Dominant spinocerebellar ataxias: a molecular approach to classification, diagnosis, pathogenesis and the future

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The capacity to use molecular techniques to establish the genetic diagnoses of the autosomal dominant ataxias has revolutionized the field. It is now possible to systematically classify these disorders according to the nature of the causative mutation, with implications for diagnostic testing, analysis of pathogenesis and therapeutic strategies. Here, the disorders are grouped into ataxias caused by CAG repeat expansions that encode polyglutamine, ataxias caused by mutations in ion channels, ataxias caused by repeat expansions that do not encode polyglutamine, and ataxias caused by point mutations. The clinical, pathological, genetic and pathogenic features of each disorder are considered and the current status and future of diagnosis and therapy are reviewed in light of this classification scheme.

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> *Social and scientific observations of* Homo sapiens *(var. medicus) have shown that he tends to function as a splitter or as a lumper. The splitter is most active during times when certain diseases are poorly understood and imperfectly treated; under these circumstances, classification, subclassifications and sub-subclassifications appear. The lumper usually belongs to the days when complicated categories of maladies give over to unification of multiple syndromes and variants, as competent causes and effective remedies make their appearance. …until recently the heredofamilial degenerations of the nervous system have been a happy ground for splitters and it is with some satisfaction that we record lumper activity in this field…* [1].

Woodworth and colleagues, writing in 1959, recognized the chaos in the nosology of the dominantly inherited ataxias that had emerged in the 65 years since Marie's first description [2]. Since 1959, the conceptualization of the dominant cerebellar ataxias has undergone two cycles of evolution. First, a simplification into a few reliable categories: the lumping foretold by Woodworth [3]. Second, a nosological scheme based on genetic etiology. The dominant cerebellar degenerative disorders are now generally referred to as spinocerebellar ataxias (SCAs), even though SCA is a hybrid term, referring to both a clinical sign and a neuroanatomical region [4]. In fact, many of the current SCAs would fall outside of the original scope implied by the term SCA. Nonetheless, as each new dominant cerebellar disorder is described and linked to a unique genomic locus, it is assigned a number by the Human Genome Organization; the current number has reached 25, though a few of these numbers do not actually have diseases assigned to them.

Epidemiology

Estimates of the worldwide prevalence of autosomal dominant cerebellar ataxias range from approximately 0.8 to 3.5 in 1000,000 [5–9]. In comparison, the prevalence of Huntington's disease (HD) in the USA and most European countries is approximately 5 in 100,000 [10]. Differences among studies in diagnosis and ascertainment, as well as regional variations in

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disease prevalence (including the concentrations of SCA2 in the Holguin Province of Cuba and SCA3 in the Azore Islands of Portugal) may be a permanent barrier to more consistent estimates. In general, SCA1, 2, 3, 6 and 7 account for a large majority of the dominant ataxias (TABLE 1).

Polyglutamine diseases

The polyglutamine ataxias comprise six disorders (in addition to SCA6): SCA1, 2, 3, 7, 17 and dentatorubro-pallidoluysian atrophy (DRPLA). It is often difficult or impossible to distinguish among them on clinical grounds. Together, they account for a large majority of dominant SCA cases. Like HD and spinal and bulbar muscular atrophy, each is caused by an expansion of a CAG trinucleotide repeat (an increase in CAG and CAA triplets in SCA17) that results in a protein with an elongated stretch of polyglutamine residues. Each polyglutamine disease is a dominant disorder characterized by clinical variability (within and between families) and anticipation (younger age of onset and more severe disease course in subsequently affected generations of a pedigree). The anticipation, and to an extent the variability, is explained by a tendency for repeats to expand during vertical transmission (particularly in paternal transmission) and for age of disease onset to inversely correlate with repeat length. Pathologically, each disease is characterized by selective neuronal vulnerability in overlapping (though not identical) cortical and subcortical regions, including the cerebellum. Despite these clinical similarities, the genes involved in each disease have little in common with each other. The presumption is therefore that polyglutamine toxicity is the root of the pathogenesis of these disorders. However, since the brain regions affected in each disease are not identical and the length of the glutamine expansion necessary to cause each disease is different, some aspects of the pathogenesis of each disease must be unique.

SCA1

Clinical diagnosis

Clinical findings vary within and between families and within the same individual over time. The mean age of onset is approximately 35 years [11], with a range of 4 [12] to 74 years [13]. Duration between onset and death is typically around 10–20 years, with a range of 12 to 38 years [14]. Death is often by pneumonia and restrictive respiratory failure [15]. Gait and limb ataxia (the usual presenting signs), dysarthria and bulbar dysfunction are universal. As the illness progresses, some patients may also have vibration and proprioception loss, abnormal saccades, nystagumus, ophthalmoparesis, mild optic atrophy, hypertonia (usually early), hypotonia (later) and decreased deep tendon reflexes. Late-stage findings include facial weakness, difficulties with swallowing or breathing and extrapyramidal signs including dystonia and chorea [16]. Features that serve to partially distinguish SCA1 from other SCAs include the speed and severity of disease progression, involvement of cranial nerves, later onset of slow saccades and lack of marked extrapyramidal signs until late in the disease course.

Pathological diagnosis

The key pathological findings are loss of cerebellar Purkinje and dentate neurons, inferior olive neurons, neurons in the red nucleus and neurons in the cranial nerve nuclei (especially the 3rd, 10th and 12th). Neuronal loss may also occur in the substantia nigra, putamen, pallidum and subthalamic nucleus [15,17].

Genetic diagnosis

SCA1 was the first SCA to be linked to a specific chromosomal locus [18,19] and the first SCA for which the causative mutation was identified: a CAG repeat expansion in a gene on chromosome 6p encoding a protein of unknown function termed ataxin-1 [20]. The normal repeat length is approximately 6–38 CAG triplets, while repeat lengths associated with disease typically range from 39 to 83 triplets. However, in some cases, alleles with as many as 44 triplets may be normal if the repeat includes CAT triplets [21]. At least one apparently sporadic case with a small expansion has been reported (onset age 60 years, repeat length 40 triplets; parents unaffected until their deaths at age 77 and 89 years) [22]. One individual with an uninterrupted repeat length of 44 triplets was reported to be asymptomatic at age 66 years [23].

SCA2

Clinical diagnosis

SCA2 is clinically characterized by cerebellar ataxia, dysarthria and abnormal eye movements in almost all patients. Neuropathy, chorea or dystonia, and dementia are frequently present and pyramidal signs are occasionally present [24–26]. Clinical features suggestive of SCA2 include lower limb hyporeflexia, oculomotor abnormalities, amyotrophy, postural tremor and gross cognitive deficits [25]. Mean age of onset is approximately 30 years, with marked variations within and between different families, partly explainable by repeat length. Disease course is also variable, with death in some pedigrees occurring approximately 10 years after disease onset, while affected members of other pedigrees can still walk 10 years after symptom onset [24].

Pathological diagnosis

Post-mortem examinations have revealed degeneration of cerebellar Purkinje and granule cells; neuronal loss in the inferior olive, pontocerebellar nuclei, substantia nigra, striatum, Clarke's column of the spinal cord and spinal ganglia; demyelination of the posterior columns and spinocerebellar tracts; and marked atrophy of the cerebral cortex in at least some cases [27,28]. The dentate nucleus is spared.

Genetic diagnosis

SCA2 was first mapped to 12q by taking advantage of the large concentration of SCA cases in the Holguin province of Cuba [29] and an independent Italian pedigree [30]. The causative mutation, a CAG repeat expansion in a gene encoding another protein of unknown origin, ataxin-2, was discovered simultaneously in 1996 by three groups using three different approaches [31–33].

Table 1. Frequency of the autosomal dominant ataxias.

Site	Number of patients	SCA1 (%)	SCA2 (%)	SCA3 (%)	SCA6 (%)	SCA7 (%)	SCA8 (%)	SCA12 (%)	DRPLA (%)	Ref.
Italy	116	24	47	0	2	2	-	-	1	[183]
Germany	77	9	10	42	22	-	-	-	-	[184]
Portugal	48	0	4	74	0	-	-	-	0	[66]
The Netherlands	137	11	10	47	20	12	-	-	-	[5]
Australia	88	16	6	12	17	2	-	-	-	[185]
Spain	87	6	15	15	1	3	-	-	1	[186]
USA	178	6	15	21	15	4	3	-	-	[140,187]
USA/Europe	177	15	14	30	5	-	-	-	0	[188]
USA	47	6	13	23	-	X	-	-	-	[24]
China	167	5	6	48	0	0	-	-	0	[189]
Korea	76	4	14	16	3	3	-		-	[190]
Taiwan	74	5	11	47	11	3	0	0	1	[165]
Japan	202	3	5	43	11	-	-	-	20	[188]
India	77	16	25	3	0	3	0	6	0	[153]
Japan	143	3	4	24	31	0	0	0	12	[191]

Note: the Korean study was not limited to autosomal dominant cases; - indicates test not performed.
X: Excluded from analysis.

Normal alleles range in length from 14 to 32 triplets, while disease alleles range from 33 to greater than 220 triplets [25,34–36]. Repeats in the 32–35 triplet range should be considered a gray zone, as at-risk but still asymptomatic individuals with repeat lengths up to 35 triplets have been reported [24,25] and laboratory error is typically at least ± 1 triplet [37]. Interpretation in this range will depend on clinical presentation in the patient and family members [25,34]. Sporadic cases with repeats of 37 and 39 triplets have also been reported [25].

SCA3

Clinical diagnosis

SCA3, also known as Machado–Joseph disease (MJD), was initially identified in the 1970s in three separate families of Portuguese–Azorean origin [38–40]. It was soon recognized that these families had the same disease [41] common in the Azores [42] and present throughout the world [43]. In the interests of clarity, SCA3 will be used here to refer to all the phenotypes that arise from an ataxin-3 expansion mutation. The central clinical feature in SCA3 is ataxia, but like SCA2, the disease phenotype is extremely variable, only explained in part by repeat length. A classification of SCA3 into clinical subtypes remains useful in organizing the large phenotypic spectrum of the disease [44–47]. Type 1, associated with long repeats and young onset, is characterized by dystonia and rigidity. Type 2, which is the most common form, is associated with early adulthood to middle-age onset (~20–45 years) and the primary clinical manifestations are cerebellar and pyramidal signs. Type 3 is characterized by onset in late mid-life (approximately 40–60 years), slow progression and predominance of cerebellar signs and peripheral neuropathy. A rare Type 4, characterized by prominent parkinsonism, has also been proposed.

Pathological diagnosis

As summarized by Paulson, SCA3 pathological findings are variable but generally include cell loss and gliosis in the globus pallidus, subthalamic nucleus, substantia nigra, dentate nucleus, pontine and cranial nerve nuclei (III, IV, VI, VII, VIII and X) and spinal neurons (anterior horn and Clarke's column) [44]. The caudate and putamen, cerebral and cerebellar cortex and inferior olives are relatively spared in most pedigrees. When present, neuropathy involves both sensory and motor neurons and myelinated and unmyelinated fibers.

Genetic diagnosis

In 1994, MJD was found to arise from a CAG expansion mutation in a gene of unknown function on chromosome 14q termed ataxin-3 [48]. SCA3, thought on the basis of phenotype to be a separate disorder, was soon shown to be caused by the same mutation [49,50]. The normal length of the repeat is approximately 12–44 triplets, while the SCA3 range is 53 to 200 triplets. At the lowest end of the expanded range, onset is likely to be late with very mild disease [51].

SCA7

Clinical diagnosis

The defining clinical feature of SCA7 is the presence of retinopathy with consequent loss of vision in most cases. This loss is accompanied by cerebellar ataxia, dysarthria and at times pyramidal signs, decreased vibration sense, dyspahgia, ophthalmoplegia, sphincter dysregulation and hearing impairment [52,54]. Extrapyramidal symptoms are relatively infrequent. The mean age of onset is approximately 30 years, with wide variation from a few months to the mid-70s. In one case with a repeat length of 306 triplets and infantile onset, the phenotype included congestive heart failure and patent ductus arteriosus, in addition to the expected CNS abnormalities (severe hypotonia, visual loss and atrophy of the cerebral cortex and the cerebellum) [55]. Various studies have found a mean survival between illness onset and death of 10–20 years, with a range of a few months to 30 years. Extreme anticipation has been observed with more severe clinical manifestations, including accelerated death, in individuals with very long repeat expansions (67 to >200 repeats) [53].

Pathological diagnosis

Neuropathologically, the most pronounced degeneration is of the retina, cerebellar Purkinje and granule cells, the dentate nuclei, the inferior olive, the subthalamic nucleus and spinal motor neurons [56].

Genetic diagnosis

Based on the extreme anticipation observed clinically, SCA7 was presumed to result from a trinucleotide expansion and the assumption was confirmed independently by three different groups [57–59]. The repeat length in the normal population ranges from 4 to 35 triplets, with approximately 75% of all alleles containing a 10-triplet repeat. Expanded repeats range from 36 (and possibly 34 [60]) to more than 300 triplets, with almost all vertical transmissions of an expanded allele resulting in further expansions, particularly in paternal transmission [54,55,60]. It appears that long normal repeats which do not cause disease themselves, may occasionally expand into the pathological range, providing a reservoir of potential mutations that perpetuate the existence of SCA7 despite its marked anticipation [61].

SCA17

Clinical diagnosis

SCA17 has been described in one isolated case from Japan [62], four Japanese pedigrees [63] and four European pedigrees [64–66]. The presenting clinical features include cerebellar ataxia and dementia, with later pyramidal and extrapyramidal signs, often including parkinsonism and either chorea or dystonia. Eye movements are normal. Seizures develop in many individuals at varying stages of the disease. Mean age of onset in the Japanese cases was 33 years (range 19 to 48), with a course that has resulted in death within 10–20 years in four cases.

Pathological diagnosis

The pathology from one case revealed loss of small neurons in the caudate and putamen, loss of Purkinje cells in the cerebellum and atrophy in the thalamus, frontal cortex and temporal cortex [63]; Purkinje cell loss with gliosis in the Purkinje cell layer was noted in a second case [65].

Genetic diagnosis

The disease is defined by an increase in the length of a repeat in the gene encoding TATA-binding protein (TBP) on chromosome 6q27. TBP is part of the RNA polymerase II transcription factor D complex; its role is to bind DNA and hence is critical for expression of most genes. The repeat is a mixture of CAG and CAA triplets, both encoding glutamine. In the normal population, this region encodes 25–44 consecutive glutamines. In SCA17, through either duplication of portions of the region or expansion of a stretch of consecutive CAG triplets within the region, a protein is encoded that contains 43–63 glutamines. The longer glutamine repeats result in an earlier age of disease onset. The overlap between the normal and disease range suggests that repeats of 43–44 (and perhaps up to 48 [67]) glutamines may be of reduced penetrance.

DRPLA

Clinical diagnosis

With adult onset, typical symptoms of DRPLA include progressive ataxia, ocular motor disturbance, chorea and dementia; the presentation may be indistinguishable from HD, though other cases may resemble a degenerative cerebellar disorder. Childhood onset is characterized by prominent progressive myoclonic epilepsy. Magnetic resonance imaging (MRI) findings typically show a more generalized cerebral atrophy than is seen in most of the SCAs, though this may be accompanied by prominent cerebellar atrophy and moderate basal ganglia atrophy [68,69].

Pathological diagnosis

As suggested by the name, the key findings are in the cerebellifugal and palidofugal systems [70–73]. The most prominent and consistent findings are dentate nucleus neuronal loss and astrocytosis and cerebellar white matter degeneration. The globus pallidus, subthalamic nucleus and red nucleus are frequently involved and multiple other regions have been reported in a few cases. The variability in neuropathology probably explains the phenotypic variability of DRPLA.

Genetic diagnosis

The gene for DRPLA, atrophin-1, was initially discovered as a cDNA fragment with a long and polymorphic CAG repeat mapped to chromosome 12 [74]. Linkage of DRPLA to this same region of chromosome 12 directed investigators to this locus, leading to the detection of the repeat expansion in DRPLA [75,76]. Unlike most other CAG repeat diseases, there is no overlap between the normal (3 to 35 triplets) and the expanded repeat range (48 to 88 triplets). An individual homozygous for a repeat of 41 triplets developed spastic paraplegia [77].

Pathogenesis of the polyglutamine diseases

Investigation into the pathogenesis of polyglutamine diseases has advanced remarkably in the past decade, addressed by well over 1000 papers that together support a complex set of interrelated hypotheses. Detailed discussion of this issue is beyond the scope of this review; numerous recent reviews emphasizing a particular disease, model system or proposed pathogenic mechanism are available [78–85]. Here, a few of the main hypotheses under consideration are noted.

The first critical step in unraveling the puzzle of polyglutamine pathogenesis was the observation that, in patients affected with one of the CAG repeat expansion diseases, the allele containing the CAG repeat expansion is expressed, yielding a protein with an expanded polyglutamine tract [86,87]. The implication that neuronal dysfunction and death results from a toxic gain of function of the expanded polyglutamine, as opposed to a loss of function of the normal protein, has been supported by almost all subsequent studies [79], though some evidence for a contributory loss of normal function has emerged, especially in HD [88]. Subsequent studies have focused on elucidating the pathways that lead from an expanded polyglutamine tract to cell damage.

Proteins with expanded stretches of polyglutamine appear to take on an abnormal configuration and undergo a sequential process, resembling amyloid formation, that results in the formation of polyglutamine aggregates [89,90]. The relationship between aggregation and neurotoxicity remains uncertain and evidence from cell and mouse models of SCA1 and HD indicate that aggregation itself is not necessary for cell toxicity [91–93]. Nonetheless, the possibility that blocking aggregation may have therapeutic potential is quite appealing [94] and a number of investigations have sought to find the link between aggregation and neurotoxicity. One proposal is that the long glutamine stretches, perhaps in the form of preaggregate protofibrils [90], may sequester other proteins, including transcription factors, that then become unavailable to perform their normal cellular duties, leading to potentially lethal consequences [95]. Alternatively, long polyglutamine tracts, either before or after forming aggregates, may interfere with the function of the ubiquitin-dependent proteasome pathway, which normally functions to degrade aberrantly folded proteins [96,97]. Failure of this system may lead to an accumulation of a variety of toxic proteins that would otherwise have been degraded. Experimental overexpression of molecular chaperones – proteins that can repair or facilitate proteasome degradation of abnormal proteins – appears to diminish the toxicity of glutamine expansions in a number of model systems without necessarily reducing polyglutamine aggregation [98–101].

Several lines of evidence suggest that proteolytic cleavage may increase the toxicity of proteins containing polyglutamine expansions [102]. Another promising line of investigation focuses on the modulatory role of histone deacetylase inhibitors [103]. Other mechanisms by which polyglutamine expansion could lead to neurotoxicity include abnormal activation of the endosomal–lysosomal pathway [104] and mitochondrial disruption [105].

While the many similarities of the polyglutamine expansion diseases have led to an emphasis on common modes of pathogenesis, the clinical, genetic and neuropathological differences also suggest that some aspects of pathogenesis will be unique to each disease. For instance, proteins that more or less specifically interact with huntingtin [106], huntingtin and atrophin-1 [107], ataxin-1 [108,109] and ataxin-7 [110] have been identified. These and other protein interactors may modulate the toxicity of the mutant protein with which they interact, leading to the selectively neuronal vulnerability that characterizes each disease.

SCAs caused by mutations in ion channels (channelopathies)

Episodic ataxia Type 1

Clinical diagnosis

Episodic ataxia Type 1 (EA1) is a very rare disorder characterized by episodes of ataxia and continuous myokemia. Attacks, often precipitated by physical or emotional stress or startle, typically last only for seconds to minutes and include trunk and limb ataxia and dysarthria [111] and sometimes seizures [112]. Disease onset is typically in childhood, with a tendency for the ataxic episodes to diminish or even disappear in adulthood. The ataxia episodes of affected individuals in some families with typical EA1 respond to carbamazepine or acetazolamide (Diamox®, Wyeth, NJ, USA).

Genetic diagnosis

EA1 is caused by at least four different missense mutations and a nonsense mutation in *KCNA1*, the gene on chromosome 12p13 that encodes the Kv1.1 potassium channel subunit [113].

Pathogenesis

KCNA1 is highly expressed in the cerebellum and in peripheral nerves. The mutations tend to occur in highly conserved amino acids and there appears to be a correlation between the location of the mutation and the nature of the clinical phenotypes [114]. For instance, typical EA1 and cases of neuromyotonia may result from mutations that only impair potassium channel kinetics [115]. More severe forms of the disorder appear to result from inability of the channel subunits to properly form tetramers and from impaired transfer of the formed channel to the cell membrane.

SCA6

Clinical diagnosis

Symptoms almost always begin with subtle gait ataxia. The mean onset age is 50 years, with longer expansions associated with earlier onset. Repeat length is typically, though not universally, stable during vertical transmission [116–118]. Anticipation, observed in a few families, may reflect ascertainment bias or other factors [119]. The course is slowly progressive and wheelchair use may not be required for 15 years. Cerebellar findings typically dominate the illness, particularly in the first 10 years or so, though mild noncerebellar signs including ophthalmoplegia, spasticity, peripheral neuro-pathy, dysphagia and parkinsonism sometimes develop later in the course of the disease [120–122].

Pathological diagnosis

Pathological investigations have shown cerebellar atrophy with loss of Purkinje cells to be more severe than loss of granule cells or neurons in the dentate nucleus, some neuronal loss in the inferior olive, and only minimal brainstem atrophy [123–125].

Genetic diagnosis

The cause of SCA6 was shown in 1997 to be modest expansions in the CAG repeat within *CACNA1A*, the gene encoding the alpha1A voltage-dependent calcium channel located on chromosome 19p13 [121]. Normal repeats range from 4 to 20 triplets in length, while disease has been associated with repeat lengths of 20–33 triplets [116,118,126].

Pathogenesis

While a direct role for polyglutamine toxicity in SCA6 pathogenesis remains unclear [127], there is evidence that the expansion mutation increases the density of the alpha1A voltage-dependent calcium channel in cell membrane [128] and/or shifts the voltage dependence of channel activation and rate of inactivation [129], both resulting in an overall increase in calcium influx. Alternatively, in a different model system and with larger than usual expansions, the mutation was shown to induce a hyperpolarizing shift in the voltage dependence of channel inactivation, considerably reducing the available channel population at a resting membrane potential with consequent reduction of calcium influx [130]. These findings suggest the possibility that SCA6 is a channelopathy and that the underlying mutation in SCA6 causes neurodegeneration through abnormal calcium flux.

EA2 & familial hemiplegic migraine

Clinical diagnosis

EA2 is an autosomal dominant disorder in which constant and progressive cerebellar signs are complicated by attacks of vertigo, visual disturbance, dysarthria and ataxia responsive to acetazolamide [131–133]. Familial hemiplegic migraine (FHM) is a rare autosomal dominant disorder characterized by migraine, at times with accompanying ictal hemiparesis, and also with progressive cerebellar degeneration in some families [134].

Genetic diagnosis

A number of point mutations causing either EA2 or FHM were found in the same calcium channel gene that is associated with SCA6 [135]. Also, some individuals with *CACNA1A* CAG repeat expansions have clinical courses that resemble EA2 more than SCA6 [118,136], headache is at times observed in SCA6 [119] and a point mutation in *CACNA1A* has been associated with a disease more closely resembling SCA6 than EA2 [137]. The overlap in disease phenotype among SCA6, EA2 and FMH supports the proposal that the repeat expansion in SCA6 causes functional impairment of the CACNA1A channel.

SCAs caused by repeat expansions that do not encode polyglutamine

SCA8

Clinical diagnosis

Findings on examination of SCA8 patients included limb and gait ataxia, dysarthria, spasticity, oculomotor abnormalities and decreased vibration sensation. MRI scans show cerebellar atrophy. Progression is slow, such that mobility aids are not required until at least 20 years of illness duration [138]. Other case series have noted similar findings, with the addition of tremor and frequent cognitive complications in a Finnish series [139] and a case of infantile onset in a Portuguese series [66].

Genetic diagnosis

SCA8 remains the most controversial of the SCAs. The disease was initially defined in 1999 when a CTG/CTA repeat expansion in an untranslated gene on chromosome 13q21 was found to segregate with SCA in a large Minnesota pedigree [140]. Repeat length in affected individuals ranged from 107 to 127 triplets, while unaffected expansion carriers had repeat lengths of 71 to 101 CTG triplets. Almost all expanded alleles were maternally inherited, with paternal transmissions usually resulting in a marked repeat contraction. The mean age of disease onset in this family is 39 years (range 13 to 65 years). However, the boundary between normal and expanded repeat length remains uncertain. It is possible that penetrance may be particularly low in both very short and very long expansions. Expansions (defined as repeats of 100 or more triplets) have been detected in 1–3% of some [139,141–144] but not all [66,140,145] control populations. While asymptomatic carriers in the large Minnesota family did not have dysmetria on quantitative testing, mild cerebellar atrophy was detected by MRI in an asymptomatic mutation-carrying father of a clinically affected daughter [146]. The frequency of SCA8 is difficult to determine because of the apparent frequency of incomplete penetrance, but may account for as many as 3–6% of autosomal dominant cases and also occasional sporadic cases. However, even if only 0.1% of all individuals carry an expansion, the frequency of nonpenetrant expansions will exceed the total of all dominant ataxia cases by a factor of between ten- and 100-fold, creating considerable difficulties in interpreting SCA8 genetic test results. It seems reasonable to conclude that the SCA8 expansion is the cause of ataxia in at least some individuals but it may only be possible to prove the causal connection in large families.

Pathogenesis

The *SCA8* gene itself is not translated into protein but overlaps the transcription and translation start sites and the first splice junction of *KLHL-1*, a gene on the antisense DNA strand from *SCA8* [147]. *KLHL-1* encodes a 748-amino acid protein expressed in multiple brain regions and in some tissues outside of the CNS. It has structural similarities to a family of proteins involved in the organization of the cytoskeletal protein actin [148]. One proposal is that SCA8 normally regulates expression

of *KLHL-1* at the RNA level and that a repeat expansion in some way disrupts this regulatory activity [140]. Alternatively, the repeat may directly affect expression of KLHL-1.

SCA10

Clinical diagnosis

The clinical phenotype of SCA10, based on five Mexican pedigrees [149,150], consists of progressive cerebellar ataxia and dysarthria, accompanied by seizures in most cases and psychiatric disturbances in a majority of cases (depression and/or aggression). Nearly half of the affected individuals have pyramidal signs and most have evidence of polyneuropathy and abnormal eye movements. Liver abnormalities were present in one family, cardiac abnormalities in a second family and members of both families had evidence of anemia. MRI scans in eight individuals revealed cerebellar atrophy with little or no cortical or brain stem atrophy. Electroencephalograms in these eight individuals were all abnormal, with focal slowing or irritability detected in five.

Genetic diagnosis

The cause of SCA10 is an expansion of an ATTCT pentanucleotide repeat located within intron 9 of a gene of unknown function termed *SCA10* located on chromosome 22q13-qter. The normal length of the repeat is 10–22 pentamers, while in affected individuals the range is approximately 800 to 4500 pentamers. There is perfect segregation between expansion and disease in these families and no expansions have yet been detected in control subjects. There is marginal correlation between age of onset and repeat length.

Pathogenesis

The mode of pathogenesis remains unknown, though the length of the repeat expansion suggests that a disruption of transcription or splicing is possible.

SCA12

Clinical diagnosis

SCA12 typically begins with action tremor of the head and upper extremities and progresses to include a wide range of signs and symptoms, including mild cerebellar dysfunction, hyper-reflexia, subtle parkinsonian features, psychiatric symptoms and dementia in older subjects [151–153]. Symptoms in most individuals begin in the fourth decade and the disease is slowly progressive thereafter. MRIs of affected individuals reveal generalized atrophy of the CNS, predominantly affecting the cerebral cortex and cerebellum. While only a single family has been discovered in American and European populations, SCA12 has now been detected in eight Indian pedigrees [152,153, S JAIN, UNPUBLISHED OBSERVATIONS] and could account for up to 6% of all dominant SCA cases in India. The higher prevalence of SCA12 in India is consistent with the finding that longer *PPP2R2B* CAG repeats are more common in India than Europe [152,153]. There is no clear association between repeat length and age of SCA12 onset, although repeat length is modestly unstable during vertical transmission.

Pathological diagnosis

Preliminary analysis of the single SCA12 brain that has come to autopsy revealed diffuse atrophy, including loss of cerebellar Purkinje cells and no evidence of abnormal tau accumulation [O'HEARN, UNPUBLISHED OBSERVATION].

Genetic diagnosis

SCA12 was initially identified in a large American pedigree of German origin using the repeat expansion detection that has also been used to find CAG/CTG expansions in SCA7 [59] and HD-like 2 [154,155]. The SCA12 CAG repeat expansion occurs in the 5′ region of *PPP2R2B*, a brain-specific regulatory subunit of the phosphatase PP2A. Normal repeat length in the population is 7–32 triplets, while expanded repeats range in length from 55 to 78 triplets. A 28 year old individual with an allele containing 45 triplets and a Iranian woman with unipolar depression and her monozygotic twin sons with schizophrenia with repeats of 53 triplets remain unaffected. Whether these individuals will eventually develop SCA12 or reflect reduced penetrance or alternative phenotypes remains unclear [156].

Pathogenesis

Preliminary evidence suggests that the SCA12 mutation may result in overexpression of PPP2R2B [156]. This rather surprising result raises the hypothesis that the ultimate effect of the mutation is to shift the substrate preference for PP2A. PP2A regulates, among other processes, cell cycle progression, tau phosphorylation and apoptosis, providing multiple mechanisms through which a substrate shift might lead to neuronal dysfunction or death.

SCAs caused by point mutations

SCA14

Clinical diagnosis

SCA14 was defined based on a three-generation Japanese family in which the mean age of onset was 28 years (range 12 to 42 years) [157]. Family members with onset later than age 38 years developed a pure cerebellar ataxia, whereas family members with onset earlier than 28 years developed axial myoclonus before ataxia. Linkage was established to chromosome 19q13.4-qter. Subsequently, a dominant spinocerebellar ataxia segregating in a four-generation family of Dutch and English ancestry was linked to the same region [158]. Ten affected family members were available for study. Age of onset ranged from 10 to 50 years, with a mean onset of 31 years. The primary clinical characteristics are gait ataxia, dysmetria, dysarthria and abnormal eye movements. Reflexes vary from hyper-reflexia to hyporeflexia and only one individual has a Babinski sign. There is no cognitive impairment, myoclonus or sensory loss. The disease is slowly progressive without an appreciable influence on lifespan. Despite differences between the phenotypes of the disease in the Japanese and the English–Dutch family, it is likely, based on common linkage to chromosome 19q13.4-qter, that these diseases are allelic.

Pathological diagnosis

The single case available for study was notable for Purkinje cell loss in the cerebellar cortex and gliosis without neuronal loss in the olivary nucleus.

Genetic diagnosis

A transition of C to T in nucleotide 301 of the *PRKCG* gene was detected in the Dutch–English family [158]. This transition falls in exon 4 of the PRKCG protein product, PKC-γ, and results in a substitution of a tyrosine for a histidine at amino acid 101. A transition of T to C in nucleotide 355, resulting in replacement of a serine with a proline at amino acid 119, was subsequently detected in an unrelated individual and her two children with an uncomplicated cerebellar ataxia. A transition of G to A in nucleotide 383, resulting in substitution of a glycine with an aspartate at amino acid 128, was detected in a sporadic case of uncomplicated cerebellar ataxia. These polymorphisms were not observed in 384 control chromosomes.

Pathogenesis

Each of the nonconservative amino acid substitutions occur at a highly conserved point in the regulatory domain of PKC-γ, potentially disrupting binding properties. Testing for these mutations is not yet available on a commercial basis. If no other mutations are found in *PRKCG*, then sequencing of exon 4 may emerge as an efficient genetic test. However, if mutations are found elsewhere in the gene, meaningful genetic testing may ultimately require the sequencing of all exons and regulatory regions of *PRKCG*.

Fibroblast growth factor 14-related SCA

Clinical diagnosis

Fibroblast growth factor (FGF)14-related SCA was identified in a three-generation Dutch pedigree, with 14 affected individuals examined. Disease onset begins with hand tremor in childhood and mild ataxia by the late-teens. Other common findings include dysmetria, dysarthria, abnormal eye movements, head tremor, subtle oral-facial dyskinesia, dysmetria and cognitive and psychiatric abnormalities. Only four affected family members completed secondary school. Cerebellar atrophy on MRI was seen in only two of nine patients.

Genetic diagnosis

The disorder was linked to chromosome 13q34. A transition of T to C at nucleotide 434 of the FGF14 open reading frame was found to segregate with the disease in the family; this mutation was not seen in a Dutch control population.

Pathogenesis

The effect of the mutation is the substitution of a serine by a phenylalanine at amino acid 145 that is predicted to destabilize FGF14. Commercial genetic testing is not yet available for this mutation and it is unknown whether FGF14 mutations exist in other SCA pedigrees.

Expert opinion

Other possible causes of autosomal dominant ataxia

The genetic cause of an estimated 30% of cases of dominant ataxia have yet to be determined. A number of families have been linked to specific chromosomal regions, with the hunt for the causative mutation still in progress (TABLE 2).

Other seemingly dominant forms of ataxia prove to be Friedreich's ataxia, a recessive disorder that is the most common form of ataxia [160]. More recently, carriers of the fragile X permutation have been found to develop ataxia during middle-age or later [161,162].

Sporadic cases of ataxia may have a genetic cause

A number of investigations have revealed that some seemingly sporadic cases of adult-onset ataxia do have a genetic cause. Reasons for the lack of family history include a mutation in the family of variable penetrance, parental death prior to disease onset, anticipation such that the affected offspring develops the disease prior to their parent, false paternity, adoption, and spontaneous mutation. In a sample of 124 sporadic cases from Germany, a genetic etiology was found in 19% [163]. Ten had Friedreich's ataxia (onset 13–36 years), nine had SCA6 (onset 47–68 years) and one had SCA2 from a *de novo* mutation inherited from an intermediate allele transmitted paternally. In a similar series of 112 carefully defined cases of sporadic adult-onset ataxia, Friedreich's ataxia was found in five patients (4%), SCA2 mutation in one (1%), SCA3 mutation in two (2%) and SCA6 mutation in seven (6%) [164]. Two of 49 sporadic cases in Taiwan had the SCA6 mutation [165].

Value of a genetic diagnosis

At the moment, obtaining a genetic diagnosis is unlikely to alter treatment, so why should patients and their physicians bother? In the case of a familial disorder, testing of other family members may already have established the diagnosis. Many patients and physicians will still want confirmatory genetic testing. In cases in which the diagnosis of other affected family members is unknown, it is a matter for each individual and their physician or genetic counselor to determine the relative value of testing. Advantages of testing, as viewed by the individual patient, may include the relief from the burden of searching for a reversible cause of the disease, the psychological value of having the disease definable as a specific entity rather than as a vague problem, the increased ease of entry into supportive networks of other patients, the ability to roughly predict clinical course, and the ability to predict risk of transmission to the next generation. The primary disadvantage, from the perspective of most patients, is the cost. The current cost at one large commercial laboratory for a panel of tests covering SCA1, 2, 3, 6, 7, 8, 10, 17, Friedreich's ataxia and DRPLA is US$2395. Most of the individual tests are available for around US$350. For some patients, this testing is not covered by insurance. Testing for rare disorders, such as EA1 and EA2, may only be available at research laboratories, while other testing, such as for SCA12, is available at both research and commercial laboratories.

Table 2. Dominant ataxias linked to a locus (gene unknown).

Disease	Linkage	Ethnicity	Primary findings	Frequent findings	Other comments	Ref.
SCA4	16q22.1	US, of Scandinavian ancestry; 6 Japanese families linked to same region	Gait and limb ataxia, axonal sensory neuropathy, hyporeflexia; no neuropathy or hyporeflexia in Japanese cases	Dysarthria, Babinksi, abnormal eye movements, distal weakness	Mean age of onset 39 in US families; 56 in Japanese family	[192–194]
SCA5	11cen	American, French	Ataxia	Nystagmus, myokymia, decreased vibration sense	Slow and relatively benign course	[195,196]
SCA11	15q14-21.3	British	Cerebellar findings	Mild hyper-reflexia and vertical nystagmus	Benign and slowly progressive	[197]
SCA13	19q13.3-13.4	French	Ataxia, motor and developmental delays	Dysphagia, urinary urgency and bradykinesia in older patients	Relatively mild course; appears proximal to SCA14 linkage	[198]
SCA15	3pter-3p24.2	Australian, of anglo-celtic ancestry	Gait and limb ataxia	Abnormal eye movements, lower limb hyporeflexia, tremor	Relatively benign and slow course	[199,200]
SCA16	8q22.1-24.1	Japanese	Gait and limb ataxia, dysarthria, nystagmus	Head tremor	Mean age of onset 40 years	[201]
SCA18/sensory/ motor neuropathy with ataxia	7q22-q32	Irish	Variable; sensory axonal neuropathy, ataxia, other cerebellar signs, pyramidal tract signs, muscle weakness		Onset in mid-teens, slowly progressive	[202]
SCA19	1p21-q21	Dutch	Mild ataxia, pyramidal signs, peripheral neuropathy, cognitive impairment	Myoclonus	Age of onset variable, possible anticipation	[203]
SCA21	Chromosome 7	French	Ataxia, dysarthria, mild cognitive impairment	Tremor, rigidity, hyporeflexia	Onest 6-30 years, possible anticipation	[204]

SCA: Spinocerebellar ataxia.

Testing methodology

Testing for repeat expansion diseases is typically performed with PCR. The size of the PCR product is evaluated with polyacrylamide gel electrophoresis (PAGE), using a radiolabeled primer to generate a radiolabeled product, a radiolabeled (CAG)n or (CTG)n oligonucleotide to probe a Southern blot of the gel, or a fluorescently tagged primer to generate fluorescent products detected by automated Applied Biosystems (ABI; CA, USA) equipment. Capillary electrophoresis is now used in place of PAGE with more recent ABI technology; the change from gels to capillaries necessitates recalibration of the assay, since products with expanded repeats may not run at identical speeds in the two systems. Control samples of known repeat length are essential, especially in interpreting borderline expansions, since repeat expansion may slightly alter the electrophoretic mobility relative to standard-size markers. Even with ideal controls, however, it is unlikely that repeat lengths can be reliably assigned without an error of a least ± 1 triplet. For longer expansions, the ability to precisely define repeat length is even less reliable, though this imprecision has little clinical consequence. Another source of variability in determining repeat length is the presence of multiple bands (on gels) or peaks (automated genotyping), instead of single bands or peaks, for expanded alleles. This represents a combination of PCR artifact and mosaicism in lymphocytes. Standard practice is to use the most prominent peak or band as the reported repeat length but at times distinguishing among the bands/peaks is arbitrary.

Interpretation of test reports

Test reports for expansion mutation diseases will generally provide the repeat length for each of the two copies of the gene in question. If the repeat lengths of each allele both fall well within the normal range, or one allele is within the normal range and the other is well within the expanded range, interpretation is straightforward. However, difficulties in test interpretation may arise in several ways. First, in some patients, only a single repeat will be detected. Usually, this result accurately reflects repeat length homozygosity, especially in SCA2 and SCA6 where heterozygosity of normal allele length is limited. However, detection of a single PCR product may also stem from failure of the PCR assay. One possibility is failure to amplify a very long expansion. This should be suspected in juvenile onset cases, most notably in SCA2, 3 and 7 in which very long expansions have been reported. A second possibility is failure to amplify an allele because of a polymorphism at a site required for primer annealing. This has not been described among the SCAs but five sites have been detected that alter amplification of the HD repeat [166–168]. In either case, a genomic Southern blot will yield a definitive result.

Second, repeat lengths may be detected at the margin of the disease range. This is problematic since laboratory precision is usually only within 1–2 triplets and because disease penetrance may be incomplete at repeat lengths near the pathogenic threshold. As additional patients are tested, the normal and expansion limits have tended to move closer to each other in all of the repeat expansion diseases. For individuals with other affected family members known to carry the same marginal expansion, the diagnosis is usually secure. If sufficient family members are available, linkage analysis can provide additional confirmation. Even if the repeat is at the margin of the expanded range, finding other relatives affected with the disease who also have repeats of similar lengths is strong evidence in support of the causative role of the repeat expansion. Thirdly, opinion differs on the utility of using repeat length as a predictor of course in symptomatic patients or disease onset in presymptomatic patients. It seems appropriate to provide patients with the complete details of the test results but to provide counseling on the limited relationship between repeat length and disease course for the particular individual. Most laboratories have consultative services to assist physicians in interpreting these test results.

Presymptomatic testing

Presymptomatic testing has become fairly routine in HD and is occasionally performed for the dominant ataxias [169]. Guidelines developed for HD apply equally to the SCAs [170,171]. Among other principles, minors should not receive presymptomatic testing, all individuals obtaining presymptomatic testing should receive pretest counseling, and post-test counseling should be available as needed. Commercial laboratories will perform presymptomatic tests, typically after written confirmation that appropriate counseling has been received and with the written, informed consent from the individual undergoing testing. Prenatal diagnosis is possible, though availability is limited [172]. Preimplantation diagnostic testing for HD is available in a few facilities [173] and is certainly feasible for the SCAs, even if not yet performed.

Treatment

There are currently no known treatments to stop the progression of any of the SCAs or related neurodegenerative disorders. A large trial of remacemide (AstraZeneca, London, UK), a noncompetitive N-methyl-D-aspartate receptor antagonist, and coenzyme Q10, a cofactor involved in mitochondrial electron transfer that can function as an antioxidant, in patients with early HD found only an insignificant trend of slower disease progression in patients taking coenzyme Q10 [174]. Transplantation of fetal striata into the striata of HD patients [175] and a trial of idebenone [176] have similarly proven disappointing. Symptomatic treatment of different components of the movement disorders found in SCA patients may prove helpful [177]. These approaches include use of benzodiazepines or B-blockers for intention tremor, and levodopa for parkinsonian syndromes. Acetazolamide and carbamazepine may be helpful for EA1 and EA2 and potentially SCA6 [178]. Branched-chain amino acids may improve motor function in a small group of patients with cerebellar degeneration of various etiologies [179], and transcranial magnetic stimulation of the cerebellum shows promise in alleviating symptoms [180]. Physical and occupational therapy coupled with environmental adaptations are often of major benefit in maintaining function, despite worsening neurological signs and symptoms.

Five-year view

In the next 5 years, it is likely that a number of additional genes that cause dominant SCA will be identified, ultimately making it possible to genetically diagnose 80–90% of cases. Genetic diagnosis itself will probably become less expensive for the repeat expansion diseases as clinical laboratories adopt multiplexing strategies for testing multiple diseases at the same time [181]. The routine adoption of ABI capillary equipment should reduce interlaboratory variability in test results. As more cases of the repeat expansion diseases are found, the prognostic significance of repeat lengths in the gray zone between normal and expanded will become more clear. On the other hand, it is likely that an increasing number of rare SCAs will be shown to result from point mutations. Frequently, many different point mutations in the same gene will cause a disease phenotype, necessitating the sequencing of exons and regulatory units of the gene for diagnosis. This is currently possible but expensive for SCAs such as SCA14 and FGF14-associated SCA. It may prove prohibitively expensive to set up these assays on a commercial basis. However, if sequencing technology continues to improve, this obstacle may substantially diminish.

Much of the excitement in this group of disorders is in the rapid progress of uncovering disease pathogenesis. The goal is to find therapeutic interventions that will lead to slowing, stopping

or preventing disease progression. It is useful to conceptualize advances in therapeutics (and in the understanding of pathogenesis) as moving along two fronts. First, what may be termed upstream therapeutics is the goal of intervening at an early stage of the pathogenic pathway. Examples include blocking the transcription or translation of a toxic mutation or, in the case of the polyglutamine diseases, preventing abnormal protein folding or pathogenic protein cleavage. Many of these strategies will be specific for a particular disease and hence will only be feasible if the disease is sufficiently common to warrant large-scale investment or for those diseases in which a specific defect can be easily identified and remedied (such as phenylketonuria). The other front, which may be termed downstream therapeutics, relies on disruption of pathways of neurodegeneration common to multiple diseases. The advantage here is that strategies developed for common diseases can be applied to rare diseases (and potentially vice-versa). The disadvantage is that finding points of intervention that do not have devastating effects on normal neuronal function has proven difficult.

Over the next 5 years, the advances on both fronts will probably be in the understanding of pathogenesis rather than in novel and effective treatments. For the polyglutamine diseases, it is likely that several trials of agents that slow disease progression in mouse models by 30–40% will begin in the next few years. It is possible that some of these treatments, which are already drugs approved for clinical use, may reach the clinic within 5 years. Major advances in therapy will probably have to wait at least 7–10 years. For the other SCAs, the picture is less clear as therapy that works for polyglutamine diseases may not be effective. Downstream therapeutics have proven elusive, while far upstream manipulations of gene transcription and translation are still in embryonic stages, though promising. It is likely that as therapies slowly emerge, diagnostic testing will take on renewed importance, since the risk–benefit ratio of a given therapy will probably vary by disease.

Conclusion

The discovery of the genetic etiology, or at least locus, for most cases of dominant SCA provides a logical structure to SCA nosology and provides clinicians, investigators and patients with a common language for discussing this group of disorders. It is now possible to conclude that most individuals with a dominant SCA have SCA1, 2, 3, 6 or 7. A large number of other SCAs appear to exist but will most likely prove exceedingly rare, except in isolated populations. Fortunately, the most common SCAs are caused by polyglutamine expansions, which likely share pathogenic pathways with each other and with HD, spinobulbar muscular atrophy and DRPLA. Treatments discovered for any of these may prove beneficial for all and perhaps to patients with other SCAs or other types of neurodegenerative disorders. While there is no treatment to stop the advance of the SCAs, a number of currently available interventions can considerably improve patient quality of life. The recent advances in understanding the SCAs provides much hope that definitive treatments will be found in the not-so-remote future.

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Key issues

- The dominant spinocerebellar ataxias (SCAs) are a heterogenous group of disorders, often involving multiple brain regions.
- It is now possible to find specific mutations that account for at least 70% of cases.
- Tests for the most common mutations are commercially available, though expensive and occasionally hard to interpret.
- No specific treatments exist to stop the underlying disease process.
- Nonspecific treatments to ameliorate the complications of the SCAs are often of considerable value.
- Major progress has been made in understanding disease pathogenesis, especially in the diseases caused by CAG repeat expansions encoding polyglutamine.
- Treatment of the underlying disease process will require a better understanding of disease pathogenesis.
- Interventions will be of two types: upstream and relatively specific to a given disease, or downstream and potentially applicable to many diseases.
- Advances in rare neurodegenerative diseases may provide important leads to the understanding and treatment of the more common neurodegenerative diseases.

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