Ataxia from *The Chambers Dictionary*

inability to co-ordinate voluntary movements (*med*; see *locomotor ataxia* under *locomotive*); lack of order (*obs*). [Gr *ataxiā* disorder, from *a*-(privative), and *taxis* order]

**atactic or ataxic**
adj.

Summary Article: Ataxia from *Encyclopedia of Movement Disorders*

The ataxias represent a diverse group of neurological disorders that affect coordination, balance, and control of movement. The ataxias discussed in this article reflect primarily cerebellar dysfunction and degeneration. There are many different etiologies for cerebellar ataxia, including sporadic disorders and hereditary ataxias. Symptoms generally involve deficits in arm and leg coordination, gait and balance, speech, swallowing, and eye movements. Although there have been tremendous advances in understanding the genetics and pathogenesis of the ataxias, improved therapeutics and disease-modifying treatments are needed.

**Keywords**
- Ataxia
- Friedreich's ataxia
- Genetics
- Multiple system atrophy
- Spinocerebellar ataxias

**Definition and History**

**Historical Concepts**

Early concepts of the cerebellum date back to Galen's time (130–200 CE). Galen proposed that the cerebellum was a valve that controlled the animal spirits flowing from spinal and cranial nerves, and was the site from which cranial nerves and the spinal cord originated. The English physician, Thomas Willis (1621–1675), discussed cerebellar control of involuntary movements as well as cardiac and respiratory functions. Subsequent animal experiments furthered our knowledge of cerebellar function and pathology. For example, after partial removal of the median lobe of the cerebellum in a goat, Luigi Rolando (1773–1831) observed that the animal swayed and fell to one side or the other. Ablative lesions in the cerebellum in animals demonstrated irregular and clumsy movements, lack of muscular coordination, and changes in gait with functional recovery in some. In the nineteenth century, gait ataxia and tremors were observed in humans and discussed by Charcot and his students in France, Hammond in America, and Gowers in Britain. Much attention was focused on the distinction between cerebellar and sensory (proprioceptive) ataxia with the latter resulting from posterior column sclerosis as in tabes dorsalis. Patients with cerebellar ataxia were noted to have a staggering gait, jerky and irregular.

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movements, but intact sensation and less postural sway with eyes closure than those patients with sensory ataxia. At the turn of the nineteenth century, the French neurologist, Babinski (1857–1932) introduced several terms that are still used today to characterize cerebellar abnormalities. He described asynergia, dysdiachokinesia, hypermetria, and deficits in acceleration and deceleration of movements. Holmes (1876–1965), an Irish neurologist, examined the effects of acute cerebellar injuries and wounds in World War I soldiers and observed hypotonia ipsilateral to the cerebellar lesion, rebound and loss of check. These clinical observations provide a basis for our neuroanatomical and phenomenological understanding of cerebellar disease and ataxia.

Cerebellar Neuroanatomy

This section briefly reviews cerebellar neuroanatomy as related to clinical findings. The cerebellum is located in the posterior fossa and consists of two large hemispheres and a midline structure, the vermis. The hemispheres are involved in motor planning and limb control, whereas the midline structures or vermis control motor execution, balance and gait, and ocular movements. The cerebellum consists of three main parts – the flocculonodular, anterior, and posterior lobes. In addition, the lobes are subdivided into lobules which carry several different names. Based on phylogenetic and embryological studies, the archicerebellum (oldest part) corresponds to the flocculonodular lobe, paleocerebellum consists of the anterior and posterior parts of the vermis except the nodulus, and the neocerebellum (newest part) corresponds to the hemispheres and the middle vermis.

Afferent projections from the vestibulocerebellum (originating from vestibular nerve and nuclei), spinocerebellum (originating from the dorsal and ventral spinocerebellar tracts), and pontocerebellum (originating from the contralateral hemisphere) correspond to the projections areas of the archicerebellum, paleocerebellum, and neocerebellum, respectively. Anatomic designation based on the efferent projections from the cerebellar cortex to the cerebellar nuclei divides the cerebellum into three longitudinal zones – medial (vermis) projecting to the fastigial nucleus, intermediate (paravermal) projecting to the interposed nuclei (globose and emboliform nuclei), and lateral (lateral hemisphere) zone projecting to the dentate nucleus. From the deep cerebellar nuclei, efferent fibers from the fastigial nucleus project to the vestibular nuclei and reticular formation via the inferior cerebellar peduncle, and are concerned with balance and ocular movements. From the interposed nuclei, efferent fibers project to the contralateral thalamus and red nucleus via the superior cerebellar peduncle and are involved in execution of movements and gait. Other efferent fibers travel from the dentate nuclei to the contralateral thalamus and then primary motor and frontal/prefrontal cortex as well as to the contralateral red nucleus and then spinal cord via the superior cerebellar peduncle and are involved in motor planning and limb coordination. Furthermore, the cerebellar cortex is somatotopically organized with two inverted homunculi (leg representation anteriorly in the anterior lobe and posteriorly in the posterior lobe).

The output neuron of the cerebellum, the Purkinje cell, is inhibitory to cerebellar nuclear neurons and uses γ-aminobutyric acid (GABA) as its neurotransmitter, whereas Purkinje cells receive indirect input from many excitatory granule cells via their input from mossy fibers, excitatory climbing fibers (mainly from the inferior olive) connect directly with Purkinje cells. Neurotransmitters in the cerebellum primarily include GABA, glutamate, norepinephrine, serotonin, histamine, and acetylcholine. Disruption of the cerebellar blood supply (posterior inferior cerebellar artery, anterior inferior cerebellar artery, and superior cerebellar artery) leads to distinct neurological deficits and stroke syndromes.
Clinical Definitions

The cerebellum functions primarily to modulate and coordinate movements. Cerebellar disease is often characterized by limb and gait ataxia, clumsy and irregular movements, and decreased coordination and balance. Ataxia means literally, without order from the Greek, taxi (order). Abnormalities in the cerebellum lead to interruptions in speed, direction, timing, amplitude, and target accuracy of movements. These disturbances reflect difficulties in initiating and terminating movements, gauging target distances and timing, changing directions, and maintaining postural reflexes.

Clinically, limb or appendicular ataxia is exemplified by dysdiadochokinesis, dysmetria, or dyssynergia (see Glossary entries and Clinical examination section). Movements may appear slowed due to either the underlying cerebellar disorder or attempts by the patient to improve accuracy of movement by slowing his movements. Tone may be reduced, and reflexes may be pendular. Kinetic or intention tremor is also a feature of cerebellar limb dysfunction, in contrast to the rest tremor of parkinsonism. Titubation and poor truncal control when seated or standing demonstrate axial involvement. Ataxic gait is characterized by a wide-based stance, irregular stride, unsteadiness when walking or turning, and difficulty performing tandem gait.

Cerebellar disease also can affect extraocular movements, speech, and cognition. Abnormalities in eye movements include nystagmus (gaze-evoked, rebound, and sometimes down-beating), square-wave jerks, abnormal saccades (hypo- or hypermetric saccades), jerky or saccadic smooth pursuit, ocular flutter, and opsinclonus. Speech disorders in cerebellar disease often have a 'scanning' quality and are described as dysarthric, hesitant, or slow. Many speech abnormalities have been described including deficits in articulation, phonation, respiration, timing, pitch, volume, and prosody. With bulbar musculature involvement, differences in labial, lingual, and palatal sounds may be seen. Patients with cerebellar disease have been shown to have deficits in motor learning, perception, and cognitive function. In some, systemic and other neurologic signs and symptoms are present and may include gastrointestinal problems, autonomic dysfunction, dizziness, spasticity, neuropathy, dystonia, and parkinsonism.

Pathogenesis/Pathophysiology

The pathogenesis of the ataxias is not surprisingly broad due to the many different types of ataxias recognized under the umbrella term of ‘ataxia.’ Much of our current understanding about the ataxias is rooted in genetics. As a result, the ataxias have often been classified as congenital, hereditary (autosomal dominant (AD), autosomal recessive (AR), X-linked, mitochondrial), or sporadic. Over the past two decades, researchers have identified specific gene mutations in many of the ataxias which provide insights into the pathogenesis of some of the hereditary ataxias. With increased understanding of the molecular basis of some of the ataxias, organization schemes that focus on disease mechanisms have been proposed, thereby classifying the ataxias as disorders of trinucleotide repeat or polyglutamine expansions, ‘gain’ or ‘loss’ of function, channelopathies, defective DNA repair, mitochondrial dysfunction, and metabolic abnormalities. This section will highlight several mechanisms of the ataxias; many of these ataxia disorders are discussed in further detail in separate entries in the encyclopedia.

Abnormal Protein Folding and Degradation: Trinucleotide or Polyglutamine Expansion Disorders

Several autosomal dominant spinocerebellar ataxias (SCAs) are caused by trinucleotide or polyglutamine expansions (CAG repeat expansions that encode the repeat of the amino acid glutamine in the disease...
protein), particularly in coding regions. The family of polyglutamine repeat disorders includes SCA1, 2, 3, 6, 7, and 17 as well as Huntington disease, spinobulbar muscular atrophy, and dentatorubropallidoluysian atrophy (DRPLA). Clinically, these SCAs share features such as anticipation and an inverse correlation of CAG repeat length to onset age. There may be an earlier age of onset with paternal transmission. These disorders also are thought to share a common toxic gain-of-function mechanism leading to the aggregation and deposition of misfolded proteins and subsequently, neuronal dysfunction and cell death. The polyglutamine aggregates form nuclear or cytoplasmic inclusions that may contain ubiquitin, HSP70, or transcription factors. Although these aggregates constitute neuropathological hallmarks of those SCAs due to repeat expansions, it is not known whether the toxicity results directly from the aggregate or is a byproduct of other ongoing processes.

There are other abnormal repeat expansions in SCA 12, 8, and 10. SCA12 is also caused by a CAG repeat expansion, similar to SCA1, 2, 3, 6, 7, and 17; however, the CAG repeat is located in the untranslated region of the PPP2R2B gene on chromosome 5, encoding a brain-specific regulatory subunit of the protein phosphatase PP2A. Since the polyglutamine expansion lies outside of the open reading frame, pathogenesis seems less likely to relate to a toxic gain of function. SCA8 is caused by a CTG repeat expansion in the 3′ untranslated region on chromosome 13. In contrast, SCA8 expansions vary greatly between generations, and correlations between repeat length and disease severity are less. Furthermore, the CTG repeat occurs as part of the natural antisense RNA of the Kelch-like 1 gene which may act in the formation or maintenance of Purkinje cell dendritic function. SCA10 is caused by an unstable ATTCT pentanucleotide repeat expansion in E46L, a novel gene of unknown function.

**Channelopathies**

Several ataxias, such as SCA6 and the episodic ataxias (EAs), are due to mutations in genes involved in calcium or potassium channel function. For example, SCA6 is caused by a CAG repeat expansion on chromosome 19p13 in the CACNA1A gene. The CACNA1A gene encodes the P/Q type voltage-gated calcium channel complex which is abundantly expressed in the cerebellum and also presynaptic neuromuscular junction. Proposed pathogenetic mechanisms include a toxic ‘gain of function’ or increased calcium entry into cerebellar cells. Mutations in the CACNA1A gene on chromosome 19 are allelic with EA type 2 (EA2) and familial hemiplegic migraine (FHM). EA-2 is caused by a point mutation in the calcium channel gene CACNA1A on chromosome 19p13. Most mutations in EA2 involve point mutations causing truncated proteins, but missense mutations have been reported. In addition, a missense mutation in CACNB4, the calcium channel β4 subunit gene, has been identified in a family with EA-2. Episodic ataxia-1, EA-1, is caused by a missense mutation in the potassium channel gene KCNA1 on chromosome 12p13. This was not only the first known ion channel mutation in the brain but also the first report of a mutation in the human potassium channel gene. The KCNA1 protein is widely expressed in the cerebellum and nodal regions in peripheral nerves. Several different missense mutations in KCNA1 have been identified. Mutations may alter potassium channel function by reducing channel expression or affecting channel gating.

**Mitochondrial Dysfunction**

Friedreich's ataxia (FRDA) is often considered a prototype for an ataxia due to abnormal mitochondria oxidative metabolism. FRDA, the most common AR ataxia, is caused by a GAA repeat expansion in the intron of the frataxin gene on chromosome 9q13. This expansion accounts for about 96% of patients with FRDA; the remainder (4–5%) is heterozygous and has a point mutation in the frataxin gene. Larger repeat expansions are associated with earlier onset of disease and more severe phenotype. However,
expansions >50 repeats form sticky DNA and may be pathological. Expanded GAA repeats suppress frataxin gene expression. Since the frataxin yeast homologue plays a role in iron, it has been proposed that decreased frataxin leads to abnormal iron accumulation in the mitochondria, increased reactive oxygen species, and disruption in mitochondrial function. Knockout models and yeast experiments suggest that frataxin is involved in iron–sulfur cluster assembly and that the impaired iron–sulfur cluster assembly may precede the iron accumulation in FRDA. Abnormal mitochondrial function forms the basis for therapeutic studies with idebenone and other free-radical scavengers.

### Defective DNA Repair

Several recessive ataxias such as ataxia-telangiectasia (AT), xeroderma pigmentosum (XP), Cockayne syndrome, and ataxia with oculomotor apraxia types 1 and 2 (AOA1, AOA2) are thought to relate to defective DNA repair. In AT, truncating mutations occur in the ataxia telangiectasia mutated (ATM) gene. The ATM protein carries a region similar to the lipid kinase phosphatidylinositol-3 kinase (PI-3K), a signal transduction mediator, and another region similar to yeast proteins involved in DNA repair. Thus, although exact mechanisms of the ATM mutation have not been elucidated, ATM may have a role in DNA damage detection, cell checkpoint control, and intracellular growth factor signaling.

Both XP and Cockayne syndrome involve multiple mutations with defective DNA repair or reduced RNA synthesis after ultraviolet damage. AOA1 is caused by missense and truncating mutations in the aprataxin (APTX) gene. The APTX gene is a member of the histidine family and may affect DNA repair by interacting with repair proteins and affecting cellular response to stress. AOA2, which is due to mutations in the SETX gene, which codes for senataxin, a protein with RNA and DNA helicase activities.

### Epidemiology/Risk Factors

Since the etiologies of ataxia are heterogeneous, many epidemiological studies focus on specific types of ataxia in the population (e.g., SCA types, FRDA, multiple system atrophy (MSA)). However, with genetic testing, the ability to diagnose patients and recognition of broader clinical phenotypes has increased; therefore, published frequencies may represent conservative estimates. This section will highlight the prevalence rates and geographic distributions for several different types of ataxia.

Prevalence rates reported for the AD SCAs range from 0.9 to 3 per 100 000. Of the SCAs, SCA2, SCA3, and SCA6 appear to be the most common. Differences in geographic region and ethnic origin occur. For example, SCA3 is one of the most common SCAs, ranging from about 20% in the US to 50% in German, Japanese, and Chinese series. SCA2 has been described in Cuban and Indian kindreds. SCA3 is frequently associated with descendants from the Azorean islands or Portuguese missionaries in Asia, from whom the disease was initially identified. SCA10 has been reported in Mexican and Brazilian kindreds, with the combination of ataxia and epilepsy described only in the Mexican families.

FRDA, an AR ataxia, is found predominantly in Caucasian populations (rare in non-Caucasian), with an incidence of 1 in 30–50 000. FRDA accounts for about 50% of the hereditary ataxias and 75% of those before age 25. AT is the second most common recessive ataxia with an incidence of 1 in 80–100 000 live births.

Regarding the sporadic ataxias, the prevalence of MSA has been reported to be 1.9–4.9 cases per 100 000 population in the US, with lower estimates from United Kingdom and France population studies. Diagnostic distinctions between MSA and idiopathic Parkinson's disease, pure autonomic failure or other atypical parkinsonian disorders, however, may be difficult, and these rates may not provide true
estimates. About 29–33% of patients with isolated late-onset cerebellar ataxia are thought to develop MSA. Some studies have reported high prevalences of antigliadin antibodies in patients with sporadic and hereditary cerebellar ataxia, thereby challenging our understanding of gluten ataxia as a distinct disorder. For example, the prevalence of antigliadin antibodies in hereditary ataxias was 14%, sporadic idiopathic ataxia 41%, MSA-C 15%, and normal controls 12% in one study, and in another, prevalent in 37% in AD ataxias and 27% in sporadic ataxias.

Clinical Features and Diagnostic Criteria

AD Ataxias

The autosomal dominant cerebellar ataxias (ADCA) were initially classified according to phenotype and accompanying signs by Harding. ADCA I consisted of cerebellar ataxia along with variable pyramidal, extrapyramidal, and neuropathic signs. ADCA II presented with cerebellar ataxia and retinal degeneration, and ADCA III manifested as a pure cerebellar ataxia (Table 1). Genetic advances have led to modification of these criteria as specific genes, and mutations responsible for cerebellar ataxias have been discovered and phenotypic heterogeneity has been observed. This section describes the clinical features of AD ataxias: selected SCAs, dentatorubral-pallidoluysian atrophy (DRPLA), and selected EAs.

Classification of autosomal dominant cerebellar ataxias (ADCA), modified from Harding

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical phenotype</th>
<th>Common genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADCA I</td>
<td>Cerebellar ataxia plus other symptoms: extrapyramidal symptoms, neuropathy</td>
<td>SCA 1, 2, 3, 4, 12, 17, 21, 23, 25, 27, 28</td>
</tr>
<tr>
<td>ADCA II</td>
<td>Cerebellar ataxia plus retinal degeneration</td>
<td>SCA 7</td>
</tr>
<tr>
<td>ADCA III</td>
<td>Cerebellar ataxia – pure</td>
<td>SCA 5, 6, 8, 10, 11, 14, 15, 16, 22, 26, 30</td>
</tr>
</tbody>
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Spinocerebellar Ataxias (SCAs)

SCA1

SCA1 is characterized by cerebellar ataxia (gait ataxia, dysarthria, slow saccades, and nystagmus), corticospinal tract signs, and neuropathy, as well as later ophthalmoplegia and bulbar dysfunction (dysphagia, tongue fasciculations). Extrapyramidal signs may be seen, but cognitive deficits are not typically present. The age of onset varies from adolescence to late adulthood with the average age of onset around third to fourth decades. Clinically, nerve conduction studies may reveal sensory axonal neuropathy, and brain magnetic resonance imaging (MRI) reveals atrophy involving the cerebellum, brainstem, and cervical spinal cord. Pathology reveals marked cerebellar atrophy with loss of Purkinje cells in cerebellar cortex and vermis in particular, atrophy of the pons and inferior olives as well as spinal cord spinocerebellar tracts and posterior columns. In addition, neuronal loss in cranial nerves III, X, and XII is seen, and ubiquitin-positive nuclear inclusions can be seen.

SCA2

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SCA2 clinically appears similar to SCA1, as it was described in a large Cuban kindred that phenotypically resembled SCA1 but lacked the same genetic mutation. However, SCA2 is distinguished by prominent slow saccades. Other clinical symptoms in its wide phenotype include ataxia, dysarthria, neuropathy, initial hyperreflexia followed by hyporeflexia, cerebellar tremor, and ophthalmoplegia. Parkinsonism, with levodopa response in some, has been reported in the literature. In other cases, myoclonus, chorea, corticospinal tract signs, and executive dysfunction have been reported. The age of onset is typically in the third or fourth decade. Sensory axonal neuropathy is present in nerve conduction studies, and neuroimaging reveals more severe cerebellar and brainstem atrophy than in SCA1 and SCA3.

Neuropathology includes loss of Purkinje cells and other cerebellar neurons, neuronal loss in the brainstem including inferior olives, degeneration in the substantia nigra, and loss of spinal cord neurons in spinocerebellar tracts, posterior columns, and anterior horn cells though neuronal inclusions are not seen. Clinically, there is no curative treatment, but parkinsonian features may respond to levodopa. Median survival after disease onset is about 25 years.

**SCA3/Machado–Joseph disease**

SCA3 and Machado–Joseph disease MJD are now known to be synonymous, sharing a genetic mutation on chromosome 14q24.3–q32. Historically, reports in the 1970s described several Azorean kindreds in the United States with dominantly inherited but clinically variable neurodegenerative conditions. Three distinct phenotypes were reported in these kindreds: Type I – early onset (<30 years), rapid progression, symptoms of spasticity, rigidity, myokymia, facial-lingual fasciculations, dystonia; Type II – intermediate onset age (age 30s), ataxia, spasticity, and extrapyramidal features; Type III – later onset (age 40–60s), ataxia, neuropathy, and variable amyotrophy. Another type, Type IV, has been described with older onset, predominantly parkinsonian phenotype with possible levodopa response, and neuropathy.

SCA3/MJD has a broad phenotype with ataxia, neuropathy, parkinsonism, dystonia, spasticity, rigidity, ophthalmoplegia, bulging eyes, facial-lingual fasciculations, amyotrophy, and sleep disturbances, such as restless legs syndrome. Dementia is not typically seen. The average age of onset is in the third to fourth decades but ranges from childhood to 70s. Death usually occurs within 20–25 years after disease onset due to complications of immobility and respiratory dysfunction. Studies reveal axonal neuropathy on nerve conduction studies and cerebellar and brainstem atrophy on neuroimaging. Marked dilatation of the fourth ventricle may be seen, and atrophy of the frontal and temporal lobes, as well as globus pallidus may be evident. Neuropathology reveals degeneration of the cerebellar tracts, spinocerebellar tracts, substantia nigra, and motor cranial nuclei with sparing of the cerebellar cortex and inferior olives in contrast to other SCAs. Neuronal inclusions, staining for ubiquitin, are widespread in the pons but also present in substantia nigra and brainstem.

**SCA4**

SCA4 is a rare spinocerebellar ataxia that manifests clinically as cerebellar ataxia, sensory axonal neuropathy, and pyramidal tract signs. Symptoms begin in the fourth to fifth decade with gait ataxia, followed by impaired fine motor function, dysarthria, hypo- or areflexia, and neuropathy (particularly vibratory and joint position sense loss). Limb weakness and extensor plantar responses may be present. Although known previously as Biemond ataxia (initially reported in 1954), genetic linkage to chromosome 16q22.1 was discovered in a large Scandinavian family in Utah with similar symptoms. More recently, a pure cerebellar ataxia syndrome in six Japanese families linked to the SCA 4 gene locus was described and may represent a phenotypic variation of the same disease.

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**SCA5**

SCA5 is largely a pure cerebellar syndrome, consistent with phenotypic ADCA III classification. Onset ranges from 10 to 68 years of age, but typically occurs in the third or fourth decade with symptoms of gait and limb ataxia and dysarthria. Extrapyramidal, corticospinal, and cognitive dysfunction are not seen. One-third of patients report mild sensory deficits. Its course is relatively slowly progressive and mild with normal life span in adult cases. However, in childhood onset, bulbar atrophy and corticospinal tract abnormalities may lead to a more rapid course. Neuroimaging reveals marked cerebellar cortical atrophy but without involvement of the brainstem, basal ganglia, or cerebral hemispheres. Pathological studies are limited but show predominantly cortical cerebellar degeneration.

**SCA6**

SCA6 has been considered to be a relatively pure cerebellar ataxia with a slowly progressive course, although extracerebellar features may occur. Clinical manifestations include gait and limb ataxia, dysarthria, downbeat or gaze-evoked nystagmus, and oculomotor findings. Unlike SCA1, 2, and 3, saccade velocity is normal. Saccades are dysmetric and smooth pursuit, optokinetic responses, and vestibular suppression, impaired. Later in the course, dysphagia, mild sensory neuropathy, corticospinal tract signs, and occasional parkinsonism or dystonia can occur. The age of onset is typically in the fourth or fifth decade, with slow progression. Brain MRI typically reveals midline cerebellar atrophy. Neuropathology demonstrates cerebellar degeneration with predominant loss of Purkinje cells and presence of cytoplasmic and nuclear polyglutamine aggregates. Based on improvement in EA2, acetazolamide, a carbonic anhydrase inhibitor, has provided modest symptomatic improvement in SCA6.

**SCA7**

SCA7, classified as ADCA II, is a progressive ataxia distinguished by retinal degeneration. The earliest sign of retinal dysfunction may be blue–yellow dyschromatoptia, followed by central vision loss (predominant macular involvement), and progression to bilateral vision loss and blindness. Other symptoms include cerebellar ataxia, dysarthria, corticospinal tract signs, hyporeflexia, decreased vibration, dysphagia, sphincter dysfunction, and ophthalmoplegia and slow saccades. The age of onset is typically in the third or fourth decade (range from infancy to over age 70). Anticipation and inverse correlation with repeat length and age of onset occur. Early-onset patients may present with visual symptoms preceding or coinciding with ataxia onset. Juvenile cases, marked by larger repeat sizes (>200) due to paternal transmission, may have cardiac involvement and seizures in addition to retinal dysfunction. Clinical tests reveal dyschromatoptia and abnormal fundoscopy with mottling of macula pigment and loss of foveal reflex. Nerve conduction studies may show subclinical sensory neuropathy. Brain MRI demonstrates marked cerebellar atrophy, especially in the superior vermis and brainstem, and moderate cortical atrophy. Neuropathology of the retina reveals degeneration of photoreceptors, bipolar and granule cells in foveal and parafoveal areas, and patchy loss of retinal epithelial cells. Brain pathology includes marked degeneration in the cerebellum (vermis greater than hemispheres) and inferior olives as well as pons, basal ganglia, and spinal cord.

**SCA8**

Clinically, SCA8 presents as a slowly progressive limb and gait ataxia with dysarthria and abnormal eye movements (impaired smooth pursuit and nystagmus). Neuropathy (reduced vibratory sensation), tremor, spastic dysarthria, and upper motor neuron findings, such as spasticity and hyperreflexia may
occur. The age of onset is from infancy to over 60 (mean onset in the fifth and sixth decades).

Neuroimaging typically reveals marked cerebellar vermian and hemispheric atrophy with relative sparing of the brainstem. Neuropathological reports are not available to date.

**SCA10**

SCA10 ataxia has been reported in Mexican and Brazilian families; only the Mexican families, to date, have had epilepsy. Symptoms include limb and truncal ataxia, dysarthria, dysphagia, abnormal eye movements (saccadic pursuit, ocular dysmetria). About 20–60% have recurrent seizures, mostly generalized motor but also complex partial seizures. Other features have included mild cognitive dysfunction, mild sensory neuropathy, and hepatic dysfunction. The age of onset ranges from 14 to 45 years. Neuroimaging reveals generalized cerebellar atrophy and EEGs, cortical dysfunction, or epileptiform discharges. Neuropathological findings are unknown presently. Although there is no known treatment for the ataxia, seizures can be managed with antiepileptic medications.

**SCA11**

SCA11 is a relatively mild, cerebellar ataxia mapped to chromosome 15q14. Symptoms include limb and gait ataxia, dysarthria, saccadic pursuit, nystagmus, and hyperreflexia. The mean age of onset in the one British family with linkage to chromosome 15q is 25 years. Life expectancy appears normal.

**SCA12**

Clinical manifestations of SCA12 include cerebellar ataxia and action tremor. Other features include dysarthria, nystagmus, hyperreflexia, axial dystonia, bradykinesia, neuropathy, psychiatric symptoms, and dementia (in cases with older age onset). The age of onset ranges from 8 to 55 years, typically in the fourth decade. Families described are German-American or Indian. Neuroimaging demonstrates generalized cortical and cerebellar atrophy. Possible treatments address specific symptoms, such as tremor, parkinsonism, and psychiatric features.

**SCA13**

SCA13 has been reported in French families with cerebellar ataxia and mild mental retardation. Other features include dysarthria, nystagmus, hyperreflexia, urinary urgency (2 cases), and absence seizures (1 case). The age of onset is usually in early childhood but ranges from infancy to 40s. Neuroimaging in two cases revealed cerebellar and pontine atrophy.

**SCA14**

Clinical presentations of SCA14 as described in Japanese and English-Dutch families and one sporadic case include cerebellar ataxia, nystagmus, dysarthria, possible hyperreflexia, and axial myoclonus especially in earlier onset cases. The age of onset ranges from 10 to 59 years, mean fourth and fifth decades. Brain MRI reveals atrophy in the cerebellum vermis and hemispheres. Neuropathology demonstrates reduced staining for protein kinase C, gamma and ataxin-1 in Purkinje cells.

**SCA15**

SCA15 has been described in an Australian family with a slowly progressive, pure cerebellar ataxia. Patients are ataxic but remain ambulatory. The age of onset ranges from 10 to 50 years, mean 25 years. Brain MRI reveals superior vermis atrophy and nerve conduction studies are normal.

**SCA16**

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SCA16 has been reported in a Japanese family as predominantly a slowly progressive, pure cerebellar syndrome accompanied by constant gaze-evoked nystagmus, dysarthria, and head tremor in some. The age of onset ranges from 20 to 66 years, mean 40 years. Anticipation was not seen in the Japanese kindred. Brain MRI reveals cerebellar atrophy and sparing of the brainstem.

**SCA17**

SCA17 is characterized by cerebellar gait ataxia and dementia with development of limb ataxia, bradykinesia, and hyperreflexia over several decades. Eye movements are normal. The age of onset ranges from 19 to 48 years, mean 33 years. SCA17 has been described in Japanese, German, and Italian families. Others have reported similarities to Huntington's disease due to the presence of dementia, psychiatric features, and chorea. Brain MRI reveals marked cerebellar atrophy and mild cortical atrophy. Neuropathology reveals moderate cerebellar degeneration, neuronal intranuclear inclusions, and mild-to-moderate changes in the basal ganglia and cortical regions.

**SCA18**

SCA18 has been designated sensorimotor neuropathy with ataxia (SMNA) and may not truly represent spinocerebellar ataxia. Features of dysmetria, hyporeflexia, muscle weakness, muscle atrophy, neuropathy with decreased vibration and proprioception, and pes cavus in some were described in a five generation American-Irish kindred. The age of onset was from 13 to 27 years. Progression was slow with normal lifespan and wheelchair use in later years. Brain MRI revealed cerebellar atrophy, electrodiagnostic studies showed sensory axonal neuropathy and denervation, and muscle biopsy revealed neurogenic atrophy.

**SCA19**

SCA19 has been described in a Dutch kindred with symptoms of mild ataxia, postural tremor, myoclonus, cognitive impairment, variable reflexes, and neuropathy. The age of onset was between 20 and 45 years. SCA19 has been mapped to chromosome 1p21–q21. Since another form of FHM links to this locus, possible disease mechanisms may relate to mutations in ion channels. Brain MRI reveals marked atrophy of cerebellar hemispheres and mild atrophy of the vermis and cerebral cortex.

**SCA20**

SCA20 has been reported in an Anglo-Celtic family with relatively pure, AD spinocerebellar ataxia. Symptoms include dysarthria, gait and limb ataxia, hypermetric saccades, mild nystagmus, mild corticospinal tract signs, palatal myoclonus, and had slow progression. The age of onset ranges from 19 to 64 years, mean 45 years. Head CT scans have revealed prominent dentate calcifications in all nine patients imaged.

**SCA21**

SCA21 has been reported in a French family with slowly progressive gait and limb ataxia, as well as variable parkinsonian signs, hyporeflexia, and cognitive impairment. The age of onset ranges from 6 to 30 years, mean 17 years. Brain MRI reveals cerebellar atrophy without brainstem involvement. More study is likely needed to define and assess parkinsonian features of SCA21 and responses to dopaminergic agents.

**SCA22**

SCA22 represents a pure AD cerebellar ataxia described in a Chinese Han family. Hyporeflexia was
also present and course was slowly progressive. The age of onset ranges from 10 to 46 years. Brain MRI reveals cerebellar atrophy.

**SCA23**

SCA23 has been described in a Dutch family with a slowly progressive gait and limb ataxia accompanied by abnormal eye movements (slow saccades, ocular dysmetria), neuropathy, and corticospinal tract signs (hyperreflexia, extensor plantar responses). The age of onset was later, ranging from 43 to 56 years. Brain MRI revealed cerebellar atrophy, and pathology demonstrated cerebellar, brainstem, and spinal cord atrophy with cell loss in Purkinje cells, dentate nuclei, and inferior olives.

**SCA25**

SCA25 involves cerebellar ataxia along with variable nystagmus, hyporeflexia, neuropathy, urinary urgency, and gastrointestinal symptoms. SCA25 has been described in a large Southeastern French family. The age of onset was from 17 months to 39 years. Brain MRI reveals cerebellar atrophy and nerve conduction studies, absent sensory nerve action potentials.

**Dentatorubral-pallidoluysian atrophy (DRPLA)**

DRPLA is an AD ataxia with phenotypic similarities to progressive myoclonic epilepsy, spinocerebellar ataxia, and Huntington's disease, depending on the age of onset. Ataxia and dementia are present regardless of the age of onset. Inverse correlation between the age of onset and CAG repeat length and anticipation, particularly with paternal transmission, occur. The age of onset is variable, ranging from childhood to late adulthood but on average, age 30. Patients with symptom onset less than age 20 share a phenotype with progressive myoclonic epilepsy with additional seizures and myoclonus. Those patients with symptom onset after age 20 are more likely to resemble either SCAs or Huntington's disease due to chorea and neuropsychiatric symptoms.

DRPLA is relatively common in Japan with a prevalence rate of 0.2–0.7 per 100 000 and is present in the United States as a variant, Haw River syndrome that has been reported in African-American kindreds in North Carolina. DRPLA is caused by a trinucleotide CAG repeat mapped to chromosome 12p, encoding atrophin-1; abnormal alleles range from 49 to 88 repeats, whereas normal alleles typically have less than 30 repeats. Neuropathological examination reveals degeneration in the dentate, red nucleus, subthalamus, and globus pallidus and accumulation of atrophin-1 in neuronal nuclei. Useful laboratory studies include brain MRI, EEG, and genetic testing. Epilepsy requires anticonvulsant treatment, but other therapies are only for symptomatic effects.

**Episodic ataxias**

The EAs are a group of AD ataxias with intermittent symptoms and different genetic mutations. To date, seven EAs have been described (EA1–EA7), with mutations identified in four genes.

In EA-1, patients have sudden episodes of dysarthria and truncal and gait ataxia with normal eye movements. Episodes are brief, lasting from seconds to a few minutes, and often triggered by startle, emotional factors, or exercise. Preceding auras with weakness, dizziness, and blurred vision may occur. Interictal examination is normal except for myokymia, particularly in periorbital areas and fingers, and seen either clinically or by electromyography (EMG) only. The age of onset ranges from 3 to 20 years. Episodes decrease with age and may remit in teenage years. Families with EA-1 may have different types of epilepsy. Episodes may respond to acetazolamide.
In contrast, EA-2 is characterized by longer episodes of ataxia lasting for hours. Symptoms include ataxia, vertigo, nausea, emesis, and headaches, and examinations reveal cerebellar ataxia, dysarthria, and nystagmus. Episodes can be triggered by stress, exercise, alcohol, and caffeine. Interictal examination may show gaze-evoked nystagmus, downbeat nystagmus, and mild truncal ataxia. The age of onset is similar to EA-1, ranging from 3 to 30 years. Brain MRI often reveals cerebellar atrophy, particularly midline. Acetazolamide may decrease the severity and frequency of episodes by stabilizing the ion channel.

AR Ataxias

Although there are numerous AR ataxias described in the literature, this section will focus on a few selected ataxias. The AR ataxias can be divided into three primary phenotypes: (1) a Friedreich ataxia (FRDA)-like phenotype without cerebellar atrophy (e.g., FRDA, ataxia with vitamin E deficiency, abetalipoproteinemia, and Refsum's disease), (2) a FRDA-like phenotype with cerebellar atrophy and possibly other neurological findings (e.g., cerebrotendinous xanthomatosis (CTX), late-onset Tay–Sachs disease, mitochondrial ataxia syndromes, and spinocerebellar ataxia with axonal neuropathy), and (3) an early-onset ataxia with cerebellar atrophy phenotype (e.g., AT, ataxia with oculomotor apraxia 1 and 2, AR ataxia of Charlevoix-Saguenay, infantile-onset spinocerebellar ataxia, Cayman ataxia, and Marinesco-Sjogrens syndrome).

Friedreich ataxia

FRDA clinically presents with gait instability and clumsiness or scoliosis diagnosed in adolescence. Neurological features include a mixed sensory and cerebellar ataxia, gait and limb ataxia, dysarthria, dysphagia, ocular fixation difficulty with square-wave jerks, areflexia, proprioceptive sensory loss, weakness, and extensor plantar responses. Cognition remains intact; optic atrophy and sensorineural hearing loss occur in some. On average, patients require a wheelchair 10–15 years after disease onset. Nonneurological abnormalities include musculoskeletal changes of kyphoscoliosis and pes cavus or equinovarus, hypertrophic cardiomyopathy (inverted T waves on electrocardiogram, symptoms of shortness of breath and palpitations), diabetes mellitus or glucose intolerance, and autonomic disturbances. In FRDA, evaluation reveals nerve conduction studies with sensory axonal neuropathy and absent sensory nerve action potentials (SNAPs), abnormal evoked potential studies (visual, brainstem, motor, and somatosensory), and atrophy of the cervical spinal cord rather than cerebellum on neuroimaging. Neuropathology demonstrates degeneration of posterior columns of the spinal cord and spinocerebellar tracts, the sensory tracts projecting to the brain and cerebellum; loss of large primary sensory neurons in the dorsal root ganglia; and mild cortical cerebellar atrophy late in the course.

Although onset is usually in adolescence, before age 20, late onset variants can occur. Late-onset FRDA (LOFA) can occur even after age 50–60; it is associated with shorter repeat lengths, and clinically may have intact reflexes, fewer skeletal deformities, and a more benign, slower progression. Another variant is FRDA with retained reflexes (FARR) which also may be milder in phenotype, and as its name suggests, patients have intact reflexes.

Ataxia with isolated vitamin E deficiency

Ataxia with isolated vitamin E deficiency (AVED) shares a phenotype with FRDA – progressive cerebellar ataxia, areflexia, proprioceptive sensory loss, and corticospinal tract signs with spastic gait and extensor plantar responses. Symptoms occur in the absence of fat malabsorption or gastrointestinal syndromes. Affected individuals may have retinal pigmentary changes but rare
oculomotor signs, skeletal deformities such as pes cavus and possibly scoliosis, and hypertrophic cardiomyopathy only in about 19%. Patients become wheelchair bound after an average of 11 years. The age of onset typically is before 20 years but has been reported in the fifth decade. AVED, due to a mutation in the α-tocopherol transfer protein (αTTP) on chromosome 8q13.1–q13.3, is a relatively rare AR ataxia with the largest group of patients found in North Africa sharing a common mutation. Since αTTP is involved in the transfer of vitamin E into circulating lipoproteins, the mutation results in the failure of incorporation of vitamin E into very low density lipoproteins in the liver. Diagnostic tests include vitamin E levels (typically <2 mg l^{-1}) and confirmatory genetic testing; other tests, such as complete blood count, creatine kinase, hepatic enzymes, copper studies, lipoproteins electrophoresis, peripheral smear for acanthocytes, and tests for steatorrhea are normal. Treatment with vitamin E at doses of 800 mg day\(^{-1}\) can reverse or slow down the ataxia.

**Abetalipoproteinemia**

Abetalipoproteinemia (also known as Bassen–Kornzweig disease) is a rare condition whose neurological manifestations are due to underlying vitamin E deficiency. As a result, abetalipoproteinemia clinically resembles AVED in the setting of a gastrointestinal malabsorption syndrome. Clinical features include cerebellar ataxia, proprioceptive sensory loss, areflexia, weakness, retinal degeneration, as well as steatorrhea, fat malabsorption, celiac syndrome, and acanthocytosis. Onset typically occurs in adolescence. Abetalipoproteinemia is caused by mutations in the gene coding a subunit of the microsomal triglyceride transfer protein (MTP) on chromosome 4q22–q24. Since MTP is necessary for lipoprotein assembly, the mutation impairs synthesis of apoB peptide of low density lipoprotein and very low density lipoprotein; this leads to impaired fat absorption and in turn, vitamin E deficiency. Levels of cholesterol and triglycerides are extremely low and apolipoprotein B-containing lipoproteins are absent. Treatment involves supplementation of fat soluble vitamins including vitamin E.

**Refsum disease**

Refsum disease, in its classic form, manifests as cerebellar ataxia, demyelinating sensori-motor polyneuropathy, and retinitis pigmentosa. Non-neurologic features include ichthyosis, deafness, multiple epiphyseal dysplasia, and cardiac arrhythmias. Onset typically occurs before the age of 20. Diagnostic studies include elevated serum phytanic acid, reduced oxidation of phytanic acid in fibroblasts, demyelinating neuropathy on nerve conduction studies, and elevated cerebrospinal fluid protein. Neuropathology demonstrates large onion bulbs and decreased myelinated axons on nerves and decreased Purkinje cells in cerebellum and neurons in inferior olive and vestibulocochlear nuclei. Refsum disease is a peroxisomal disorder due to an inability to degrade phytanic acid, a branched-chain fatty acid, with mutations in the gene coding phytanoyl-CoA hydroxylase on chromosome 10pter–p11.2. As a result, phytanic acid accumulates in body tissues. Treatment involves dietary restriction of phytanic acid to less than 10 mg day\(^{-1}\). Dietary measures may improve ataxia and neuropathy but not vision and hearing loss.

**Cerebrotendinous xanthomatosis**

CTX is a rare AR ataxia that involves both neurologic and systemic features. CTX typically presents after puberty with progressive cerebellar ataxia, neuropathy, pseudobulbar dysfunction, parapesis, and myoclonus and dementia, in some. Systemically, premature atherosclerosis, cataracts, and xanthelasma with thickened tendons (cholesterol deposition) occur. Nerve conduction studies reveal axonal loss and biopsies demonstrate axonal loss with demyelination in some patients. Laboratory testing is diagnostic.

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revealing increased serum cholestanol and increased urinary bile alcohol. Plasma cholesterol concentrations are low normal in CTX. The defect in CTX is due to mutations in the \textit{CYP27A1} gene on chromosome 2q33–qter, which is involved in bile acid synthesis pathway. Treatment involves administration of chenodeoxycholic acid to compensate for the pronounced deficiency of chenodeoxycholic acid in the intrahepatic pool. Some series of CTX patients have revealed improvement in neurological features (ataxia, neuropathy, dementia) in patients after at least 1 year of treatment. Management of atherosclerosis with HMG-CoA reductase inhibitors may also be necessary.

\textbf{Ataxia-telangiectasia (AT)}

AT, caused by a mutation in the \textit{ATM} gene on chromosome 11q22–23, manifests itself as a progressive cerebellar ataxia, also complicated by systemic features. Neurologic signs and symptoms include limb and gait ataxia, oculomotor apraxia, choreoathetosis, dystonia, dysarthria, hyporeflexia, sensory loss, distal muscular atrophy, and impaired cognition. Nonneurologic features include oculocutaneous telangiectasias (occur after neurologic symptoms), impaired humoral and cellular immunity resulting in sinopulmonary infections, high incidence of malignancy, such as leukemia and lymphoma, radiosensitivity, infertility, and diabetes mellitus. Onset begins around age 1–2 years with truncal ataxia and oculomotor problems. Children may be wheelchair bound by age 10 and death occurs between 20 and 30 years of age. Adjunctive diagnostic studies include elevated serum \( \alpha \)-fetoprotein and carcinoembryonic antigen, abnormalities in immunoglobulins (particularly absence or low level of serum IgA), neuroimaging revealing cerebellar atrophy, and genetic testing. No specific pharmacologic treatment for neurologic symptoms exists, but ongoing trials are assessing \( \alpha \)-lipoic acid and PARP-1 inhibitor. Patients should be monitored for infections and malignancy; antibiotics should be used for sinopulmonary infections but treatment of malignancies with radiation may be problematic due to radiosensitivity.

\textbf{Ataxia-ocular apraxia (AOA) types 1 and 2}

Ataxia-ocular apraxia Type 1 (AOA1), caused by mutations in the APTX protein located on chromosome 9p13, is a slowly progressive, childhood disorder with limb and gait ataxia, oculomotor apraxia, motor and sensory neuropathy, and extrapyramidal features, such as dystonia and hypomimia. In addition, hypoalbuminemia and hypercholesterolemia may occur. The mean age of onset is 5 years. Epidemiology reveals a Portuguese and Japanese predominance. Laboratory studies support axonal neuropathy on nerve conduction studies, mild loss of myelinated axons on nerve biopsy, and cerebellar atrophy with possible brainstem involvement on neuroimaging.

Ataxia-ocular apraxia Type 2 (AOA2), caused by a mutation in the senataxin protein on chromosome 9q34, presents later than AOA1 with the age of onset from 10 to 22 years and with severe gait ataxia, variably present oculomotor apraxia, slow saccades, choreoathetosis and dystonia, sensory-motor neuropathy, areflexia, and extensor plantar responses. Serum \( \alpha \)-fetoprotein and creatine kinase may be elevated, but chromosomal instability and radiosensitivity are absent.

\textbf{Spastic ataxia of Charlevoix-Saguenay (ARSACS)}

ARSACS, caused by mutations on chromosome 13q12 in the \textit{sacsin} gene, is characterized by cerebellar ataxia, spasticity, and prominent retinal myelinated fibers. Onset is typically around age 1–2 years with gait ataxia and lower limb spasticity, increased cerebellar signs around adolescence, motor axonal polyneuropathy in the third decade, and loss of ambulation around age 40. Other features include pes cavus or equinovarus, saccadic smooth pursuit, and distal amyotrophy, but absence of cardiac disease.

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as in FRDA. ARSACS is prevalent in Charlevoix-Saguenay, a region in Northeastern Quebec. Diagnostic studies reveal abnormal fundoscopy, early demyelination and axonal neuropathy on nerve conduction studies, neurogenic atrophy of muscle biopsy, loss of large myelinated axons on nerve biopsy, and cerebellar atrophy of the superior vermis and later hemispheres on neuroimaging. No specific treatment is available for the ataxia but antispasticity medications may be considered.

**X-Linked Ataxias**

**Fragile X-associated tremor-ataxia syndrome**

The clinical syndrome of fragile X-associated tremor-ataxia syndrome (FXTAS) includes progressive gait ataxia, action tremor, parkinsonism, cognitive decline/executive dysfunction, polyneuropathy, and autonomic dysfunction. The features typically occur in males over age 50, who are often the male grandparents of patients with FMR syndrome. Many patients have been previously diagnosed as having essential tremor, parkinsonism, or MSA. Neuroimaging reveals increased T2 signal in middle cerebellar peduncles and adjacent white matter. Neuropathology in mice and humans demonstrates eosinophilic, ubiquitin-staining, intranuclear inclusions in neurons and astrocytes throughout the brain and hippocampus. Treatments so far include symptomatic therapies for tremor, parkinsonism, and cognitive dysfunction.

Fragile X is caused by a CGG repeat expansion in the 5′ untranslated region of the fragile X mental retardation 1 (FMR1) gene with full mutation expansion lengths >200 CGG repeats. Instead, FXTAS is due to premutations in the FMR1 gene with CGG repeat lengths of 55–200. The frequency of the premutation is 1/259 in females and 1/813 males in the general population. In FMR, the CGG repeat expansion leads to methylation and transcriptional silencing of the FMR1 gene. In premutation carriers, however, levels of FMR1 mRNA are elevated thereby, suggesting a possible toxic ‘gain of function’ mechanism. FMR protein production is reduced due to reduced translational efficiency of FMR1 mRNA. CGG repeat length appears to influence FMR1 mRNA levels (elevated in premutation carriers) and position of transcription start (farther upstream with increasing repeats).

**Sporadic or Nonhereditary Ataxias**

Sporadic ataxias may be diverse in etiology. Differential diagnosis is influenced by the tempo of the ataxia and presence of systemic or neurologic abnormalities. Causes for sporadic ataxia include MSA, autoimmune disorders such as glutamic decarboxylase (GAD) antibodies, infections such as viral or prion disease, endocrine dysfunction such as hypothyroidism or hypoparathyroidism, gastrointestinal disorders such as celiac ataxia or Whipple’s disease, paraneoplastic syndromes, toxins, trauma, neoplastic, and vascular events, among others.

**Multiple system atrophy**

MSA is a progressive neurodegenerative disorder with elements of parkinsonism, cerebellar ataxia, and autonomic dysfunction. Although previously classified as striatonigral degeneration, Shy-Drager syndrome, and olivopontocerebellar atrophy (OPCA, sporadic), MSA is currently defined by the predominant clinical presentation with parkinsonism (MSA-P) in 80% or cerebellar ataxia (MSA-C) in 20% of patients. Clinical features of MSA-P include: parkinsonism with tremor (more commonly action or postural than rest tremor), akinesia, and rigidity, often symmetrical; autonomic disorders with lightheadedness, recurrent syncope, urinary incontinence or incomplete emptying, and impotence; and cerebellar dysfunction with limb and gait ataxia, nystagmus, and tremor. Other manifestations include corticospinal tract signs with hyperreflexia and extensor plantar responses, inspiratory stridor,
antecollis, myoclonus, rapid eye movement (REM) behavior disorder, facial dystonia, and cold or dusky hands. Clinical features of MSA-C include: impaired balance with ataxia, nystagmus, tremor, dysarthria; autonomic dysfunction with lightheadedness and syncope, bladder dysregulation and impotence; parkinsonism, and corticospinal tract signs. Patients typically have a poor and nonsustained response to levodopa although some benefit initially. Late-onset cerebellar ataxia and sporadic OPCA both may represent forms of MSA-C. Of patients diagnosed with OPCA followed longitudinally, about 25% developed MSA. The mean age of onset for MSA-P and MSA-C is around 50 years of age and survival, about 10 years. Average incidence rate for MSA is 3 new cases/100 000 person-years.

Diagnostic criteria for MSA have been established by Quinn et al., Gilman et al., and recently revised by Gilman et al. with possible, probable, or definite MSA designations. Definite MSA requires neuropathological demonstration of α-synuclein-positive glial cytoplasmic inclusions in the central nervous system with neurodegenerative changes in striatonigral or olivopontocerebellar structures. Probable MSA requires a sporadic, progressive, adult-onset disorder meeting criteria for autonomic failure and poorly levodopa-responsive parkinsonism or cerebellar ataxia. Possible MSA also requires a sporadic, progressive, adult-onset disorder with parkinsonism or cerebellar ataxia but at least one feature suggesting autonomic dysfunction plus either a clinical or neuroimaging abnormality. Neuroimaging with MRI may be helpful when characteristic findings are present. In MSA-P, putaminal hypointensity with a lateral hyperintense rim on T2 weighted images may occur. In MSA-C, the ‘hot cross bun’ sign with cerebellar atrophy and increased T2 signal in the pons may be seen. Variable sensitivity and specificity has been reported. PET imaging reveals decreased cerebral glucose metabolic rates in the striatum in MSA-P and brainstem and in the cerebellum in MSA-C. Studies related to autonomic failure indicate a preganglionic defect in MSA; cardiac SPECT imaging with I metaiodobenylguanidine (MIBG) which labels postganglionic adrenergic neurons may reveal significant decreases of uptake in PD but not in MSA due to its preganglionic deficit. Rectal sphincter EMG is a sensitive measure for denervation but may be abnormal in PD. Neuropathology of MSA includes degeneration of the striatum, substantia nigra, locus ceruleus, inferior olives, brainstem, cerebellum, interomedial cell columns, and Onuf’s nucleus. The pathological hallmark is the glial cytoplasmic inclusion, an α-synuclein and ubiquitin staining inclusion found in oligodendrocytes in the cortex, striatum, brainstem, and interomedial cell column.

Gluten ataxia

Neurological features of celiac disease or sprue, a gluten-sensitive enteropathy due to T cell mediated immune responses to ingested gluten in genetically susceptible populations, including ataxia, peripheral neuropathy, myopathy, and headaches. White matter changes on MRI have been reported. Cerebellar dysfunction manifests as truncal or gait ataxia, dysarthria, and oculomotor signs with a mean age of onset of about 50–60 years. Gluten sensitivity may present with neurological dysfunction in the absence of gastrointestinal or systemic symptoms. Diagnostics tests include IgG and IgA antibodies to gliadin, but antiendomysial, and tissue transglutaminase antibodies may offer greater specificity despite being less common in neurological dysfunction alone. Duodenal biopsy typically reveals absent villi with hyperplastic crypts and inflammatory and lymphocytic infiltration. Cerebellar atrophy may be present on brain MRI. Treatment involves a gluten-free diet; however, unlike gastrointestinal symptoms, improvement in ataxia may not be as robust.

Cerebellar syndrome with anti-GAD antibodies

Cerebellar ataxia with anti-GAD antibodies is a variant of stiffperson syndrome (SPS) which presents as
a slowly or subacutely progressive cerebellar ataxia involving the limbs and trunk, nystagmus, and
dysarthria. Stiffness is less prominent than in SPS, occurring in about 15%, and the brainstem is
unaffected. Similar to SPS, autoimmune diseases, such as diabetes mellitus, thyroiditis, and
polyendocrine syndrome may be present. Paraneoplastic syndromes should be excluded. The age of
onset ranges from 20 to 75 years with a female predominance. Laboratory tests reveal high titers of
anti-GAD antibodies and also anti-parietal cell antibodies. Neuroimaging may be normal or exhibit
cerebellar atrophy. There are no specific treatments for the cerebellar syndrome but case reports or
series cite some response to steroids and intravenous immunoglobulin.

Paraneoplastic syndromes

Ataxia may be a presenting feature of a paraneoplastic cerebellar degeneration syndrome (PCD). Paraneoplastic antibodies are thought to react with antigens in the cancer and nervous system, targeting antigens on Purkinje cells in cases with cerebellar ataxia. Onset typically precedes the neoplasm by months to even years. Symptoms of limb and gait ataxia, dysarthria, nystagmus, and oculomotor dysfunction may progress rapidly over weeks to months and then plateau.

PCD has been described most often with cancers of the lungs (small cell), ovaries, breast, and
lymphoma, but other cancers have been reported. Specific paraneoplastic antibodies associated with
PCD include: Hu – small cell lung cancer, Yo – ovarian or breast cancer, Ri – breast cancer, Tr and
metabotropic glutamate receptor R1 (mGlur1) – Hodgkin's lymphoma, Ma – breast, colon, or large cell
lung cancer, Ma2 – testicular cancer, CV2 (CRMP5) – small cell lung cancer or thymoma, voltage gated
calcium channels (VGCC) – small cell lung cancer, and Zic4 – small cell lung cancer. Diagnostic studies
focus on serum antibodies and detection of underlying cancer. Increased protein, IgG synthesis,
oligoclonal bands, and paraneoplastic antibodies may be found in cerebrospinal fluid. MRI, however, may
not demonstrate cerebellar atrophy initially. Pathology reveals degeneration of cerebellar Purkinje cells,
inflammatory infiltrates, and Purkinje cells that stain for specific paraneoplastic antibodies. Treatment
usually involves cancer management but responses to intravenous immunoglobulins or plasmapheresis
have been reported, particularly with Lambert–Eaton myasthenic syndrome, paraneoplastic
encephalomyelitis or sensory syndromes, and in cerebellar degeneration. However, despite decreased
titers of paraneoplastic antibodies with cancer resection and treatment, improvement of ataxia may be
disappointing due to neuronal destruction.

Prion disease

Cerebellar ataxia may be a component of prion diseases and has been described in familial and sporadic
Creutzfeld–Jacob disease (CJD), Kuru, and familial Gerstmann–Straussler–Sheinker disease (GSS).
Clinical features associated with CJD include progressive cerebellar ataxia, myoclonus, corticospinal
tract and extrapyramidal signs, visual disturbances and oculomotor dysfunction, as well as dementia and
behavioral problems. Patients with sporadic CJD carrying the valine–valine (VV) or methionine–valine
(MV) polymorphism at codon 129 of the prion protein gene (PRNP) and PrPSc type 2 may present with
a cerebellar form of CJD. In addition, sporadic CJD patients with MV polymorphism and type 1 PrPSc
may demonstrate ataxia and sensory deficits before cognitive decline. Point mutations on chromosome
20 in familial CJD (P102L) and GSS (G131V or H187R) may present as a classical ataxic forms. Diagnostic
tests include detection of 14–3–3 protein in cerebrospinal fluid, periodic sharp wave activity on EEG,
hyperintense signal in the basal ganglia on MRI, and possible biopsies of tonsils and brain, although these
tests vary in sensitivity and specificity for prion disease. More recently, genotype–phenotype
correlations can be made by evaluating different polymorphisms at codon 129 in the PRNP and

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different types of PrP$^{\text{Sc}}$. Neuropathology of prion diseases reveals spongiform encephalopathy but specific patterns of spongiform degeneration, astroglialosis, and neuronal loss depends on the subtype of CJD.

## Differential Diagnosis
See Table 2 for salient SCA features.

ADCAs classified by presence of neurologic signs and symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>SCA/Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure cerebellar ataxia</td>
<td>SCA 5, 6 (see Table 1)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>SCA 1, 2, 3, 4, 18, 25</td>
</tr>
<tr>
<td>Corticospinal tract signs</td>
<td>SCA 1, 3, 6, 7, 8, 12</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>SCA 2, 3, 12, 21</td>
</tr>
<tr>
<td>Dystonia</td>
<td>SCA 3, 12, 17</td>
</tr>
<tr>
<td>Chorea</td>
<td>SCA 1, 17; DRPLA</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>SCA 2, 14, 19; DRPLA</td>
</tr>
<tr>
<td>Ophthalmoplegia</td>
<td>SCA 1, 2, 3</td>
</tr>
<tr>
<td>Slow saccades</td>
<td>SCA 1, 2, 3, 7</td>
</tr>
<tr>
<td>Nystagmus (downbeat)</td>
<td>SCA 6</td>
</tr>
<tr>
<td>Pigmentary retinopathy</td>
<td>SCA 7</td>
</tr>
<tr>
<td>Cognitive impairment/dementia</td>
<td>SCA 2, 13, 17, 19, 21; DRPLA</td>
</tr>
<tr>
<td>Seizures</td>
<td>SCA 10, 17; DRPLA</td>
</tr>
<tr>
<td>Dentate calcifications on CT</td>
<td>SCA 20</td>
</tr>
</tbody>
</table>

## Diagnostic Work-Up/Tests
When approaching a patient with ataxia, an organized, step-wise process is important (see Figure 1). There are several key components in addition to a comprehensive neurological examination that will aid in developing a differential diagnosis and in some cases, deciding on acute medical intervention. The clinician must first ‘localize the lesion’ and determine whether the ataxia is due to cerebellar disease or to other neurologic problems such as in the vestibular or sensory/proprioceptive systems. If the deficits result from cerebellar dysfunction, one should then assess whether the syndrome is purely cerebellar or has other associated neurologic or systemic features (‘cerebellar-plus’). A detailed family history is necessary. Further investigation may require supplemental neuroimaging, electrophysiological studies, laboratory tests, and genetic tests.
Proposed diagnostic algorithm for evaluating ataxia patients.

Clinical History

Key features in the history of a patient with ataxia include: the onset age, time course and progression, and medical, social, and family history. In children, congenital ataxias, metabolic disorders, infectious/acute cerebellitis, posterior fossa tumors, and hereditary ataxias are often part of the differential diagnosis, whereas in adults, the sporadic and hereditary ataxias predominate. The time course of the ataxia is important. Acute ataxias are more likely to be vascular, metabolic/toxic, infectious, inflammatory, or traumatic in origin. Subacute causes may include metabolic/toxic, infectious, inflammatory, or paraneoplastic, tumor processes. Chronic ataxias are more likely genetic or degenerative. Accompanying symptoms such as headache, nausea, or vomiting may signify an acute cerebellar hemorrhage or increased intracranial pressure as in childhood posterior fossa tumors. Systemic signs such as weight loss, gastrointestinal symptoms, autonomic dysfunction, skin changes or other neurological signs, such as parkinsonism, dystonia, spasticity, neuropathy may be present. The course of the ataxia may be stable, progressive, or episodic. Medications such as anticonvulsants (phenytoin, barbiturates), lithium, immunosuppressants (methotrexate, cyclosporine), or antineoplastic agents (fluorouracil, cytarabine) may contribute to ataxia symptoms. Other medical problems such as cancer, infections, HIV, thyroid disease, gastrointestinal disease (malabsorption, celiac), or multiple sclerosis may be the cause of ataxia. Ascertaining the patient’s history of alcohol or substance use and toxin exposures (heavy metals, solvents, thallium) is important. Lastly, obtaining a detailed family history is imperative. The presence of ataxia, similar symptoms, or other neurologic disease should be recorded for at least three generations to best determine the mode of inheritance and identify phenotypic heterogeneity.

Clinical Examination

In addition to the general physical and neurological examination, one should pay attention to several specific elements of cerebellar function: speech, ocular movements (nystagmus, smooth pursuit, hypo or hypermetric saccades), limb coordination, tremor, stance, and gait. Cerebellar function, especially appendicular function, can be tested at the bedside with the following maneuvers: for dysmetria (finger–nose–finger, heel–knee–shin), dysdiadochokinesia (rapid alternating movements of tapping the palmar and dorsal surfaces of the hands), dyssynergia (tapping of hands, fingers, feet, and other multijoint movements), rebound (application of a downward tap on the patient’s outstretched arm which
produces a rapid, excessive upward displacement), and impaired check (sudden release of the patient’s flexed arm which leads to the inability of the patient to stop the movement). Tremor is more typically present with action and increases as the limb approaches the end-point or target (intention tremor). Tremor may be slow (2–5 Hz) and more proximal with wide amplitude. One should assess the patient’s sitting position for titubation, stance (typically wide based), and ability to perform tandem gait, single leg stance, and stand with and without eye closure. Furthermore, the comprehensive neurological examination should include evaluation of mental status, cranial nerves (vision, bulbar involvement, asymmetry), tone (hypotonia, rigidity, spasticity), strength, reflexes, sensation (presence of neuropathy), and movement disorders (parkinsonism, dystonia, myoclonus, chorea, tremor). Abnormalities in these other neurological systems may provide diagnostic clues (vision loss in SCA7, ophthalmoplegia and/or parkinsonism and/or dystonia in SCA3, areflexia and neuropathy in FRDA, etc.). General physical examination should include assessment of blood pressure for orthostatic hypotension (MSA), thyroid, eyes, cardiac (FRDA), endocrine, skin (AT), nail changes, and skeletal system.

**Rating Scales**

Specific ataxia rating scales can be used to monitor ataxia for both clinical management and research studies. The International Cooperative Ataxia Rating Scale (ICARS) rates gait, kinetic functions (limb ataxia), speech/dysarthria, and oculomotor findings, with scores ranging from 0 to 100; the ICARS demonstrates high-reliability as well as high test–retest reliability and internal consistency but has several overlapping, interdependent items that may affect its practicability. The Scale for the assessment and rating of ataxia (SARA) is a short, quick, semiquantitative scale that evaluates gait, stance, sitting, speech, and limb kinetic functions, but not oculomotor function; scores range from 0 to 40. The Unified Multiple System Atrophy Rating Scale (UMSARS) is a longer scale validated for MSA; it includes a historical interview, motor and autonomic examination, and global disability scale. Scales proposed for FRDA including the Friedreich Ataxia Rating Scale (FARS) which combines scores for ataxia, activities of daily living, and neurological examination. Other scales for tremor and parkinsonism (e.g., Unified Parkinson's Disease Rating Scale) may be useful. Details and clinimetric properties of these scales are discussed in other encyclopedia entries.

**Studies of Potential Utility in Patients With Ataxia**

This section describes tests that may be useful in the evaluation of a patient with ataxia. However, pursuit of these tests should be guided by the patient’s history, family history for inheritance patterns, and examination, among other factors, particularly since many of the specialized tests are very expensive.

Laboratory studies to be considered (depending on clinical situation) include: thyroid function, vitamin B12, vitamin E, vitamin B1, heavy metal screen, antigliadin antibodies, GAD antibodies, serum cholesterol and plasma lipoprotein profile, peripheral blood smear for acanthocytes, serum lactate and pyruvate, very long chain fatty acids, hexosaminidase A or B, paraneoplastic antibodies, toxicology screen, α-fetoprotein and immunoglobulins, serum ceruloplasmin and 24 h urinary copper, and phytic acid. Cerebrospinal fluid analysis may be used to assess protein, oligoclonal bands, 14–3–3 protein, GAD antibodies, or paraneoplastic antibodies. Many genetic tests are now commercially available, and some are available on a research basis. To date, genetic tests include SCA1, 2, 3, 5, 6, 7, 8, 10, 13, 14, 17, 27 (for SCA5, 13, 14, and 27, the analysis is of the entire coding region: sequence analysis, whereas the other SCAs have targeted mutation analysis); DRPLA; FRDA; Ataxia with oculomotor apraxia types 1 and 2 (APTX and senataxin); Fragile X DNA; Rett syndrome; X-linked sideroblastic anemia and ataxia;
ataxia telangiectasia; ARSACS (targeted mutation analysis); TTPA gene for ataxia with vitamin E deficiency; SIL1 for Marinesco–Sjogren syndrome; mitochondrial recessive ataxia syndrome (MIRAS)-specific POLG1; and EAs type 1 and 2 (sequence analysis). Tissue biopsies of muscle, skin, rectum, bone marrow, tonsil, or brain may be considered in appropriate circumstances.

Neuroimaging with MRI of the brain and possibly, cervical spine may be useful in excluding structural causes, multiple sclerosis, or assessing regional atrophy (i.e., in the cerebellum, brainstem, or cervical cord). In some cases, magnetic resonance spectroscopy may be helpful. Electrodiagnostic tests such as nerve conduction studies and EMG may be used to evaluate neuropathy which is often associated with the ataxias or other neuromuscular abnormalities; electroencephalography, evoked potentials, electroneystagmography, or electroretinography may be considered in selected circumstances. Tests of autonomic dysfunction for tilt-table tests, sympathetic skin responses, cardiac I\textsuperscript{23}.MIBG–SPECT scans, or anal sphincter EMG, particularly in MSA. Ophthalmologic examination may be targeted for pigmentary retinopathy, macular degeneration, cataracts, Kayser–Fleischer rings.

Management

Treatment of cerebellar ataxias encompasses both pharmacologic and nonpharmacologic strategies and in some cases, depends on the specific etiology of the ataxia. Some of the management issues have been previously discussed in the individual ataxia sections and where available, specific trials will be noted. In addition to management of neurologic systems, one must pay attention to systemic disorders affecting cardiac, endocrine, gastrointestinal, and skeletal systems as well as underlying neoplasms. Trials of medications for cerebellar ataxia mainly consist of open label studies or case reports, and better therapeutics and double-blind, placebo-controlled trials are needed. Lastly, genetic counseling is an important aspect of the management of hereditary ataxias.

Pharmacologic Strategies

First, treatable causes of ataxia will be mentioned. Although not curative, high doses of vitamin E can improve neurologic symptoms in ataxia with vitamin E deficiency (AVED) and Abetalipoproteinemia. Phytanic acid should be restricted to less than 10 mg day\textsuperscript{−1} in Refsum disease. Gluten ataxia may improve with restriction of wheat and products containing gluten. Ataxia due to CTX should be treated with chenodeoxycholic acid and possibly other cholesterol medications. Of course, ataxia due to infectious (including Whipple’s disease) or vascular etiologies may have disease-specific treatments. Paraneoplastic cerebellar syndromes may respond to treatment of underlying cancer and immunotherapies, such as intravenous immunoglobulin, plasmapheresis, and steroids. However, due to cerebellar neuronal damage, the ataxia symptoms may have modest response to these treatments. Cerebellar ataxia with GAD antibodies has been reported to respond to immunotherapies. EAs, particularly EA-1, 2, and 4, are acetazolamide-responsive. A recent open label trial of the potassium channel blocker 4-aminopyridine (4-AP) in three EA-2 patients reported prevention or decreased attacks during treatment and recurrence when 4-AP was stopped.

For FRDA, treatment focuses on rehabilitation and orthopedic interventions for gait and limb difficulty and skeletal deformities and cardiac and endocrine monitoring. Idebenone, a free radical scavenger, as other antioxidants such as vitamin E, coenzyme q10, and selenium have been studied in FRDA. Most trials with idebenone have been open label although a recent randomized, placebo-controlled study has been reported. Unfortunately, despite reduction of oxidative stress markers and decreased cardiac hypertrophy in some studies with idebenone, significant improvement in ataxia largely has been lacking.

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Management for MSA is generally tailored to specific symptoms. Dopaminergic medications may provide some improvement in parkinsonian features (bradykinesia, rigidity, or rest tremor), particularly early in the course. Improvement, however, is not as dramatic or sustained as in idiopathic Parkinson's disease. Orthostatic hypotension can be managed with increased salt and caffeine intake, pressurized stockings, and elevation of the head of the bed. Several trials including double-blind studies have assessed fludrocortisone and midodrine in orthostatic hypotension, but the use of these medications is limited by supine hypertension. A prospective open label trial by Singer et al. evaluating the acetylcholinesterase inhibitor, pyridostigmine, in the treatment of neurogenic orthostatic hypotension in patients with MSA, PD, and diabetic, amyloid, or idiopathic autonomic neuropathy demonstrated significant improvement in orthostatic blood pressure, peripheral resistance index, and orthostatic symptoms with only a moderate and nonsignificant increase in supine blood pressure. Bladder frequency and urgency may be treated with agents, such as oxybutynin and tolterodine. REM behavior disorder responds well to clonazepam.

The neurochemistry of the cerebellum has led to investigations of serotonergic, dopaminergic, GABAergic, and cholinergic treatments in cerebellar ataxias, although symptomatic benefits have been modest. Several studies have examined buspirone, a 5HT1A serotonin agonist with weak dopaminergic properties, in the cerebellar ataxias. An open label trial by Lou et al. with 20 patients with mixed cortical or OPCA received buspirone 60 mg day\(^{-1}\) for 8 weeks followed by a washout period; nine patients with mild or moderate symptoms had significant improvement in clinical and subjective ratings but not in motor function or posturography and few patients with severe symptoms showed improvement. Trouillas et al. performed a double-blind, placebo controlled study with buspirone in 19 patients with cortical cerebellar atrophy for 4 months found improvement only in subscores such as intensity of body sway and time of standing and kinetic score. A double-blind, placebo-controlled study by Botez et al. with amantadine (200 mg day\(^{-1}\)), an NMDA antagonist with some dopaminergic properties, was performed with 27 patients with FRDA and 39 patients with olivopontocerebellar ataxias for 3–4 months. Improvement was greater in the olivopontocerebellar ataxia group with improvement in visual and auditory reaction time and movement time. Other studies with amantadine have shown less positive results. An open label trial by Gazzula et al. with gabapentin, a GABAergic medication, in 10 patients (seven with sporadic cortical cerebellar atrophy and three with an unknown ADCA) reported a significant improvement in ataxia scores after single doses of 400 mg day\(^{-1}\) and 4 week treatment with 900–1600 mg day\(^{-1}\). Double-blind, placebo-controlled, crossover studies have investigated the cholinergic system with physostigmine, an acetylcholinesterase inhibitor, and l-acetylcarnitine, a cholinomimetic agent, in mixed ataxia populations without any effect on ataxia in the former and significant improvement in coordination but not total ARS score in the latter trial.

Several trials have addressed specific pharmacologic treatments in the SCAs, using a variety of agents but with mixed results. These reports include: zolpidem in five SCA2 patients; buspirone, a 5HT1A serotonin agonist with weak dopaminergic properties, in a single SCA3 patient; tandospirone, also a 5HT1A agonist, in case reports and open label studies in SCA3; fluoxetine in open label study of 13 SCA3 patients; trimethoprim–sulfamethoxazole in a double-blind, placebo-controlled crossover trial in 22 genetically confirmed SCA3 (no effect); acetazolamide in open label studies in small numbers of SCA6 (mixed results in clinical measures and posturography sway); and intravenous lidocaine in a case report of SCA6. More recently, Zesiewicz and Sullivan reported three patients with SCA3 and SCA14 who had improvement in ataxia symptoms with varenicline, a partial agonist selective for \(\alpha_4\beta_2\) nicotinic acetylcholine receptors and prescribed for smoking cessation. Based on a recent SCA1
knockout mice study in which lithium improved motor function and learning, a safety trial with lithium in SCA1 is currently underway.

**Nonpharmacologic Strategies**

Although clinical studies are lacking for nonpharmacologic treatments of ataxias, these modalities can be helpful. Physical and occupational therapy may be useful in gait and balance training, safety mechanisms, decreasing spasticity or rigidity, and reducing musculoskeletal problems such as contractures. Occupational therapists may help patients find adaptive devices to improve functional use of upper extremities. Speech therapists can evaluate dysphagia with bedside tests or more formal radiographic studies and teach swallowing techniques, modify diets, and work on dysarthria. Social services and supportive care also are important aspects.

**Genetic Counseling**

Genetic counseling is extremely important in the management of hereditary ataxias. Patients and families need to be counseled on underlying inheritance and risks of developing disease. Genetic counselors are valuable allies when discussing genetic testing; ethical concerns; potential social, medical, or insurance issues; and family planning with patients and families. Presymptomatic testing in adults, in general, is not routinely performed. In a study on the impact of presymptomatic genetic testing in 50 subjects with hereditary ataxias and neuromuscular disease, testing was reported as helpful in 84%, but increased anxiety at some point in the study occurred in 18 subjects with persistence at follow up and depression occurred in three (of whom two had negative results) in post-test period. Reasons for genetic testing included explanation for symptoms, emotional relief, and family planning.

**See also**

Aprataxin; Ataxia-Telangiectasia; Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS); Friedreich’s Ataxia and Variants; Friedreich’s Ataxia Rating Scale (FARS); Idebenone and Friedreich Ataxia; International Cooperative Ataxia Rating Scale (ICARS); Multiple System Atrophy; Paraneoplastic Movement Disorders; Refsum Disease- a Disorder of Peroxisomal Alpha-oxidation; SCA1; SCA2; SCA3, Machado–Joseph Disease; SCA4; SCA5; SCA6; SCA7, Spinocerebellar Ataxia with Macular Dystrophy; SCA8; SCA10; SCA11; SCA12; SCA13, 14, 15, and 16; SCA17; SCA27; Scale for the Assessment and Rating of Ataxia (SARA); Senataxin; Spinocerebellar Ataxia Type 19, 20, 21, 22, 23, 26; Spinocerebellar Ataxias Genetics; Tocopherol Transfer Protein and Ataxia with Vitamin E Deficiency

**Relevant Websites**


[www.geneclinics.org](http://www.geneclinics.org) – Geneclinics

Neuromuscular Disease Center at Washington University – [www.neuro.wustl.edu](http://www.neuro.wustl.edu)

**Glossary**

**Anticipation**

Increased symptom severity and earlier onset of symptoms in subsequent generations.

**Dysdiadochokinesia**

The breakdown or decomposition of coordination of different single-joint movement components

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when performing rapidly alternating or fine repetitive movements.

**Dysmetria**

Inaccuracy in judgment of distance of the trajectory of a body part during active movement, in range, direction, and speed. Hypermetria involves overshooting the target, and hypometria, undershooting the target.

**Dyssynergia or asynergia**

Often referred to as decomposition of movement, disruption of normal coordination and execution of a voluntary movement, particularly with multijoint movements.

**Trinucleotide repeat disorders or polyglutamine disorders**

Disorders due to CAG repeat expansions that encode the repeat of the amino acid glutamine in the disease protein; includes SCA1 2, 3, 6, 7, and 17, Huntington disease, spinobulbar muscular atrophy, and dentatorubropallidoluysian atrophy.

**Further Reading**

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