based on clinical findings 	<ul style="list-style-type: none"> Use standardized scale to establish baseline for ataxia (SARA).¹ Consider electrophysiologic studies (EMG & NCS) to detect neurogenic changes or signs of neuropathy. Brain MRI to evaluate presence & severity of cerebellar atrophy
	Refer to neuromuscular clinic (OT / PT / rehab specialist).	To assess gross motor & fine motor skills, ambulation, & need for adaptive devices & PT
Speech	For those w/dysarthria &/or other speech-language difficulties	Refer to SLP.
Feeding	For those w/frequent choking or severe dysphagia, assess nutritional status & aspiration risk.	Consider involving a gastroenterology/nutrition/feeding team.
Respiratory	For those w/respiratory symptoms or muscular involvement, obtain pulmonary function tests & sleep study.	Consider involving pulmonary specialist & sleep specialist.
Cognitive/ Psychiatric	Assess for cognitive dysfunction assoc w/cerebellar cognitive & affective syndrome (executive function, language processing, visuospatial/visuoconstructional skills, emotion regulation).	Consider use of: <ul style="list-style-type: none"> CCAS scale² to evaluate cognitive & emotional involvement; Psychiatrist, psychologist, neuropsychologist if needed.
Musculoskeletal	Assess for skeletal involvement, mainly scoliosis & pes cavus.	Consider involving orthopedic specialist or orthotics specialist.
Genetic counseling	By genetics professionals ³	To inform affected persons & their families re nature, MOI, & implications of their diagnosis to facilitate medical & personal decision making
Family support & resources	Assess need for: <ul style="list-style-type: none"> Community or online resources such as Parent to Parent; Social work involvement for parental support; Home nursing referral. 	

CCAS = cerebellar cognitive affective syndrome; EMG = electromyogram; LMN = lower motor neuron; NCS = nerve conduction study; OT = occupational therapy/therapist; PT = physical therapy/therapist; SARA = Scale for the Assessment and Rating of Ataxia; SLP = speech-language pathologist; UMN = upper motor neuron

1. Schmitz-Hübsch et al [2006]

2. Hoche et al [2018]

3. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

The goals of supportive care are to maximize function and reduce complications. Depending on the clinical manifestations, affected individuals benefit from supportive care by a multidisciplinary team of specialists

including neurologists, occupational therapists, physical therapists, physiatrists, orthopedists, nutritionists, speech-language pathologists, pulmonologists, and mental health specialists.

Table 7. Treatment of Manifestations in Individuals with a Hereditary Ataxia

Manifestation	Treatment	Considerations/Other
Ataxia	Care by physiatrist, OT/PT	<ul style="list-style-type: none"> Consider adaptive devices to maintain/improve independence in mobility (e.g., canes, walkers, ramps to accommodate motorized chairs), feeding (e.g., weighted eating utensils), & dressing (e.g., dressing hooks). PT (balance exercises, gait training, muscle strengthening) to maintain mobility & function ¹ OT to optimize ADL Inpatient rehab w/OT/PT may improve ataxia & functional abilities in persons w/degenerative ataxias. ^{2, 3} Weight control to avoid obesity Home adaptations to prevent falls (e.g., grab bars, raised toilet seats)
	Pharmacologic treatment	Consider riluzole (100 mg/d ³), the only drug shown to improve ataxia symptoms in persons w/ataxia of mixed etiologies; use requires monitoring of liver enzymes.
	Transcranial magnetic stimulation	Consider transcranial magnetic stimulation over cerebellum, ² which may improve cerebellar motor signs after 21 daily treatments (tested in persons w/various causes of spinocerebellar degeneration).
UMN involvement (spasticity)	Pharmacologic treatment	Baclofen, tizanidine, or dantrolene may relieve muscle spasms & spasticity.
Dysarthria	Speech-language therapy	Consider alternative communication methods as needed (e.g., writing pads & digital devices).
Dysphagia	Modify food consistency to ↓ aspiration risk.	Video esophagram may help define best consistency.
Poor weight gain	Nutrition assessment	Consider nutritional & vitamin supplementation to meet dietary needs.
Scoliosis / Skeletal involvement	Surgical treatment	Refer to orthopedic surgeon when required.
Cognitive/ Psychiatric	Pharmacologic treatment	Standard treatment for psychiatric manifestations (e.g., depression, anxiety, & psychosis)
	Psychotherapy / neuropsychological rehab	Consider cognitive & behavioral therapy, incl Goal Management Training®. ⁴

ADL = activities of daily living; OT = occupational therapy/therapist; PT = physical therapy/therapist; UMN = upper motor neuron

1. Martineau et al [2014]

2. Zesiewicz et al [2018]

3. van de Warrenburg et al [2014]

4. Ruffieux et al [2017]

Surveillance

There are no published surveillance guidelines for hereditary ataxias in general.

Table 8. Recommended Surveillance for Individuals with a Hereditary Ataxia

System/Concern	Evaluation	Frequency
Neurologic	<ul style="list-style-type: none"> Neurologic assessment for progression of ataxia, UMN or LMN signs, & history of falls Monitor ataxia progression w/standardized scale (SARA). ¹ Physiatry, OT/PT assessment of mobility, & self-help skills as they relate to ataxia, spasticity, & weakness 	Annually; more often for an acute exacerbation
Dysarthria	Need for alternative communication method or speech therapy	Per symptom progression
Dysphagia	Assess aspiration risk & feeding methods.	
Cognitive/ Psychiatric	Evaluate mood, signs of psychosis, & cognitive complaints to identify need for pharmacologic & psychotherapeutic interventions.	Per symptom progression & development of psychiatric symptoms
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

LMN = lower motor neuron; OT = occupational therapy; PT = physical therapy; SARA = Scale for the Assessment and Rating of Ataxia; UMN = upper motor neuron

1. Schmitz-Hübsch et al [2006]

Chapter Notes

Author Notes

As a Clinical Professor of Neurology, Dr Perlman is involved in the diagnosis and treatment of cerebellar ataxia and other neurogenetic disorders. She conducts research on collaborative natural history, biomarker, and clinical trials in spinocerebellar ataxia, Friedreich ataxia, ataxia-telangiectasia, late-onset Tay-Sachs disease, and Huntington disease.

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Author History

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Revision History

- 16 June 2022 (bp) Comprehensive update posted live
- 5 March 1999 – 25 July 2019 (tb) >70 revisions initiated by author Tom Bird
- 11 June 2015 (tb/aa) Revision: addition of *SNX4* (SCAR20), *RNF216* (Gordon Holmes syndrome), and citations
- 16 October 2014 (aa) Revision: addition of SCA40, caused by mutation of *CCDC88C*
- 14 August 2014 (me) Comprehensive update posted live
- 17 February 2011 (me) Comprehensive update posted live
- 6 January 2009 (cd) Revision: 260-kb duplication of 11q12.2-11q12.3 identified as probable cause of SCA20
- 27 June 2007 (me) Comprehensive update posted live
- 8 February 2005 (me) Comprehensive update posted live
- 14 October 2004 (tb/cd) Revision
- 27 May 2004 (ca) Revision: addition of SCA world map (Figure 1)
- 27 February 2003 (me) Comprehensive update posted live
- 28 October 1998 (me) Overview posted live
- 23 June 1998 (tb) Original submission

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