

## REVIEW ARTICLE

# Recent Advances in Hereditary Spinocerebellar Ataxias

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### Abstract

In recent years, molecular genetic research has unraveled a major part of the genetic background of autosomal dominant and recessive spinocerebellar ataxias. These advances have also allowed insight in (some of) the pathophysiologic pathways assumed to be involved in these diseases. For the clinician, the expanding number of genes and genetic loci in these diseases and the enormous clinical heterogeneity of specific ataxia subtypes complicate management of ataxia patients. In this review, the clinical and neuropathologic features of the recently identified spinocerebellar ataxias are described, and the various molecular mechanisms that have been demonstrated to be involved in these disorders are discussed.

**Key Words:** Cerebellar ataxia, DNA repair, Polyglutamine, Transcription, Trinucleotide expansion.

### INTRODUCTION

The problem of a rational nosologic classification of the degenerative cerebellar ataxias has haunted clinicians for about 150 years. The problem was conceptually resolved by Anita Harding when she proposed a genetic subdivision into dominant, recessive, and sporadic spinocerebellar ataxias (1). The development of statistical and molecular genetic analytic tools has resulted in the identification of the loci and mutated genes associated with the various spinocerebellar ataxias, allowing us to unravel the underlying mechanisms of cerebellar neurodegeneration. However, the expanding number of genes has created novel challenges, such as defining the most efficient diagnostic approach and how to pursue the ultimate goal of finding rational therapies.

We will review the various spinocerebellar ataxias that have now unambiguously been identified, present data on the corresponding clinical and neuropathologic features, and examine the various molecular mechanisms that have been demonstrated to be involved in these particular neurodegenerative disorders.

### AUTOSOMAL DOMINANT CEREBELLAR ATAXIAS (ADCAs)

Since the identification of the first gene involved in dominant ataxia, spinocerebellar ataxia (SCA) 1, in 1993, 24 genetic loci and 9 genes have been described (Table 1) (1). The first SCA genes (SCA1, 2, 3, 6, and 7) identified all share as their mutational mechanism an expanded repeat of coding CAG sequences (2–6). These repeats are translated into an expanded polyglutamine (polyQ) stretch in the cognate proteins, which are termed ataxines but which are otherwise unrelated. SCA8, 10, and 12 are caused by a noncoding CTG, ATTCT, and CAG repeat expansion, respectively (7–9), although the pathogenicity of the SCA8 mutation is still under debate. The SCA10 and SCA12 mutations seem to be confined to specific populations (10–12).

Because of significant clinical overlap between the various SCAs and the phenotypic variability of single subtypes, it is hazardous to clinically predict the SCA genotype in individual patients. There are, nevertheless, some specific clinical clues that can be used to adopt a rational first-line genetic testing strategy (Table 1) (13). Characteristics of the most recently identified SCA loci and genes are discussed below. SCA subtypes discovered earlier have been reviewed previously (13, 14).

### NOVEL SCA SUBTYPES

#### SCA12 (OMIM 604326)

This very rare genotype has been described in a pedigree of German descent, as well as in 6 families from India (7, 10, 11). Onset varies between age 8 and 55 years, although an insidiously progressive postural tremor precludes exact onset determination. Progressive ataxia, extrapyramidal features, and ultimate dementia are characteristic. SCA12 is caused by an expanded noncoding CAG repeat in the *PPP2R2B* gene that encodes a brain-specific regulatory subunit of the phosphatase PP2A (7).

#### SCA13 (OMIM 605259)

To date, only one French family linked to this chromosome 19q13.3-13.4 locus has been described (15). The clinical features clearly distinguish SCA13 from the other SCA subtypes: onset of ataxia in early childhood (although with very slow disease progression), delay of motor milestones, and mild mental retardation or deterioration. Additional signs include pyramidal tract signs, swallowing difficulties, urinary urgency, and extrapyramidal features like torticollis or bradykinesia.

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**TABLE 1. Dominant Genotypes According to Type of Mutation**

Mutational Mechanism	Locus	Gene	Gene Product	Distinctive Clinical Feature
Coding CAG repeat expansion				
SCA1	6p22-23	SCA1	Ataxin-1	
SCA2	12q23-24.1	ACA2	Ataxin-2	Marked slowing of saccades; pontine atrophy on neuroimaging
SCA3	14q24-qter	SCA3/MJD	Ataxin-3	Pronounced parkinsonism, spasticity, neuropathy, or motor neuron disease may be present
SCA6	19p13	CACNA1A	$\alpha$ 1-subunit of voltage-gated $Ca^{2++}$ -channel type P/Q	Relatively late-onset (>50 years); may be found in 'sporadic' ataxia
SCA7	3p12-21.1	SCA7	Ataxin-7	Macula degeneration
SCA17	6q27	TBP	TATA box binding protein	Marked dementia, chorea, parkinsonism, and/or psychiatric symptoms; may be resemble Huntington's disease
Noncoding repeat expansion				
SCA12 (CAG)	5q31-33	PPP2R2B	Brain-specific regulatory subunit phosphatase PP2A	Action tremor head and arms as first feature
SCA8 (CTG)	13q21	SCA8	Antisense RNA-transcript (KLHL1)	
SCA10 (ATTCT)	22q13-qter	SCA10	?	Seizures; all families reported so far are of Mexican descent
Point mutations				
SCA6	19p13	CACNA1A	$\alpha$ 1-subunit of voltage-gated $Ca^{2++}$ -channel type P/Q	
SCA14 'FGF14'	19q13.4-qter 13q34	PRKCG FGF14	Protein kinase C type $\gamma$ Fibroblast growth factor 14	Dynstonia or axial myoclonus if onset <30 years Childhood hand tremor; orofacial dyskinesias
Unknown				
SCA4	16q22.1	?	?	Coexisting sensory axonal neuropathy
SCA5	11p11-q11	?	?	
SCA11	5q14-21.3	?	?	
SCA13	19q13.3-13.4	?	?	Onset <10 years, psychomotor retardation
SCA15	3p24.2-pter	?	?	
SCA16	8q23	?	?	Rotary head tremor
SCA18	7q22-q32	?	?	Onset <20 years, marked sensory neuropathy
SCA19 / SCA22	1p21-q23	?	?	Holmes-like tremor, myoclonus, frontal executive dysfunction
SCA20 (SCA5?)	11	?	?	Dysphonia, palatal or lip tremor, calcifications of dentate nucleus
SCA21	7p21.3-p15.1	?	?	Extrapyramidal features
SCA23	20p13-p12.2	?	?	
SCA25	2p15-p21	?	?	Occasional very early onset, prominent sensory neuropathy

### SCA14 (OMIM 605361)

A small number of families with linkage to the SCA14 locus on chromosome 19q13.4-qter have been reported. A slowly progressive isolated cerebellar syndrome with a markedly variable age at onset was reported, with extrapyramidal features such as focal dystonia or axial myoclonus in early onset disease (16–18). Five different missense mutations have been described in exon 4 of the *PRKCG* gene that encodes protein kinase C $\gamma$  (PKC $\gamma$ ): 301C→T, 355T→C, 383G→A, 353G→A, and 380A→G (18–20). These 5 mutations all affect the regulatory domain of PKC $\gamma$ . Recently, a mutation in exon 18 that affects the catalytic domain of the protein was identified in a French SCA14 family with additional cognitive disturbances and myoclonus (21). Neuropathologic examination has shown patchy Purkinje cell loss without glial proliferation,

mild gliosis in the medulla oblongata and inferior olives without neuronal loss, and with normal findings in the basis pontis, basal ganglia, and cerebral cortex (17, 20).

### SCA15 (OMIM 606658)

Pure cerebellar ataxia in an Australian family was linked to the 3p24.2-pter region (22). A Japanese SCA family was reported recently with possible linkage to a locus on 3p26.1-25.3, which partly overlaps the SCA15 locus (23). Most of the affected subjects in this family showed additional postural and action tremor of the trunk and hands.

### SCA16 (OMIM 606364)

Linkage to a locus on 8q22.1-24.1 has been found in a large Japanese ADCA family with a late-onset isolated

cerebellar ataxia and coexisting rotatory head tremor in 3 subjects (24).

### **SCA17 (OMIM 607136)**

This rare SCA subtype is caused by an expanded CAG/CAA repeat in the *TATA binding protein (TBP)* gene that results in an expanded polyQ tract in the encoded TATA-binding protein, a transcription factor. Normal alleles carry 29 to 42 CAG/CAA repeats; expansions between 46 and 66 are associated with spinocerebellar ataxia (25–27). Controversy exists about the meiotic stability of the SCA17 repeat and the occurrence of nonpenetrance, complicated by marked variability in the age of onset, ranging from 18 to 55 years (26, 28–30). Clinical features encompass a variable combination of progressive cerebellar ataxia, psychiatric disturbances, dementia, and extrapyramidal features such as parkinsonism, dystonia, and chorea (25, 26, 28). A Huntington disease-like phenotype has been documented (31). Hyperreflexia is frequently present, and some patients develop seizures, spasticity, dysphagia, sphincter abnormalities, or an axonal neuropathy (25, 26, 30). Imaging studies revealed cerebellar and cerebral cortical atrophy (25, 29, 30).

Neuropathologic examination has demonstrated 1) marked cerebellar atrophy with mild cerebral cortical atrophy, 2) moderate to severe Purkinje cell loss, 3) moderate loss of neurons in the caudate nucleus, putamen, locus ceruleus, thalamic and hippocampal regions, 4) neuronal loss with spongiotic changes in various cerebral cortical regions, 5) relatively mild brainstem involvement, and 6) the presence of extensive intranuclear ubiquitinated polyQ containing neuronal inclusions in a wide range of both affected and nonaffected brain regions (25, 26, 28, 31).

### **SCA18 (OMIM 607458)**

This 7q22-q32 locus was mapped in an Irish-American family. Onset of disease, which consisted of a sensory ataxia due to a sensory axonal neuropathy, was mostly before the age of 20 years. Later, some individuals developed cerebellar ataxia with mild cerebellar atrophy on neuroimaging, pyramidal tract signs, and neurogenic muscle weakness and atrophy (32). Phenotypically, this family seems to present an overlap between the SCAs and the hereditary sensory neuropathies.

### **SCA19 and SCA22 (OMIM 607346)**

The SCA19 locus on chromosome 1p21-q21 was identified in one Dutch family (33). Affected individuals displayed a late-onset mild cerebellar ataxia, hyporeflexia, and frontal executive dysfunction (34). Tremor and myoclonic movements were occasionally observed. Before the SCA19 locus had been published, the name SCA22 was assigned to a 1p21-q23 locus that resulted from a linkage study in a Chinese SCA family (35). Although extracerebellar signs were absent in the Chinese family, these 2 loci might represent the same condition (36).

### **SCA20 (OMIM 608687)**

This locus on the pericentromeric region of chromosome 11 covers the SCA5 locus (37). Clinically, this Australian family is clearly different from the original SCA5 family.

Disease onset varied from 19 to 64 years and dysarthria was a relatively frequent presentation. Besides ataxia, subjects displayed dysphonia, palatal or lip tremor, and bradykinesia. Neuroimaging disclosed calcifications in the area of the dentate nucleus. SCA5 and SCA20 may be allelic or phenotypic variants of the same mutated gene or are indeed distinct genetic disorders.

### **SCA21 (OMIM 607454)**

Linkage to 7p21.3-15.1 was described in a single French family (38). Ataxia onset ranged from 6 to 30 years. Mild akinesia with or without limb rigidity, resting and postural limb tremor, mild cognitive impairment, and hyporeflexia were observed.

### **SCA23**

SCA23, its locus on 20p13-p12.2, is clinically characterized by an isolated cerebellar ataxia that starts after age 40 years. Neuropathology in one affected subject showed the following: neuronal loss in the Purkinje cell layer, dentate nuclei, and the inferior olives; thinning of cerebellopontine tracts; demyelination of the spinocerebellar afferent tracts; and ubiquitin-positive intranuclear inclusions in substantia nigra neurons (39).

### **SCA24 (OMIM 607317)**

The SCA24 designation has been assigned to a family with late-onset spinocerebellar ataxia, increased saccadic speed, pyramidal tract signs, axonal neuropathy, mild pes cavus, and myoclonic jerks (40). However, the pedigree of the family referred to suggests an autosomal recessive mode of inheritance.

### **SCA25 (OMIM 608703)**

A 2p15-p21 locus has been mapped in a French family (41). Age at onset varied from 17 months to 39 years. In addition to cerebellar ataxia, sensory neuropathy was a prominent feature and some subjects showed severe neuropathy with only little cerebellar involvement. Scoliosis, facial tics or myokymia, and gastric pain were noted in some subjects. Like SCA18, SCA25 seems to lie within a spectrum of SCAs and hereditary sensory neuropathies.

### **SCA26**

This locus on 19q13.2 has been mapped in a Norwegian American family with a pure cerebellar ataxia (personal communication, Howell MJ, 2004).

### **FGF14 (OMIM 601515)**

The *fibroblast growth factor 14 (FGF14)* mutation associates an unexpected category of genes/proteins with spinocerebellar ataxia (42). Affected members of the single Dutch FGF14 family showed ataxia onset between 28 and 40 years, but most patients had hand tremor since childhood. Head tremor, orofacial dyskinesias, low cognitive performances, and aggressive outbursts were frequently present. The *FGF14* mutation on chromosome 13q34 consists of a missense mutation (434T→C) in exon 4. The function of wild-type Fgf14 is unclear; how this mutation induces neurodegeneration

is unknown. Functional studies indicate that the mutation might affect Fgf14 protein stability.

### RECESSIVE AND SPORADIC EARLY ONSET ATAXIAS

The group of recessive ataxias is clinically even more heterogeneous than the dominant forms and often manifest as multisystem disorders. However, the various genotypes can be grouped into recognizable and more or less specific phenotypes (Table 2). We will review autosomal recessive diseases with cerebellar ataxia as the core feature; recessive diseases with ataxia as an additional feature (e.g. Refsum disease) are not discussed.

#### Ataxias With Neuro(no)pathy

A large group of recessive ataxias is characterized by prominent peripheral nerve involvement that accompanies the spinocerebellar ataxia. This peripheral nerve involvement encompasses a more or less typical dying-back axonopathy that mainly affects the lower limbs. Less commonly, a nongradient neuropathy or ganglionopathy of both upper and lower limb is encountered.

#### Friedreich's Ataxia (FA) (OMIM 229300)

The most common and best known recessive ataxia is FA; its estimated prevalence in the western world is about 2 in 100,000. The estimated gene carrier frequency is about 1:100 (43–45). FA is the sole example of an intronic expanded trinucleotide (GAA) repeat, located in intron 1 of the 9q12 *frataxin* gene (46). In most control alleles, the repeat length ranges from 6 to 9. A small subset of large-normal alleles (14–34 repeats) exists that may be the unique source of further expansions into an intermediate (up to 90 repeats) or clearly disease causing range (90–1,700 repeats) (44, 46–48). *Frataxin* gene point mutations have been described, but such alleles may only be pathogenic in conjunction with a GAA-expanded allele (49).

For a detailed overview of the clinical hallmarks of FA, we refer to the paper by Dürr (45). Apparently, the clinical spectrum of FA is much wider than initially defined and currently includes onset ages over 30 years, a much milder disease course than usually recognized, spastic ataxia, and even extrapyramidal movement disorders such as myoclonus or chorea (50). Cardiomyopathy is present in most cases, although its manifestations are variable and may often remain undetected (51).

#### FRDA2 (OMIM 601992)

A second locus, on 9p23-p11, was found to cosegregate with a disorder that was phenotypically described as classic Friedreich's disease (52). No progress has been reported on this entity.

#### Hereditary Ataxia With Vitamin E Deficiency (AVED) (OMIM 277460)

This rare condition clinically resembles FA: early onset progressive spinocerebellar ataxia with marked proprioceptive loss and areflexia due to prominent peripheral nerve pathology (53). The crucial lab finding is a very low serum concentration of vitamin E/tocopherol. The molecular defect turned out to be mutations in the *alpha-tocopherol transfer* protein gene (*alpha-TTP*), which is localized on chromosome 8q13 (54). Most

known patients originate from Tunisia where the prevalence may be as high as 1 per 100,000 (55).

Another, extremely rare form of recessive ataxia with dystonia is encountered on one of the Cayman Islands only. The mutated protein, called caytaxin (OMIM 601238), shares a so-called CRAL-TRIO domain with the *alpha-TTP* protein (56). This motif binds small lipophilic proteins like vitamin E, retinal, and squalene, a cholesterol precursor. Thus, vitamin E may not be the only culprit in the pathogenesis of these types of ataxia. Still, vitamin E should be supplemented to patients with AVED as trials have suggested a stabilization of neurologic decline after treatment initiation (57). Apart from AVED, other causes of low serum vitamin E concentration may lead to cerebellar ataxia, spinal chord degeneration, and neuropathy (58).

#### X-Linked Sideroblastic Anemia With Ataxia (OMIM 301310)

This very rare disorder consists of juvenile onset non-progressive ataxia, pyramidal tract signs, and a sideroblastic anemia in affected males. Heterozygote women may show ring sideroblasts on bone marrow examination, a dimorphic peripheral blood smear, and raised free red cell protoporphyrin (59). Missense mutations have been found in a nuclear mitochondrial ATP-binding cassette transporter (ABC7) (60, 61).

#### Infantile Onset Spinocerebellar Ataxia (IOSCA) (OMIM 271245)

IOSCA has been described exclusively in a small founder group of Finnish patients. Onset is between ages 1 and 2 years of age. Features include progressive ataxia, athetosis, muscle hypotonia, areflexia, ophthalmoplegia, hearing loss, and sensory neuropathy. Female hypogonadism and epilepsy are late manifestations (62). The IOSCA locus was mapped to 10q24, but a gene has not been found yet (63). Two published autopsy cases showed the following: patchy cerebellar cortical and severe dentate nuclear atrophy; extensive involvement of brainstem structures such as the cerebellar peduncles, inferior olives, the eighth cranial nerve and nucleus, the tegmental nuclei and tracts, the oculomotor nuclei, and periaqueductal gray matter; severe atrophic changes in the spinal cord, particularly the dorsal roots, the posterior columns and posterior spinocerebellar tracts; and a severe axonal loss in the sural nerve (64).

#### Spinocerebellar Ataxia with Axonal Neuropathy (SCAN1) (OMIM 607250)

This recessive ataxia, recently described in a Saudi Arabian family, is characterized by mild ataxia and cerebellar atrophy, axonal mixed neuropathy, distal muscle atrophy, pes cavus, and a steppage gait as is seen in Charcot-Marie-Tooth disease (65). A homozygous 1478A→G transition mutation in the Tyrosyl-DNA phosphodiesterase 1 (*TDPI*) DNA repair enzyme was identified (65).

#### Early Onset Cerebellar Ataxia (with Retained Tendon Reflexes)

This designation was, again, introduced by Anita Harding in 1981 as a denominator for patients with a phenotype that is distinct from classical FA: a slower rate of progression, less (or no) cardiac abnormalities, absence of scoliosis, and prominent

**TABLE 2. Recessive Genotypes According to Phenotype**

Syndromal Phenotype	Clinically Defined Disease	Locus	Gene
Ataxia with neuro(no)pathy	Friedreich's disease (FA)	9q12	Frataxin
	FRDA2	9p23-p11	
	Hereditary ataxia with vitamin E deficiency	8q13.1-q13.3	Alpha-tocopherol transfer protein
	X-linked sideroblastic anemia with ataxia	Xq13.1-q13.3	ATP-binding cassette (ABC) transporter
	Infantile onset spinocerebellar ataxia	10q24	
	Cayman type ataxia	19p13.3	Atcay (Caytaxin)
	Spinocerebellar ataxia with axonal neuropathy (SCAN1)	14q31-q32	Tyrosyl-DNA phosphodiesterase 1 (TDP 1)
Spastic ataxia	Early onset cerebellar ataxia (EOCA)		
	Autosomal recessive ataxia of Charlevoix-Saguenay	13q12	SACS (Sacsin)
Ataxia with oculomotor apraxia	Ataxia telangiectasia (AT)	11q22.3	ATM
	hMRE11 associated AT	11q21	MRE11
	Ataxia with oculomotor apraxia (AOA1)	9p13.3	APTX (Aprataxin)
	Ataxia with oculomotor apraxia (AOA2)	9q34	SETX (Senataxin)
Ramsay Hunt syndrome			

cerebellar atrophy on MRI (66–68). Contrary to the name, areflexia may evolve during the course of the disease. The prevalence of EOCA is unknown, but estimates yielded about half of the prevalence of FA (66). As most of the publications date from prior to the discovery of the FA gene and given the clinical heterogeneity associated with the FA mutation, inclusion of FA cases in these series must be suspected. These cases are now considered to represent a clinically and genetically heterogeneous group of recessive ataxias with, in general, a slower disease course and a better prognosis than classical FA (69).

**Spastic Ataxias**

In some ataxias, lower limb spasticity is so prominent that a separate phenotype may be recognized. At least 1 dominant form, SAX1 (70), as well as recessive forms are currently recognized.

**Autosomal Recessive Ataxia of Charlevoix-Saguenay (OMIM 270550)**

This disorder was first described in 1978 in a group of families from the two eponymic Quebec regions that were both related to a common founder (71). Clinical features of the original families included cerebellar ataxia, lower limb spasticity, distal muscle wasting, and foot deformities. Specific features appeared to be retinal striation reminiscent of early Leber's atrophy, mild mental retardation, and frequent mitral valve prolapse. Disease onset was very early, none of the patients ever walked normally, but little disease progression was noted after age 20 years. Shared homozygosity analysis identified a locus on 13q11 and 2 distinct ancestral haplotypes were revealed (72). The mutated gene, *SACS*, encodes a novel protein, called saccin. Additional families have been reported from Turkey, Tunisia, Italy, and Japan (73–78). It now appears

that neither retinal striation nor mitral valve prolapse is as specific as initially reported.

**Ataxia Telangiectasia-like Disorders**

This group of ataxias is characterized by early onset cerebellar ataxia, muscle wasting, prominent extrapyramidal features, and a rather specific eye movement abnormality called oculomotor apraxia. Ataxia telangiectasia is the best known of these disorders, but at least two novel forms have been identified.

**Ataxia Telangiectasia (AT) (OMIM 208900)**

The incidence of AT has been estimated at about 0.3 to 1.0 per 100,000 live births (79). The AT-mutated gene carrier frequencies in western populations may be 0.5 to 1.0%, but percentages as high as 3.5 have been suggested (79, 80).

The disease typically starts in early childhood with progressive cerebellar ataxia. Oculomotor apraxia with absent optokinetic nystagmus is highly characteristic. Chorea, dystonia, and related extrapyramidal features occur in many patients. Deep tendon reflexes become diminished or absent by age 8 and patients later develop diminished large-fiber sensation (81). Progressive spinal muscular atrophy that affects mostly hands and feet debuts at an older age and leads to striking combined flexion-extension contractures of the fingers. Nonneurologic manifestations in homozygotes consist of conjunctival telangiectasias, frequent respiratory tract or other infections, radiosensitivity, and a predisposition to various forms of cancer. The most common malignancies associated with homozygous AT are leukemia and B-cell lymphomas. Diagnostic laboratory features are elevated serum alpha-fetoprotein and carcinoembryonic antigen concentrations, dysgammaglobulinemias, and impairment of cellular immunity. The gene responsible for ataxia telangiectasia is called *ATM* (*AT-mutated*) (82).

The neuropathology of AT is not very specific. In advanced cases, the cerebellum is severely atrophic due to thinning of the molecular layer, granule cell depletion, and loss of Purkinje cells. Additional affected structures include the dorsal root ganglia and the spinal cord, where dorsal column demyelination with neuroaxonal dystrophy, astrocytic proliferation, and anterior horn cell degeneration may be observed. Abnormalities may also occur in brainstem nuclei such as the trigeminal mesencephalic nucleus and the substantia nigra (83–85). Intracerebral vascular abnormalities have been described that may be part of the pathobiology of the disease (86).

Two families have been described in which affected individuals suffered from an AT-like disease and in whom, instead of *ATM* mutations, a mutation in the *hMRE11* gene was detected (87).

### Ataxia with Oculomotor Apraxia Type 1 (AOA1) (OMIM 208920)

Another AT-like phenotype consists of oculomotor apraxia, with added features of early onset cerebellar ataxia, choreoathetosis, peripheral nerve involvement, and, in a subset of patients, mental retardation (88, 89). Telangiectasias or frequent infections were specifically absent, while hypoalbuminemia and hyperlipidemia were present in many patients. The gene was mapped to 9p13 and the mutated protein that causes AOA1 was called *aprataxin* (*APTX*) (90, 91).

### Ataxia with Oculomotor Apraxia Type 2 (AOA2) (OMIM 606002)

A second locus on 9q34 was identified in two nonrelated families. (92) Clinically, these patients had late childhood or adolescent onset ataxia, inconsistent oculomotor apraxia, and elevated levels of serum creatine kinase, gamma-globulin, and alpha-fetoprotein (92, 93). The gene associated with this disorder has been designated *senataxin* (94).

### Ramsay Hunt Syndrome (Dyssynergia Cerebellaris Myoclonica)

This entity basically constitutes a syndrome that consists of ataxia and myoclonus, with or without epilepsy. Many different diseases may manifest as a Ramsay Hunt syndrome, such as mitochondrial disorders, sialidosis type I, FA, celiac disease, or the various progressive myoclonic epilepsies (95–99). This syndromal diagnosis may thus be a useful step in restricting the search for the underlying molecular pathology.

## PUTATIVE DISEASE MECHANISMS

Reviewing the various mutations that cause the spinocerebellar ataxias, a limited number of disease mechanisms seem to emerge that underlie the degeneration of spinocerebellar pathways (Table 3). These mechanisms have been implied in other forms of neurodegeneration, but by studying the spinocerebellar degenerations, their interplay may be illustrated.

### Trinucleotide Repeat Expansions

Expanding trinucleotide repeats represent the most common cause of spinocerebellar degeneration. The CAG repeats in SCA1, 2, 3, 6, 7, and 17 are expressed as expanded

polyQ sequences in the cognate proteins. The mechanism by which these polyQ proteins cause neurodegeneration is still unknown. Relevant data, however, also come from work on two other polyQ-associated neurodegenerative diseases: Huntington disease (HD) and spinal bulbar muscular atrophy (SBMA). A hallmark of polyQ diseases is the presence of nuclear or cytoplasmic inclusions that reflect the propensity of polyQ proteins to aggregate (100). Ubiquitinated polyQ-containing aggregates have been found in neuronal nuclei of SCA1, 3, 7, and 17 and in the cytoplasm of SCA2 (101, 102). In SCA6 brains, nonubiquitinated aggregates have been found exclusively in the cytoplasm of Purkinje cells (103). Many issues are still unresolved. Does pathology depend on the polyQ stretch only, on a (partial) loss of wild-type protein function, or on a toxic “gain of function” of the wild-type protein? Are polyQ aggregates themselves toxic, or are soluble polyQ-containing protein fragments the culprits? Which downstream cellular mechanisms are affected by polyQ proteins? By now a large number of such possible downstream mechanisms have been proposed; these are described below.

### Transcriptional Regulation

The function of some transcription factors or transcriptional coactivators has been found to be impaired by an interaction with polyQ proteins or by being sequestered into the polyQ aggregates (104). Examples are the interaction between ataxin-7 and the homeodomain transcription factor Crx, interactions between polyQ and TAF<sub>II</sub>-130, and the sequestration of the CREB-binding protein CBP into polyQ aggregates (105–107). This may result in transcriptional shutdown and subsequent neuronal degeneration (108). Current data suggest that the normal function of some of the ataxins is transcriptional regulation (109). SCA17 is caused by a mutation in the TATA-binding protein TBP, an important general transcription initiation factor (27). Wild-type ataxin-7 may be a subunit of TFIIIC-like transcriptional factor (110). Therefore, the term “transcriptionopathies” for polyQ diseases has been advocated.

**TABLE 3.** Putative Disease Mechanisms in Dominant and Recessive Ataxias

Disease Mechanism Affects...	(May be) Involved in...
Transcriptional (dys)regulation	SCA17, SCA7
Mitochondrial function	FA, AVED, X-SAA
Calcium signaling	SCA6, (SCA14)
Phosphorylation	SCA12, SCA14
DNA repair	AT, AOA1, AOA2, SCAN1
Ubiquitin/proteasome function	SCA3
Protein misfolding and chaperone function	ARSACS
Growth factors	FGF14

FA, Friedreich's ataxia; AVED, ataxia with vitamin E deficiency; X-SAA, X-linked sideroblastic anemia with ataxia; AT, ataxia telangiectasia; AOA, ataxia with oculomotor apraxia; ARSACS, autosomal recessive ataxia of Charlevoix-Saguenay; FGF14, fibroblast growth factor 14.

## Mitochondrial Dysfunction

Mitochondrial dysfunction may cause spinocerebellar ataxia. This is not only demonstrated by (spino)cerebellar ataxia as (part of) the phenotype of mitochondriopathies (111), but also by the molecular pathology of FA, AVED, and X-linked sideroblastic anemia with ataxia. The large GAA expansions in the *frataxin* gene suppress gene expression, thus causing a classical recessive genotype and loss of function of the frataxin protein, a mitochondrial matrix protein (112). In vitro deletion of a yeast *frataxin* homologue YFH1 resulted in considerable oxidative damage to both mitochondrial and nuclear DNA (113). FA must therefore be considered as a nuclear encoded mitochondrial disorder.

Ataxia with vitamin E deficiency may result from a similar mechanism. Alpha-TTP is responsible for selective retention of alpha-tocopherol from dietary vitamin E. The alpha-TTP-mediated transfer of alpha-tocopherol into nascent VLDL constitutes the major determinant of plasma alpha-tocopherol levels in humans. AVED patients have an impaired ability to incorporate alpha-tocopherol into lipoproteins secreted by the liver. The resulting loss of vitamin E-dependent free radical scavenging and anti-oxidant capabilities may lead to mitochondrial dysfunction, similar to FA.

Finally, in X-linked sideroblastic anemia with ataxia, the mutated gene *ABC7* is a nuclear mitochondrial ATP-binding cassette (ABC) transporter that localizes to the mitochondrial inner membrane and is involved in iron homeostasis (60, 61). Thus, as in FA, mitochondrial iron homeostatic impairment may be linked to cerebellar dysfunction.

## Defective Intracellular Calcium Signaling

The SCA6 expanded CAG repeat is found in the *CACNA1A* gene that encodes the  $\alpha_{1A}$ -subunit of a voltage-gated calcium channel. Contrary to SCA1 or SCA3, polyQ-containing aggregates in SCA6 neurons are nonubiquitinated and exclusively cytoplasmic (103). Episodic or progressive cerebellar ataxia have also been described in patients with point mutations rather than repeat expansions in the *CACNA1A* gene (114). Thus, rather than being caused by a polyQ-dependent toxic insult to Purkinje cells, SCA6 may result from an alteration of normal calcium channel function (115). In a study of HD patient cell lines and transgenic mice, the mitochondrial calcium homeostasis was found to be impaired in such a way that depolarization occurred more rapidly when the mitochondria were challenged repeatedly (116). Also, specific interactions have been observed between mutant huntingtin and the type I inositol(1, 4, 5)-triphosphate receptor, an intracellular calcium release channel involved in neuronal calcium signaling. These data clearly link alterations in intracellular calcium signaling to polyQ diseases.

## Dysregulation of Phosphorylation

SCA12 and SCA14 imply interference with protein phosphorylation and its associated signaling alterations as another possible mechanism of cerebellar degeneration. The expanded SCA12 CAG repeat is located in the promoter region of the *PPP2R2B* gene that encodes a brain specific regulatory subunit (B) of the PP2A trimeric holoenzymes (7). These are protein serine/threonine phosphatases that regulate

phosphorylation in a large number of cellular processes (117). Evidence suggests that the CAG repeat alters *PPP2R2B* gene expression (117).

*PRKCG*, the mutated SCA14 gene, encodes PKC $\gamma$ , a member of a serine/threonine kinase family and a mediator of second messenger signaling pathways involved in multiple cellular processes, particularly calcium-sensitive second messenger signaling pathways (19, 118). PKC $\gamma$  may be linked to the ataxin-1 disease pathway, as SCA1 transgenic mice showed reduced PKC $\gamma$  protein levels in Purkinje cells, while the majority of Purkinje cells in the single autopsied SCA14 patient showed absence of ataxin-1 staining (19, 119).

## Axonal Transport Impairment

Some studies in HD and SBMA suggest that the onset of neurologic symptoms does not reflect loss of neurons but rather neuronal dysfunction due to dendritic and axonal pathology following obstruction of axonal transport by cytoplasmic polyQ-containing proteins (120–122).

## DNA Repair

AT, AOA1, AOA2, and SCAN1 are all caused by mutations in DNA repair proteins. *ATM* is a protein kinase that belongs to a highly conserved family of phosphatidylinositol 3-kinase (PI3K)-like protein kinases (PIKKs) with serine/threonine-kinase activity (82). *ATM* appears to be functionally located at the top of the response cascade that senses, responds to, and repairs DNA damage. Its role has been particularly well described in the very rapid response to double strand DNA breaks, initiating a large number of various protein phosphorylation pathways (82, 123). *ATM* may also play a role in processes such as telomere length maintenance, V(D)J recombination, cell cycle checkpoint regulation, and oncogenesis (123). Mutations in the AT-phenocopy *hMRE11* affect a protein that complexes with the hRad50 and the Nbs1 proteins, apparently impairing the same DNA damage response pathway as the *ATM* mutations (87).

*Aprataxin*, the gene associated with AOA1, turned out to be a member of the histidine triad (HIT) superfamily (91). A long-form splice variant of *aprataxin* has been found to interact with XRCC1 (x-ray repair cross-complementing group 1), constituting a multiprotein complex that is involved in single-strand DNA break repair (124).

*Senataxin*, associated with AOA2, shares extensive homology to fungal Sen1p proteins that are involved in splicing and termination of tRNA, small nuclear RNA, and small nucleolar RNA. *Senataxin* may have RNA and DNA helicase activity and act in the DNA repair pathway (94). Finally, the homozygous A1478G transition mutation in the Tyrosyl-DNA phosphodiesterase 1 (*TDPI*), a DNA repair enzyme, was identified as the cause of SCAN1 (65).

## Ubiquitin-Proteasome Pathways

PolyQ aggregates may affect protein clearance. Important components of the ubiquitin/proteasome system are sequestered into polyQ aggregates. This impairs the proteolytic capacity of the system needed to maintain normal protein homeostasis (125, 126). In an attempt to degrade polyQ proteins, accumulation of polyQ fragments within the proteasome

may inactivate the proteasome (127). Recently, ataxin-3 has been shown to be a poly-ubiquitin binding protein, which implicates a direct role of ataxin-3 in protein clearance (31).

### Protein Misfolding and Chaperone Dysfunction

PolyQ aggregates have been considered to be misfolded proteins, and inadequate chaperone function may contribute to this misfolding. Overexpression of the chaperone protein HDJ-2/HSDJ in HeLa cells decreases the frequency of ataxin-1 (SCA1) aggregation (128), and SCA1 transgenic mice that overexpress the molecular chaperone inducible Hsp70 were protected against neurodegeneration (129). The *sacsin* gene, mutated in ARSACS, contains heat-shock domains, which suggests a function for *sacsin* in chaperone-mediated protein folding (130).

### Growth Factor Alterations

Missense mutations in the *FGF14* gene suggest growth factors as candidate culprits involved in neurodegeneration. They have been implicated previously in HD, albeit secondary to transcriptional alterations (131, 132).

### CONCLUSION

In conclusion, the clinical overlap between the various ataxias, the unexpected genetic heterogeneity, and the occasional atypical presentation of some subtypes truly complicates the clinical management of patients with cerebellar ataxia. On the other hand, the recent advances of molecular research have now provided us a glimpse at the complex pathophysiology of these diseases. Extensive functional studies are needed to identify the most important mechanisms of disease. Novel genes will add data to unravel the molecular pathways of cerebellar degeneration. The ultimate challenge will be the development of disease-modifying drugs that are awaited most by the patients suffering from these devastating diseases.

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