Published in final edited form as:
J Neuroophthalmol. 2009 September ; 29(3): 227–237. doi:10.1097/WNO0b013e3181b416de.

The Spinocerebellar Ataxias

Henry L. Paulson, MD, PhD
Dept Neurology, University of Michigan Health Systems, Ann Arbor, MI, Email: henryp@umich.edu

Abstract

Slowly progressive ataxia accompanied by cerebellar degeneration is often genetic in origin. The past fifteen years have witnessed a revolution in our understanding of the causes of dominantly inherited ataxias, now known as the spinocerebellar ataxias (SCAs). Nearly 30 distinct genetic causes of SCA are known, numbered chronologically in order of discovery. All SCAs display classic cerebellar signs and many display disabling noncerebellar features, most commonly brainstem dysfunction. Eye movement abnormalities are common, reflecting cerebellar and brainstem degeneration. Visual loss from retinal degeneration is rare in SCA, occurring most commonly and profoundly in SCA7. Although the SCAs are relentlessly progressive and currently untreatable, recent scientific advances have begun to shed light on various disease mechanisms that may lead to preventive therapies.

The definition of ataxia is loss of coordination, particularly of gait. Thus, when a clinician diagnoses someone with ataxia, it typically is someone with gait imbalance associated with limb incoordination including problems with gross and fine motor control. Ataxia in adults can be an acquired or genetic disorder. The timing of disease and the family history are key elements in distinguishing acquired from probable genetic causes. A genetic form of ataxia is suggested by insidious onset, slow and inexorable progression, and generally symmetrical findings on exam. A positive family history of ataxia or gait imbalance in a patient's father or mother strongly suggests a dominantly-inherited disorder. (1) (2) (3)

In most individuals presenting with heritable degenerative ataxias, symptoms begin with gait imbalance followed by appendicular ataxia. Soon afterward, dysarthria usually begins and visual problems can occur. These may include difficulty with focusing (especially in a moving environment), diplopia, and problems with rapid eye movements (saccades). Eye movement abnormalities that are noncerebellar can include gaze palsies, slowed saccades, ocular "stare", blepharospasm, and ptosis. Classic cerebellar findings include dysmetria and intention tremor on finger to nose testing, rebound phenomena, widened stance and difficulty with gait, particularly when turning. For some patients early in disease, gait imbalance may only be elicited by testing tandem walk (or, as patients often call it, the "drunk driving test").

Spinocerebellar Ataxias (SCAs)

The dominantly inherited ataxias, now called spinocerebellar ataxias (SCAs), are progressive disorders in which the cerebellum slowly degenerates, often accompanied by degenerative changes in the brainstem and other parts of the central nervous system (and less commonly the peripheral nervous system) (4). The number of known SCAs continues to grow. It now includes at least 27, numbered in the order of discovery of the defective gene (Table 1). Very likely additional quite rare SCAs have not yet surfaced.

Not very long ago dominant ataxias were classified according to the pattern of brain degeneration: olivopontocerebellar atrophy, spinopontine atrophy, or pure cortical cerebellar atrophy. This classification proved confusing partly because the affected brain regions could vary among affected persons, sometimes even in the same family. These diseases are vexing

because they tend to display a wide range of clinical heterogeneity. During the past two decades of gene discovery, the molecular genetic reasons underlying this confusing and daunting clinical variability have become much clearer.

Disease-causing mutations have been discovered in at least 16 of the 28 named SCAs (those marked by asterisks in Table 1). What have these genetic discoveries told us? Perhaps most importantly that cerebellar dysfunction and degeneration can occur when any one of a diverse range of biological pathways is perturbed by genetic defects. The cerebellum and its connections, it seems, are a very sensitive "readout" for genetic lesions.

Genetic Features

There are three major genetic categories of SCAs (5): 1) expanded CAG/polyQ ataxias; 2) non-protein coding repeat expansion ataxias; and 3) ataxias caused by conventional mutations (missense, deletion, insertion, duplication). Perhaps the most important unifying feature among SCAs is the pattern of neurodegeneration. Neurologists understandably associate these disorders with the clinical features reflecting cerebellar damage. Indeed, many SCAs have extensive cerebellar atrophy involving all regions of the cerebellum--the molecular, Purkinje cell, and granule cell layers, as well as deep cerebellar nuclei. Many SCAs, however, are distinguished almost as much by their extracerebellar brain involvement. For example, all but one of the six polyQ SCAs display substantial brainstem involvement. The exception, SCA6, is typically a "pure" cerebellar ataxia in which Purkinje cells degenerate but very little else does. Basal ganglionic involvement is also common in some SCAs, and cerebral cortical involvement contributes substantially to clinical features in a few SCAs, most notably SCA17. Spinal cord and peripheral nerve involvement are also common. In contrast, some features are relatively unique to specific SCAs, such as retinal degeneration in SCA7 and epilepsy in SCA10.

A second feature of SCAs is the remarkably wide range in phenotype. This heterogeneity stems primarily from the fact that DNA repeat expansions, which cause the most common SCAs, can vary greatly in size. The tendency for expansions to change size is why these mutations are described as "dynamic." Larger expansions typically cause more severe, earlier-onset disease. Smaller expansions cause later-onset disease with a more circumscribed pattern of degeneration. SCA3, also known as Machado-Joseph disease, illustrates well this repeat length-dependent, variable phenotype. The largest SCA3 expansions cause disease onset in childhood or teenage years, manifesting with widespread dystonia, spasticity, and ataxia. In contrast, smaller SCA3 expansions lead to late-onset ataxia, commonly with a degree of peripheral neuropathy and motor neuron loss. The smallest SCA3 expansions, those very close to the lower limit of disease repeats, may result in restless leg syndrome and very little else.

The dynamic nature of expanded SCA repeats is illustrated by the fact that they often expand further when transmitted from one generation to the next. The intriguing clinical phenomenon of "anticipation" is explained by this molecular phenomenon. Anticipation is the tendency for disease to worsen from generation to generation within a family. Two facts conspire to explain anticipation: 1) expansions frequently enlarge upon transmission, and 2) larger expansions typically cause earlier onset disease. Anticipation does not occur in every SCA, only in those due to expanded repeats (which also happen to be the most common ones). Among the SCAs due to repeat expansions, anticipation occurs more robustly in some disorders than in others. Anticipation is particularly severe in SCA7, where it can result in extremely large expansions causing disease in newborns.

The dynamic nature of repeat expansions also explains the continuing appearance of new disease-causing expansions in the population. New cases arise from intermediate-sized repeats that, while not large enough to cause disease, are large enough to be prone to further expansion

in the next generation. Thus, in an individual with slowly progressive adult-onset ataxia without a family history of similar disease, the clinician should consider the possibility of a new-onset expansion in one of the known SCAs. An affected person with no family history of similar disease most commonly is found to have SCA6 or SCA2, in which "new" mutations are not uncommon.

Genetic Testing

Genetic testing for SCA has exploded in the past decade (2) (6) (4). More than a dozen SCA genes can now be tested through commercial labs, and the number seems to grow every year.

There are five distinct scenarios in which gene testing can be used by clinicians: diagnostic testing, predictive testing, prenatal testing, carrier testing, and risk factor assessment. In reality, however, only diagnostic and predictive testing concern the practicing neuro-ophthalmologist or neurologist. Gene tests are a powerful new addition to our diagnostic arsenal; we use them primarily to achieve an accurate diagnosis in a patient with specific neurologic symptoms.

A gene test does not differ much from testing blood chemistry profiles to establish a medical diagnosis. A positive test result, however, carries profound implications for patients and their families. Thus, genetic testing should be performed only after the patient has been counseled on the potential consequences of the results, both positive and negative. Once a genetic diagnosis is made in a symptomatic patient, we may be asked to assist other family members in obtaining predictive testing (screening for a mutation in someone who is at risk for a familial disease). Handling such queries from patients and their families is an unavoidable part of modern medicine. Web sites that provide useful updated information on genetic diseases, genetic tests, genetic counseling and the human genome include www.genetests.org, www.nsgc.org, www.genome.gov, and www.ncbi.nlm.nih.gov. Www.genetestsorg, the most useful site, contains frequently updated reviews of neurogenetic disorders and searchable lists of testing labs with contact information.

The primary benefit of diagnostic genetic testing is that it may provide a specific and accurate diagnosis. For example, an SCA gene test in a patient whose symptoms are consistent with a genetic form of ataxia, but whose family history is uncertain or absent, can confirm the clinical diagnosis with efficiency, economy, and certainty. In an ataxic patient, gene tests are sensitive and specific, whereas brain MRI is not. In SCAs, gene testing can specify a diagnosis from among a group of clinically similar genetic conditions. Even when a condition is currently incurable, as with the SCAs, establishing a specific diagnosis can put an end to the quest for an accurate diagnosis, permit an informed discussion of the prognosis and available treatments, and facilitate discussions of genetic risk to other family members. The psychological lift of simply putting a name to a previously mysterious disease, even if there is no cure, should not be underestimated for some patients.

Current commercially available genetic test "panels" include only the most common (SCA1, 2, 3, 6, and 7) and some less common (SCA 5, 8, 11, 10, 12, 13, 14 and 17), comprising 75% of the known SCA genes. Whereas a positive gene test for a specific SCA establishes the diagnosis, an entirely "negative" SCA gene test panel does not exclude a hereditary ataxia. Accordingly, physicians must take great care in conveying the significance of negative gene test results to their patients. When a person's ataxia has slowly progressed over 10 years and is symmetrical in its clinical and radiographic features, the disease very likely has a genetic basis whether or not the genetic panel detects it. In the absence of a family history of ataxia, an autosomal recessive cause is probably more likely than an autosomal dominant cause. The most common recessive ataxia is Friedreich ataxia, for which genetic testing is highly sensitive and specific (7).

Clinical Features

Many hereditary ataxias, including most of the more common SCAs, manifest significant central nervous system involvement beyond the cerebellum to the brainstem and spinal cord, hence the designation “spinocerebellar” ataxia (3,8). For example, there can be brainstem motor neuron loss manifesting as tongue atrophy, facial weakness, temporalis muscle atrophy and fasciculations. Upper motor neuron involvement can lead to spasticity and hyperreflexia. Peripheral nerve involvement is common in some SCAs, causing both sensory and motor problems. In some SCAs, particularly earlier-onset forms, basal ganglionic involvement can cause generalized dystonia or bradykinesia.

Some SCAs, however, tend to present as “pure” cerebellar disorders, SCA6 being the most common. Individuals with SCA6 display classic cerebellar findings, including nystagmus and saccadic pursuit. They tend not to develop the noncerebellar features so common in other SCAs. While pure cerebellar disease does lead to a wheelchair-bound state with loss of motor control, many of the complications referable to cerebral, brainstem, and spinal cord involvement do not occur. Thus, pure cerebellar ataxia is often compatible with a normal life span.

The clinical features are best established for those SCAs in which a specific genetic defect has been identified, now numbering 16. (SCAs 1, 2, 3, 6 and 7 comprise ~60% of identified SCAs in the United States.)

SCA1

SCA1 is the first dominantly-inherited ataxia for which the locus and gene defect were identified (9). Like most other SCAs, SCA1 begins as a gait disorder, evolving to severe four-limb ataxia with dysarthria and leaving most patients wheelchair-bound within 15-20 years. SCA1 is caused by polyQ-encoding CAG repeat expansions. As a result of this expansion, the SCA1 disease protein, ataxin-1, has an abnormally long stretch of the amino acid glutamine. Like other polyQ diseases, SCA1 shows remarkable phenotypic variability and anticipation that primarily reflects differences in repeat size among affected persons. Most individuals with SCA1 manifest signs of widespread cerebellar and brainstem dysfunction with relatively little supratentorial involvement. Neuropathologic findings include neuronal loss in the cerebellum and brainstem, and degeneration of spinocerebellar tracts. SCA1 is better understood at the molecular level than any other SCA. Although SCA1 may not be the most common SCA, studies of this disease continue to lead the way in our understanding of the entire class of polyQ neurodegenerative diseases(9) (10).

SCA2

Initially described in a large Cuban family, SCA2 has a highly variable phenotype that is most often characterized by ataxia, dysarthria, slow saccades, and peripheral neuropathy(4). Extremely slow saccades are very common but not pathognomonic, as such eye movements also can be seen, albeit less commonly, in several other SCAs, including SCA1 and SCA3. Peripheral neuropathy, areflexia, facial myokymia, and dementia are also common. The expanded CAG repeat in SCA2 encodes polyQ in the disease gene product, ataxin-2. Normal alleles are between 15 to 32 repeats in length, and expanded alleles are 35 to 77 repeats in length. There exists a “zone of reduced penetrance” (32-34 repeats) in which not all individuals develop signs of disease in their lifetime. Anticipation can be marked in SCA2. Together with SCA6, SCA2 is the form most likely to occur sporadically (without a family history in prior generations), reflecting further expansion of a modestly enlarged repeat upon transmission from one generation to the next. A modest expansion may not cause disease until very late in life, when the neurological problems may be dismissed as “old age,” while a larger expansion

in the next generation causes earlier-onset disease that is undeniably not the byproduct of old age.

SCA3/Machado-Joseph Disease (MJD)

One of the most common dominantly inherited ataxias (11), SCA3/MJD most often begins as a progressive ataxia accompanied by lid retraction and infrequent blinking (creating “staring eyes”), ophthalmoparesis, and impaired speech and swallowing. Although staring eyes are more common in SCA3 than in other SCAs, they are not pathognomonic for SCA3. Neuropathological findings include widespread degeneration of cerebellar afferent and efferent pathways, pontine and dentate nuclei, and the cell bodies of the substantia nigra, subthalamic nucleus, globus pallidus, cranial motor nerve nuclei and anterior horns. The mutation in SCA3 is an expanded CAG repeat that encodes polyQ in the disease gene product ataxin-3. This repeat is 12 to 42 in health and approximately 52 to 84 repeats in disease. The phenotype in SCA3/MJD varies widely depending on repeat length: early onset rigidity and dystonia for the largest expansions, adult onset ataxia for the medium sized expansions), and late-onset ataxia accompanied by neuropathy for thesmallest expansions. Some patients develop parkinsonism that responds to dopamine treatment. Only a few individuals have been described with “intermediate alleles” (approximately 50-55 repeats), which can cause isolated restless legs syndrome. The most variable feature of SCA3 is the degree of peripheral nervous system involvement; some patients may develop marked distal amyotrophy with areflexia and sensory disturbances.

SCA5

This rare and relatively pure form of slowly progressive dominant cerebellar ataxia is sometimes reported as the “Lincoln family ataxia” because an ataxic family was reported with two major branches descended from the paternal grandparents of Abraham Lincoln. The defective gene was recently discovered to be the SPTBN2 gene encoding ß-III spectrin(12).

SCA6

In contrast to the other relatively common SCAs (1, 2, 3 and 7), SCA6 represents a “milder” disease, most often manifesting as a “pure” cerebellar ataxia accompanied by dysarthria and gaze-evoked nystagmus. Onset is typically at about age 50 but ranges widely. Compared to other SCAs, noncerebellar symptoms occur much less frequently in SCA6; they may include decreased vibration and position sense, impaired upward gaze, and, late in the disease, spasticity and hyperreflexia. Eye movements are among the key findings in SCA6, ranging from difficulty fixating on moving objects to diplopia without marked ductional deficits. The disease progresses more slowly than in other SCAs and is usually compatible with a normal life span. In some populations SCA6 is fairly common, accounting for about 30% and 20% of the ataxic families in Japan and Germany, respectively. SCA6 is caused by a uniquely small CAG/polyQ repeat expansion in the CACNA1 gene encoding a voltage-dependent calcium channel alpha subunit (13). Intriguingly, this is the same gene in which other non-repeat mutations cause episodic ataxia type 2 and familial hemiplegic migraine. This finding illustrates the important point that clinically distinguishable disorders can arise from different mutations in the same gene.

SCA7

SCA7 is distinguished from other SCAs by the nearly universal presence of retinal degeneration (14). It is the only SCA in which patients tend to go blind. A careful ophthalmoscopic examination, therefore, is necessary in any patient presenting with progressive ataxia. In other respects, SCA7 resembles the other SCAs characterized by ataxia and brainstem findings. The pathogenic expansion in SCA7 is highly variable, ranging from 34 to greater than 200 repeats,

whereas normal alleles range from 7 to 17 repeats. Although repeat instability upon transmission is common in many polyQ diseases, it is particularly so in SCA7. Instability is especially striking with paternal transmission, leading in some cases to massive expansions that cause disease in infancy or in utero.

SCA8

SCA8 clinically resembles most other SCAs in manifesting adult-onset ataxia with variable brainstem signs. In a study of a large family (15), the main clinical symptoms were prominent gait and limb ataxia accompanied by abnormalities of swallowing, speech, and eye movements. Koob et al (16) identified the genetic defect in SCA8 as an unstable CAG/CTG repeat expansion in the SCA8 gene(16). Most, but not all, SCA8 expansions are associated with progressive ataxia. Thus, one needs to use caution when interpreting a positive SCA8 gene test result.

SCA10

Described primarily in families of Mexican descent, SCA10 is characterized by prominent cerebellar symptoms and seizures. Matsuura et al (17) discovered that the genetic defect is a novel type of expanded repeat, an extremely large expansion arising from a pentanucleotide (ATTCT) repeat in an intron of the SCA10 gene. Normally 10-22 ATTCT repeats in length, the SCA10 repeat becomes grossly expanded in affected individuals, in some cases to several thousand. The molecular mechanism is uncertain.

SCA11

This SCA represents a relatively “pure” cerebellar syndrome with mild pyramidal signs. It was originally described in two British families with a relatively benign, slowly progressive form of gait and limb ataxia that mapped to chromosome 15. The genetic basis was recently discovered to be mutations in the tau tubulin kinase gene, TTBK2 (18).

SCA12

SCA12 is caused by a CAG expansion in the 5’ untranslated region of the protein phosphatase gene PP2RB (19). SCA12 is more common in India than in the United States. Age at onset ranges between 8 to 60 years, with the first symptom typically being an action tremor of the arms. The tremor is eventually accompanied by head tremor, ataxia, and sometimes bradykinesia and sensory neuropathy.

SCA13

This ataxia has a widely varying age of onset, sometimes even commencing in childhood with delayed motor development and mental retardation. Common features are ataxia, dysarthria, nystagmus, and occasionally hyperreflexia. MRI usually shows cerebellar and pontine atrophy. Recently SCA13 was shown to be caused by mutations in the KCNC3 gene, which encodes a voltage-gated potassium channel subunit (20).

SCA14

This ataxia shows considerable phenotypic variability even though it is not an expanded repeat ataxia. Most affected individuals develop slowly progressive ataxia with dysarthria in early adulthood. In late-onset cases, SCA14 can manifest as a relatively pure cerebellar ataxia. In earlier-onset cases, however, the ataxia can be accompanied by facial myokymia, hyperreflexia, axial myoclonus, dystonia, and vibratory loss. It is usually compatible with a normal life span, although affected individuals can become wheelchair-bound later in life, and cognitive complaints are relatively common. SCA14 is caused by mutations in the PRKCG gene encoding a serine-threonine protein kinase (21-23). Because SCA14 is not caused by an

expanded repeat mutation but by various mutations scattered throughout the gene, genetic testing for SCA14 requires sequencing of all exons and flanking sequences in the disease gene.

SCA15/16

These two disease recently were discovered to be allelic (the mutation is in the same gene). It is a slowly progressive, pure cerebellar ataxia originally described in Australian and Japanese families. Dysarthria, horizontal gaze-evoked nystagmus, and impaired smooth movement of the eyes are present in some patients. Approximately one third of patients have a head tremor. The disease is caused by small genomic deletions encompassing the IPTR gene (24,25).

SCA17

Originally described in Japan (26), SCA17 is rare in the United States. More than any other SCA, SCA17 manifests with widespread cerebral as well as cerebellar dysfunction. Affected persons typically present in young-adulthood or mid-adulthood with progressive gait and limb ataxia that is usually accompanied by dementia, psychiatric symptoms, and varying extrapyramidal features, including parkinsonism, tremor, dystonia, and sometimes chorea. Ataxia may not be the predominant feature. In some cases, SCA17 even resembles Huntington disease. Seizures have been reported in some patients. Consistent with this more widespread neurological phenotype, the MRI findings in SCA17 include diffuse cerebral and cerebellar atrophy.

SCA20

Reported in a single Australian family, SCA20 has a slowly progressive phenotype in which the initial symptom is dysarthria rather than gait ataxia, accompanied by palatal tremor, hypermetric saccades, and dentate calcification in the cerebellum. Recently a 260 kb duplication on chromosome 11 was discovered as the genetic defect (27), although the critical genetic element in this segment is unknown. SCA20 represents the first genomic duplication as a cause of ataxia. Currently, only research based genetic testing is available for this condition.

SCA27

This early-onset ataxia has been described in a three-generation Dutch family. Affected individuals manifest first with hand tremor in childhood followed by progressive ataxia, cognitive difficulties, and psychiatric problems in the second and third decades of life. SCA27 is caused by mutations in the FGF14 gene encoding fibroblast growth factor 14(28).

Other Dominantly Inherited Ataxias

The following three causes of dominantly inherited ataxia are not within the SCA grouping, but should be considered in the ataxic individual with an appropriate family history: dentatorubropallidoluysian atrophy (DRPLA) and episodic ataxias type 1 and 2 (EA1, EA2).

DRPLA

DRPLA commonly manifests with ataxia and, like many SCAs, is caused by a polyQ expansion. A highly variable disorder, DRPLA is characterized by progressive ataxia, choreoathetosis, dementia, seizures, myoclonus, and dystonia. As in other polyQ diseases, larger expansions in DRPLA cause more severe disease manifesting earlier in life, and anticipation occurs frequently. Patients with onset before age 20 nearly always have seizures and display more of a progressive myoclonic epilepsy phenotype. In contrast, older onset individuals typically develop ataxia with choreoathetosis and dementia. DRPLA is most prevalent in Japan and quite rare in the United States. One well-characterized African American

family in North Carolina has a phenotypic variant known as the Haw River Syndrome, in which seizures and cerebral calcifications accompany the ataxia.

EA1 and EA2

Two well-established forms of episodic ataxia, EA1 and EA2, are caused by mutations in a voltage-gated potassium channel and calcium channel, respectively. In EA1, which is due to mutations in the KCNA1 gene, affected individuals typically have brief episodes of ataxia lasting only minutes, in some cases precipitated by stress, exercise or sudden change in posture. Myokymia is common in EA1. In EA2, which is due to mutations in the CACNA1A gene (the same gene as in SCA6), patients usually have longer episodes of ataxia that can last for hours or days, often precipitated by stress, exercise, or fatigue. Acetazolamide may help for either ataxia, but is more often beneficial for EA2. In all cases of episodic ataxia, a trial of acetazolamide is warranted. Several other EAs have recently been described, but they are less common than EA1 and EA2. In some of these patients, vestibular symptoms, including vertigo, are prominent during episodes.

Pathogenetic Mechanisms and Approaches to Therapy in SCAs

PolyQ SCAs

Following the discovery that many neurodegenerative disease are caused by expansion of polyQ-encoding CAG repeats, the prevailing view has been that the toxic action of the mutations occurs primarily at the protein level (5,9,29). Most evidence from in vitro, cellular, and animal models of disease supports this view. The discovery over a decade ago that polyQ disease brain contains intracellular inclusions of the disease protein suggested that the expansion promotes misfolding of the disease protein, resulting in aggregation. In vitro studies with recombinant polyQ disease proteins have supported this model: expanded polyQ proteins are intrinsically prone to aggregate, forming amyloid-like aggregates in vitro. Importantly, the repeat length threshold for aggregation in vitro closely mirrors the repeat length known to cause disease. Further supporting a “toxic protein” model is the fact that expanded CAG repeats engineered to be expressed at the mRNA level, but not at the protein level, tend to display little or no toxicity when introduced into cells or animals. Thus, polyQ protein aggregation, or at least a biochemical process associated with aggregation, seems integral to the disease process.

Less clear is the precise relationship between protein misfolding, the biochemical process of aggregation, and the formation of macroscopic inclusions observed in disease brain tissue. While inclusions may represent a biomarker of protein misfolding and accumulation, they are not always found in affected brain cells, and in some studies correlate with neuronal survival rather than neuronal cell death. Thus, inclusions may reflect a protective response to the presence of accumulated abnormal protein, a pathway by which neurons “wall off” abnormal polyQ protein.

The focus of research has shifted to earlier steps in the aggregation pathway. Small oligomers of mutant protein may prove to be the toxic species, engaging in deleterious interactions with additional polyQ proteins and other cellular proteins. In contrast, larger fibrillar complexes formed further downstream in the aggregation pathway may contain mutant protein “packaged” into relatively neutral structures.

Perturbations in protein quality control—Precisely why polyQ disease proteins are toxic to neurons remains unclear. One possibility is that the production of misfolded polyQ protein places a continual burden on quality control pathways in cells. Neurons possess hundreds of proteins that facilitate the correct folding of proteins and the efficient refolding, disaggregation, and degradation of abnormally folded or aggregated proteins. If this elaborate

machinery for maintaining protein homeostasis is impaired by mutant polyQ protein, then other proteins that otherwise would fold correctly might also accumulate as misfolded proteins. Using the worm as a model system, Morimoto et al showed that this is indeed the case (30). When mutant polyQ proteins were expressed in the worm, other temperature-sensitive cellular proteins were driven to misfold. Thus, expression of mutant polyQ protein can induce global misfolding in cells.

The cellular routes to handle abnormal polyQ proteins include three major pathways: molecular chaperones, the ubiquitin-proteasome degradation, and autophagy. All three pathways have been implicated in the polyQ disorders, and there is growing consensus that they are functionally linked. For example, a quality control protein recently shown to modulate polyQ toxicity is carboxy-terminus of Hsc70 interacting protein (CHIP) (31). CHIP functions both as a co-chaperone and as a ubiquitin ligase, thereby linking the chaperone and proteasome pathways(32). Numerous molecular chaperones, including Hsp70, Hsp40, and the cytosolic chaperonin TRiC(33,34) (35), have been shown to suppress polyQ aggregation and or toxicity in various model systems.

Aberrant protein interactions—Perturbations in protein quality control are compatible with the hypothesis that the mutant polyQ protein interacts aberrantly with various cellular proteins, including its normal partners and novel interactors. Because the polyQ diseases presumably share elements of pathogenesis, some overlap in interacting proteins is expected, but the complete set of interacting proteins for each disease protein will be unique. This fact would help explain the disease-specific deleterious consequences of mutant polyQ proteins. Lim et al (36) reported a systematic analysis of SCA protein-protein interactions consistent with this model. Recent findings further supporting this model include aberrant interactions between polyQ proteins and transcription factors and nonhistone chromatin proteins in the nucleus (37) (38) (39) (40). Alterations in protein quality control pathways could promote such aberrant interactions and thus further impair the exquisite regulation of neuronal gene expression.

Nucleus as site of toxicity—As most polyQ proteins normally reside in the nucleus or become concentrated in the nucleus during disease, the hypothesis that they trigger disease by perturbing gene expression is attractive (39). Expanded polyQ proteins or polyQ-containing proteolytic fragments engage in aberrant protein-protein interactions in the nucleus, including associations with important transcriptional components and chromatin proteins. Interactions with polyQ oligomeric complexes may functionally deplete certain transcription factors and other important nuclear proteins in affected neurons, resulting in altered activity at specific promoters and perturbed chromatin modification by histone acetyltransferases. In addition, several polyQ disease proteins are directly involved in transcription. The SCA7 protein ataxin-7 is now known to be part of the STAGA transcriptional complex (38), and the SCA17 protein is the basal transcription factor, TATA-binding protein. Other SCA proteins, such as ataxin-1, interact with and regulate specific transcriptional complexes (41) (42), and at least one SCA protein, ataxin-2, acts more distally in regulating gene expression (43,44).

Transcriptional dysregulation caused by mutant polyQ proteins partly reflects changes in histone acetylation. Certain transcription factors known to interact with polyQ proteins, such as CREB Binding Protein (CBP), possess histone acetyltransferase (HAT) activity. PolyQ proteins can inhibit HAT activity and thereby repress transcription. The administration of histone deacetylase (HDAC) inhibitors, therefore, represents a potential route to therapy (45). Based on recent studies in transgenic flies, HDAC inhibitors have rescued polyQ toxicity in cells and flies. The HDAC inhibitor, phenylbutyrate, has already been tested in subjects with Huntington Disease (HD), another polyQ disease, with phase II trial results still pending. If

this compound or another HDAC inhibitor proves effective in HD, it should be tested promptly in one or more polyQ SCAs.

Influence of protein context: unique proteins in each disease—The marked clinical differences among the polyQ SCAs despite their shared mutational mechanism illustrates the importance of disease protein context in pathogenesis. For example, the toxicity of the SCA1 disease protein ataxin-1 depends on protein elements far removed from the actual polyQ expansion. A nuclear localization signal and phosphorylation of a specific serine residue are both required for mutant ataxin-1 to mediate toxicity (10). Recent evidence also links ataxin-1 toxicity to changes in its ability to associate with at least two proteins, the transcriptional repressor Capicua and the RB17. Ataxin-1 also forms a complex with RORalpha, a transcription factor important for cerebellar development. Expression of mutant ataxin-1 depletes this critical transcription factor, which likely contributes to pathogenesis. These data strongly support a model of toxicity in which specific protein interactions engaged in by ataxin-1, interactions which require the surrounding protein context of ataxin-1, are essential to pathogenesis.

Its small size notwithstanding, the SCA3/MJD protein ataxin-3 functions in diverse cellular pathways. Ataxin-3 is a ubiquitin-binding protein and de-ubiquitinating enzyme that participates in the “handling” of abnormal proteins in the cell (46,47) (48). An important relationship of normal ataxin-3 function to disease was suggested by studies in Drosophila showing that normal ataxin-3 suppresses toxicity induced by various mutant polyQ proteins (49). This suppressor activity, which is closely associated with ataxin-3’s ubiquitin-linked functions, appears to be partly retained by expanded ataxin-3. Remarkably, mutant ataxin-3 may possess intrinsic functional properties that suppress its own polyQ-based toxicity. This unusual feature may explain why full length mutant ataxin-3 does not cause human disease until the repeat is at least 55 residues in length, much larger than the repeats in other polyQ diseases.

Potential routes to therapy for polyQ SCAs—Very few preventive clinical trials have been performed in the SCAs. A recent study showing benefit of lithium in mouse models of SCA1 (50) is a hopeful sign. Nearly all human clinical trials in polyQ diseases have focused on HD, thanks in part to the well-developed clinical trial structure in the HD clinical community. Clues to preventive therapy in the polyQ SCAs may come from these HD studies. Any trial drug that benefits HD patients immediately becomes a candidate for testing in any of the polyQ SCAs, especially if the compound’s mechanism of action counteracts a shared feature of expanded polyQ proteins rather than a unique property of the HD protein huntingtin.

Among candidate therapies tested thus far, the electron transport molecule coenzyme Q10 slowed disease progression in HD mouse models and led to a positive trend, albeit statistically insignificant, in a carefully controlled trial in HD subjects (51). One can only hope that higher doses of coenzyme Q10, soon to be tested in HD, will show benefit. In a short term HD human trial (52), oral administration of creatine, another compound to counteract cellular energy depletion, proved beneficial in HD mouse models and reduced 8-hydroxydeoxyguanosine, a marker of DNA damage. HDAC inhibitors also hold promise (45) based on successful treatment trials in mouse and fly models of disease. Given the central role of protein aggregation in disease, the search for anti-aggregation compounds (53) may yield a compound that acts on all members of the polyQ disease class. RNA interference or antisense approaches to decrease expression of the mutant gene product have been successful in mouse models of SCAs (54), but the preclinical studies required to bring this approach to the clinic will take much more work (55).

Noncoding Repeat SCAs

This class comprises those SCAs that are caused by DNA repeat expansions falling outside the protein coding region of the respective disease genes. In other words, the pathogenic expansion does not encode glutamine or any other amino acid in the disease protein. Ataxias included in this category are SCAs 8, 10, and 12, although there is some uncertainty about the pathogenic mechanism in SCA8.

Although it is not yet certain how these noncoding repeats cause neurodegeneration, the prevailing theory is that they act through a dominant toxic mechanism occurring at the RNA level (56). This proposed mechanism is reminiscent of what occurs in myotonic dystrophy, a common neuromuscular disorder in which expanded RNA repeats sequester RNA-binding proteins in muscle cells and thereby perturb RNA splicing (57). Fragile X-associated tremor ataxia syndrome (FXTAS), a progressive neurodegenerative ataxia that occurs in older men who carry a “premutation” expansion in the FMR1 gene (58), also belongs to this class of diseases although it is not an SCA.

SCA8 is associated with a large CAG/CTG repeat expansion that is not fully penetrant in carriers. This unstable CAG/CTG repeat occurs at the 3′ end of a fully processed RNA transcript that does not encode a known protein (16). Because the SCA8 repeat may be expressed in both directions, it is best to think of the repeat as a CAG/CTG repeat (CAG in one direction, CTG in the other direction). Recent studies in mouse (59) (60) and Drosophila (61) models provide insight into the cellular role of the SCA8 locus and the role of the repeat expansion in disease. The mechanism of pathogenesis in SCA8 is debated, with recent studies suggesting bidirectional expression leading to both an RNA-mediated toxicity and a polyQ-mediated toxicity.

SCA10 is a distinctive ataxia syndrome because, unlike other SCAs, it is so often accompanied by seizures. It is caused by a huge ATTCT expansion in an intron of the ATXN10 gene. This gene encodes the novel protein ataxin-10, whose function is unknown (17). Thus far the SCA10 mutation has been restricted to individuals of Amerindian ancestry. In a mouse model of SCA10, the mutant ATXN10 allele was transcribed at normal levels; in patient-derived cells, the pre-mRNA was processed correctly. While SCA10 null mice exhibit embryonic lethality, heterozygous mutants are normal (62), suggesting that a partial loss of ATXN10 function is not the major pathogenic mechanism in SCA10.

Conventional mutation SCAs

This category contains SCAs that are not due to repeat expansions, but instead to conventional mutations in specific genes or genomic segments (deletions, insertions, missense, nonsense and splice site mutations). Just a few years ago, no SCAs were known to belong to this category. Now, however, at least seven are known: SCAs 5, 11, 13, 14, 15/16, 20, and 27. The genes mutated in these SCA’s disorders are not obviously linked to a single biological pathway. This feature suggests that cerebellar and brainstem degeneration can be the biological consequence of perturbations in one of many distinct cellular pathways. This category of SCAs will continue to grow in the coming years as the technology to pinpoint genetic defects in rare disorders gets better.

With the identification in SCA5 of mutations in the SPTBN2 gene, β-III spectrin became recognized as an ataxia disease gene (12). Mutations in this cytoskeletal protein have directed attention towards the possible pathogenic role of organelle stability/trafficking and altered membrane protein dynamics in neurons. The fact that partial loss of β-III spectrin causes cerebellar degeneration suggests that mechanical properties of cerebellar neurons may be as

important as altered Ca (2+) homeostasis, transcriptional dysregulation, and impaired protein degradation in causing neurodegeneration.

SCA11 was recently shown to be due to mutations in the gene that encodes tau tubulin kinase 2 (TTBK2) (18). Aberrantly phosphorylated tau is a neuropathological hallmark of Alzheimer Disease and frontotemporal dementia but has not been implicated in cerebellar degeneration. Interestingly, the cerebellum in SCA11 reveals not only cerebellar degeneration, but also tau deposits. The dominant basis of disease may reflect aberrant action of TTBK2 on tau.

SCA13 is caused by mutations in the KCNC3 gene, which encodes a voltage-gated K+ channel (Kv3.3) highly enriched in the cerebellum (20). Mutations in this gene have a dominant effect on electrophysiological properties of this multisubunit channel. At least two missense mutations have been well studied in Xenopus oocyte expression systems. Kv3.3 with a mutation in the voltage-sensing domain, $KCNC3^{R420H}$, possessed no channel activity when expressed alone and had a dominant-negative effect when co-expressed with the wild-type channel subunit. $KCNC3^{F448L}$ negatively shifted the activation curve and slowed channel closing. Based on these results, these mutations would be expected to change the output characteristics of fast-spiking cerebellar neurons, in which KCNC channels confer the capacity for high-frequency firing.

SCA14 is caused by various missense, deletion, and splice site mutations in the PRKCG gene encoding protein kinase Cγ (21,22).(23) This member of the family of serine/ threonine kinases is highly expressed in Purkinje cells. Nearly 20 mutations have been reported, many of them located in exon 4, which encodes an important subdomain of PKCγ. The clinical features caused by PRKCG mutations can be quite heterogeneous. The mechanism by which mutations in PKCγ cause this condition is still unknown.

The discovery that SCA15 and SCA16 are both due to deletions in the inositol 1, 4, 5-triphosphate receptor 1 (ITPR) gene represented the first example of a dominant ataxia caused by a gene deletion. In this case, heterozygous deletion causes disease, hence the dominant pattern of inheritance. The molecular basis of disease likely reflects deleterious partial loss of ITPR gene function (haploinsufficiency for this gene), inasmuch as mice lacking a functional copy of this gene develop a similar movement disorder. ITPR is expressed at high levels in Purkinje cells. After the discovery of ITPR deletions in SCA15, a family with SCA16 was also shown to have a heterozygous deletion in the same gene (24). Hence, SCA15 and SCA16 are the same disease.

SCA20, a very rare ataxia, is due to a genomic duplication that spans at least 10 genes. The critical gene or genes in this region is not known.

SCA27 is caused by mutations in the fibroblast growth factor 14 (FGF14) gene (28). The discovery of the SCA27 mutation was precipitated by the finding that Fgf14 knockout mice have ataxia, impaired synaptic transmission, and impaired short-term and long-term potentiation (63) (64). These findings suggest a novel role for FGF14 in regulating synaptic plasticity by controlling the engagement of synaptic vesicles at presynaptic active zones. But why is disease dominantly inherited? Recent studies show that mutant FGF14 can interfere with the interaction between wild-type FGF14 and Na(v) channel alpha subunits, thereby altering neuronal excitability.

The rapid rate at which SCAs caused by conventional mutations were identified in the past five years suggests that still more genetic causes of SCA will be uncovered in the next decade. The diverse range of genes already implicated in degenerative ataxias implies that multiple pathways can be perturbed to induce cerebellar dysfunction and atrophy. A task for scientists

and clinicians will be to identify which pathways are central to cerebellar integrity so that preventive and symptomatic therapies might be developed for individuals with SCA.

Acknowledgments

This work was supported by National Institutes of Neurological Disorders and Stroke Grant NS038712 and the Fauver Family Ataxia Research Fund at the University of Michigan

References

1. Bird TD. Approaches to the patient with neurogenetic disease. Neurologic clinics 2002 Aug;20(3): 619–26. v. [PubMed: 12432823]
2. Nance MA. Genetic testing in inherited ataxias. Seminars in pediatric neurology 2003 Sep;10(3):223–31. [PubMed: 14653410]
3. Klockgether T. The clinical diagnosis of autosomal dominant spinocerebellar ataxias. Cerebellum (London, England) 2008;7(2):101–5.
4. Taroni F, DiDonato S. Pathways to motor incoordination: the inherited ataxias. Nat Rev Neurosci 2004 Aug;5(8):641–55. [PubMed: 15263894]
5. Duenas AM, Goold R, Giunti P. Molecular pathogenesis of spinocerebellar ataxias. Brain 2006 Jun; 129(Pt 6):1357–70. [PubMed: 16613893]
6. Paulson HL. Diagnostic testing in neurogenetics. Principles, limitations, and ethical considerations. Neurologic clinics 2002 Aug;20(3):627–43. v. [PubMed: 12432824]
7. Fogel BL, Perlman S. Clinical features and molecular genetics of autosomal recessive cerebellar ataxias. Lancet neurology 2007 Mar;6(3):245–57. [PubMed: 17303531]
8. Perlman SL. Ataxias. Clin Geriatr Med 2006 Nov;22(4):859–77. vii. [PubMed: 17000340]
9. Orr HT, Zoghbi HY. Trinucleotide repeat disorders. Annual review of neuroscience 2007;30:575–621.
10. Zoghbi HY, Orr HT. Pathogenic mechanisms of a polyglutamine-mediated neurodegenerative disease, spinocerebellar ataxia type 1. The Journal of biological chemistry 2009 Mar 20;284(12): 7425–9. [PubMed: 18957430]
11. Paulson HL. Dominantly inherited ataxias: lessons learned from Machado-Joseph disease/ spinocerebellar ataxia type 3. Seminars in neurology 2007 Apr;27(2):133–42. [PubMed: 17390258]
12. Ikeda Y, Dick KA, Weatherspoon MR, Gincel D, Armbrust KR, Dalton JC, et al. Spectrin mutations cause spinocerebellar ataxia type 5. Nature genetics 2006 Feb;38(2):184–90. [PubMed: 16429157]
13. Kordasiewicz HB, Gomez CM. Molecular pathogenesis of spinocerebellar ataxia type 6. Neurotherapeutics 2007 Apr;4(2):285–94. [PubMed: 17395139]
14. Garden GA, La Spada AR. Molecular pathogenesis and cellular pathology of spinocerebellar ataxia type 7 neurodegeneration. Cerebellum (London, England) 2008;7(2):138–49.
15. Day JW, Schut LJ, Moseley ML, Durand AC, Ranum LP. Spinocerebellar ataxia type 8: clinical features in a large family. Neurology 2000 Sep 12;55(5):649–57. [PubMed: 10980728]
16. Koob MD, Moseley ML, Schut LJ, Benzow KA, Bird TD, Day JW, et al. An untranslated CTG expansion causes a novel form of spinocerebellar ataxia (SCA8). Nature genetics 1999 Apr;21(4): 379–84. [PubMed: 10192387]
17. Matsuura T, Yamagata T, Burgess DL, Rasmussen A, Grewal RP, Watase K, et al. Large expansion of the ATTCT pentanucleotide repeat in spinocerebellar ataxia type 10. Nature genetics 2000 Oct; 26(2):191–4. [PubMed: 11017075]
18. Houlden H, Johnson J, Gardner-Thorpe C, Lashley T, Hernandez D, Worth P, et al. Mutations in TTBK2, encoding a kinase implicated in tau phosphorylation, segregate with spinocerebellar ataxia type 11. Nature genetics 2007 Dec;39(12):1434–6. [PubMed: 18037885]
19. Holmes SE, Hearn EO, Ross CA, Margolis RL. SCA12: an unusual mutation leads to an unusual spinocerebellar ataxia. Brain research bulletin 2001 Oct-Nov 1;56(34):397–403. [PubMed: 11719278]
20. Waters MF, Minassian NA, Stevanin G, Figueroa KP, Bannister JP, Nolte D, et al. Mutations in voltage-gated potassium channel KCNC3 cause degenerative and developmental central nervous system phenotypes. Nature genetics 2006 Apr;38(4):447–51. [PubMed: 16501573]

21. Chen DH, Brkanac Z, Verlinde CL, Tan XJ, Bylenok L, Nochlin D, et al. Missense mutations in the regulatory domain of PKC gamma: a new mechanism for dominant nonepisodic cerebellar ataxia. American journal of human genetics 2003 Apr;72(4):839–49. [PubMed: 12644968]
22. Dalski A, Mitulla B, Burk K, Schattenfroh C, Schwinger E, Zuhlke C. Mutation of the highly conserved cysteine residue 131 of the SCA14 associated PRKCG gene in a family with slow progressive cerebellar ataxia. Journal of neurology 2006 Aug;253(8):1111–2. [PubMed: 16649092]
23. Vlak MH, Sinke RJ, Rabelink GM, Kremer BP, van de Warrenburg BP. Novel PRKCG/SCA14 mutation in a Dutch spinocerebellar ataxia family: expanding the phenotype. Mov Disord 2006 Jul; 21(7):1025–8. [PubMed: 16547918]
24. Iwaki A, Kawano Y, Miura S, Shibata H, Matsuse D, Li W, et al. Heterozygous deletion of ITPR1, but not SUMF1, in spinocerebellar ataxia type 16. Journal of medical genetics 2008 Jan;45(1):32–5. [PubMed: 17932120]
25. Hara K, Shiga A, Nozaki H, Mitsui J, Takahashi Y, Ishiguro H, et al. Total deletion and a missense mutation of ITPR1 in Japanese SCA15 families. Neurology 2008 Aug 19;71(8):547–51. [PubMed: 18579805]
26. Nakamura K, Jeong SY, Uchihara T, Anno M, Nagashima K, Nagashima T, et al. SCA17, a novel autosomal dominant cerebellar ataxia caused by an expanded polyglutamine in TATA-binding protein. Human molecular genetics 2001 Jul 1;10(14):1441–8. [PubMed: 11448935]
27. Knight MA, Hernandez D, Diede SJ, Dauwerse HG, Rafferty I, van de Leemput J, et al. A duplication at chromosome 11q12.2-11q12.3 is associated with spinocerebellar ataxia type 20. Human molecular genetics 2008 Dec 15;17(24):3847–53. [PubMed: 18801880]
28. van Swieten JC, Brusse E, de Graaf BM, Krieger E, van de Graaf R, de Koning I, et al. A mutation in the fibroblast growth factor 14 gene is associated with autosomal dominant cerebellar ataxia. American journal of human genetics 2003 Jan;72(1):191–9. [PubMed: 12489043]corrected
29. Williams AJ, Paulson HL. Polyglutamine neurodegeneration: protein misfolding revisited. Trends in neurosciences 2008 Oct;31(10):521–8. [PubMed: 18778858]
30. Gidalevitz T, Ben-Zvi A, Ho KH, Brignull HR, Morimoto RI. Progressive disruption of cellular protein folding in models of polyglutamine diseases. Science (New York, NY) 2006 Mar 10;311 (5766):1471–4.
31. Williams AJ, Knutson TM, Colomer Gould VF, Paulson HL. In vivo suppression of polyglutamine neurotoxicity by C-terminus of Hsp70-interacting protein (CHIP) supports an aggregation model of pathogenesis. Neurobiology of disease 2009 Mar;33(3):342–53. [PubMed: 19084066]
32. Dickey CA, Patterson C, Dickson D, Petrucelli L. Brain CHIP: removing the culprits in neurodegenerative disease. Trends in molecular medicine 2007 Jan;13(1):32–8. [PubMed: 17127096]
33. Behrends C, Langer CA, Boteva R, Bottcher UM, Stemp MJ, Schaffar G, et al. Chaperonin TRiC promotes the assembly of polyQ expansion proteins into nontoxic oligomers. Molecular cell 2006 Sep 15;23(6):887–97. [PubMed: 16973440]
34. Tam S, Geller R, Spiess C, Frydman J. The chaperonin TRiC controls polyglutamine aggregation and toxicity through subunit-specific interactions. Nature cell biology 2006 Oct;8(10):1155–62.
35. Kitamura A, Kubota H, Pack CG, Matsumoto G, Hirayama S, Takahashi Y, et al. Cytosolic chaperonin prevents polyglutamine toxicity with altering the aggregation state. Nature cell biology 2006 Oct;8 (10):1163–70.
36. Lim J, Hao T, Shaw C, Patel AJ, Szabo G, Rual JF, et al. A protein-protein interaction network for human inherited ataxias and disorders of Purkinje cell degeneration. Cell 2006 May 19;125(4):801–14. [PubMed: 16713569]
37. Qi ML, Tagawa K, Enokido Y, Yoshimura N, Wada Y, Watase K, et al. Proteome analysis of soluble nuclear proteins reveals that HMGB1/2 suppress genotoxic stress in polyglutamine diseases. Nature cell biology 2007 Apr;9(4):402–14.
38. Helmlinger D, Hardy S, Abou-Sleymane G, Eberlin A, Bowman AB, Gansmuller A, et al. Glutamine-expanded ataxin-7 alters TFTC/STAGA recruitment and chromatin structure leading to photoreceptor dysfunction. PLoS Biol 2006 Mar;4(3):e67. [PubMed: 16494529]
39. Riley BE, Orr HT. Polyglutamine neurodegenerative diseases and regulation of transcription: assembling the puzzle. Genes & development 2006 Aug 15;20(16):2183–92. [PubMed: 16912271]

40. Friedman MJ, Shah AG, Fang ZH, Ward EG, Warren ST, Li S, et al. Polyglutamine domain modulates the TBP-TFIIB interaction: implications for its normal function and neurodegeneration. Nature neuroscience 2007 Dec;10(12):1519–28.
41. Lam YC, Bowman AB, Jafar-Nejad P, Lim J, Richman R, Fryer JD, et al. ATAXIN-1 interacts with the repressor Capicua in its native complex to cause SCA1 neuropathology. Cell 2006 Dec 29;127 (7):1335–47. [PubMed: 17190598]
42. Serra HG, Duvick L, Zu T, Carlson K, Stevens S, Jorgensen N, et al. RORalpha-mediated Purkinje cell development determines disease severity in adult SCA1 mice. Cell 2006 Nov 17;127(4):697–708. [PubMed: 17110330]
43. Satterfield TF, Pallanck LJ. Ataxin-2 and its Drosophila homolog, ATX2, physically assemble with polyribosomes. Human molecular genetics 2006 Aug 15;15(16):2523–32. [PubMed: 16835262]
44. Nonhoff U, Ralser M, Welzel F, Piccini I, Balzereit D, Yaspo ML, et al. Ataxin-2 interacts with the DEAD/H-box RNA helicase DDX6 and interferes with P-bodies and stress granules. Molecular biology of the cell 2007 Apr;18(4):1385–96. [PubMed: 17392519]
45. Butler R, Bates GP. Histone deacetylase inhibitors as therapeutics for polyglutamine disorders. Nat Rev Neurosci 2006 Oct;7(10):784–96. [PubMed: 16988654]
46. Burnett BG, Pittman RN. The polyglutamine neurodegenerative protein ataxin 3 regulates aggresome formation. Proceedings of the National Academy of Sciences of the United States of America 2005 Mar 22;102(12):4330–5. [PubMed: 15767577]
47. Zhong X, Pittman RN. Ataxin-3 binds VCP/p97 and regulates retrotranslocation of ERAD substrates. Human molecular genetics 2006 Aug 15;15(16):2409–20. [PubMed: 16822850]
48. Winborn BJ, Travis SM, Todi SV, Scaglione KM, Xu P, Williams AJ, et al. The deubiquitinating enzyme ataxin-3, a polyglutamine disease protein, edits Lys63 linkages in mixed linkage ubiquitin chains. The Journal of biological chemistry 2008 Sep 26;283(39):26436–43. [PubMed: 18599482]
49. Warrick JM, Morabito LM, Bilen J, Gordesky-Gold B, Faust LZ, Paulson HL, et al. Ataxin-3 suppresses polyglutamine neurodegeneration in Drosophila by a ubiquitin-associated mechanism. Molecular cell 2005 Apr 1;18(1):37–48. [PubMed: 15808507]
50. Watase K, Gatchel JR, Sun Y, Emamian E, Atkinson R, Richman R, et al. Lithium therapy improves neurological function and hippocampal dendritic arborization in a spinocerebellar ataxia type 1 mouse model. PLoS Med 2007 May;4(5):e182. [PubMed: 17535104]
51. A randomized, placebo-controlled trial of coenzyme Q10 and remacemide in Huntington's disease. Neurology 2001 Aug 14;57(3):397–404. [PubMed: 11502903]
52. Hersch SM, Gevorkian S, Marder K, Moskowitz C, Feigin A, Cox M, et al. Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG. Neurology 2006 Jan 24;66(2):250–2. [PubMed: 16434666]
53. Berthelier V, Wetzel R. Screening for modulators of aggregation with a microplate elongation assay. Methods Enzymol 2006;413:313–25. [PubMed: 17046403]
54. Xia H, Mao Q, Eliason SL, Harper SQ, Martins IH, Orr HT, et al. RNAi suppresses polyglutamine-induced neurodegeneration in a model of spinocerebellar ataxia. Nature medicine 2004 Aug;10(8): 816–20.
55. Gonzalez-Alegre P, Paulson HL. Technology insight: therapeutic RNA interference--how far from the neurology clinic? Nature clinical practice 2007 Jul;3(7):394–404.
56. Dick KA, Margolis JM, Day JW, Ranum LP. Dominant non-coding repeat expansions in human disease. Genome Dyn 2006;1:67–83. [PubMed: 18724054]
57. Osborne RJ, Thornton CA. RNA-dominant diseases. Human molecular genetics 2006 Oct 15;15(Spec No 2):R162–9. [PubMed: 16987879]
58. Berry-Kravis E, Abrams L, Coffey SM, Hall DA, Greco C, Gane LW, et al. Fragile X-associated tremor/ataxia syndrome: clinical features, genetics, and testing guidelines. Mov Disord 2007 Oct 31;22(14):2018–30. [PubMed: 17618523]quiz 140
59. Moseley ML, Zu T, Ikeda Y, Gao W, Mosemiller AK, Daughters RS, et al. Bidirectional expression of CUG and CAG expansion transcripts and intranuclear polyglutamine inclusions in spinocerebellar ataxia type 8. Nature genetics 2006 Jul;38(7):758–69. [PubMed: 16804541]

60. He Y, Zu T, Benzow KA, Orr HT, Clark HB, Koob MD. Targeted deletion of a single Sca8 ataxia locus allele in mice causes abnormal gait, progressive loss of motor coordination, and Purkinje cell dendritic deficits. J Neurosci 2006 Sep 27;26(39):9975–82. [PubMed: 17005861]

61. Mutsuddi M, Marshall CM, Benzow KA, Koob MD, Rebay I. The spinocerebellar ataxia 8 noncoding RNA causes neurodegeneration and associates with staufen in Drosophila. Curr Biol 2004 Feb 17;14 (4):302–8. [PubMed: 14972680]

62. Wakamiya M, Matsuura T, Liu Y, Schuster GC, Gao R, Xu W, et al. The role of ataxin 10 in the pathogenesis of spinocerebellar ataxia type 10. Neurology 2006 Aug 22;67(4):607–13. [PubMed: 16924013]

63. Xiao M, Xu L, Laezza F, Yamada K, Feng S, Ornitz DM. Impaired hippocampal synaptic transmission and plasticity in mice lacking fibroblast growth factor 14. Molecular and cellular neurosciences 2007 Mar;34(3):366–77. [PubMed: 17208450]

64. Wozniak DF, Xiao M, Xu L, Yamada KA, Ornitz DM. Impaired spatial learning and defective theta burst induced LTP in mice lacking fibroblast growth factor 14. Neurobiology of disease 2007 Apr; 26(1):14–26. [PubMed: 17236779]

Table 1

Spinocerebellar Ataxias (SCA's)

Disease	Locus	*Gene*/Protein	Mutation (size range)
SCA1*	6p	*ATXN1*/Ataxin-1	**CAG/polyQ exp. (39-82)**
SCA2*	12q	*ATXN2*/Ataxin-2	**CAG/polyQ exp. (33-64)**
SCA3*	14q	*ATXN3*/Ataxin-3	**CAG/polyQ exp. (52-86)**
SCA4	16q	Unknown	Unknown
SCA5*	11p	*SPTBN*/ Beta-III spectrin	Nonrepeat mutations
SCA6*	19p	*CACNA1*/ Calcium channel	**CAG/polyQ exp. (19-30)**
SCA7*	3p	*ATXN7*/Ataxin-7	**CAG/polyQ exp. (37-200)**
SCA8*	13q	*SCA8*	CAG/CTG exp. (107-128)
SCA10*	22q	SCA10	ATTCT exp. (1000-4000)
SCA11*	15q	*TTBK2*/ tau kinase	Nonrepeat mutations
SCA12*	5q	*PPP2R2B*/posphatase	CAG exp. (66-78)
SCA13*	19q	*KCNC3*/ potassium channel	Unknown
SCA14*	19q	*PKC* γ/ protein kinase C	Nonrepeat mutations
SCA15/16	3p	*ITPR*/ IP3 receptor	Nonrepeat mutations
SCA17*	6q	*TBP*/ TATA binding protein	**CAG/polyQ exp. (50-63)**
SCA18	7q	Unknown	Unknown
SCA19	1p	Unknown	Unknown
SCA20	11	Unknown	Genomic duplication
SCA21	7p	Unknown	Unknown
SCA22	1p	Unknown	Unknown
SCA23	20p	Unknown	Unknown
SCA24	19	Unknown	Unknown
SCA25	2p	Unknown	Unknown
SCA26	19p	Unknown	Unknown
SCA27*	13q	*FGF14*/fibroblast growth factor	nonrepeat mutations
SCA28	18p	Unknown	Unknown
SCA29	3p	Unknown	Unknown

Asterisks denote SCAs for which clinical genetic testing is currently available. SCAs in bold type represent CAG/polyQ diseases.

Abbreviations: polyQ: polyglutamine; exp.: expansion; IP3: Inositol-1, 4, 5-triphosphate