Autosomal dominant cerebellar ataxias: polyglutamine expansions and beyond

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Cerebellar ataxias with autosomal dominant transmission are rare, but identification of the associated genes has provided insight into the mechanisms that could underlie other forms of genetic or non-genetic ataxias. In many instances, the phenotype is not restricted to cerebellar dysfunction but includes complex multisystemic neurological deficits. The designation of the loci, SCA for spinocerebellar ataxia, indicates the involvement of at least two systems: the spinal cord and the cerebellum. 11 of 18 known genes are caused by repeat expansions in the corresponding proteins, sharing the same mutational mechanism. All other SCAs are caused by either conventional mutations or large rearrangements in genes with different functions, including glutamate signalling (SCA5/*SPTBN2*) and calcium signalling (SCA15/16/*ITPR1*), channel function (SCA13/*KCNC3*, SCA14/*PRKCG*, SCA27/*FGF14*), tau regulation (SCA11/*TTBK2*), and mitochondrial activity (SCA28/*AFG3L2*) or RNA alteration (SCA31/*BEAN-TK2*). The diversity of underlying mechanisms that give rise to the dominant cerebellar ataxias need to be taken into account to identify therapeutic targets.

Introduction

The autosomal dominant cerebellar ataxias (ADCAs) are a rare cause of cerebellar ataxia. Most cases of cerebellar ataxia are sporadic, and diagnostic work-up remains a challenge.[1,2] The ADCAs, referred to as spinocerebellar ataxias (SCAs) in genetic nomenclature, are a group of inherited neurological disorders that are clinically and genetically very heterogeneous. They are progressive neurodegenerative diseases that are characterised by cerebellar ataxia, resulting in unsteady gait, clumsiness, and dysarthria. The cerebellar syndrome is often associated with other neurological signs such as pyramidal or extrapyramidal signs, ophthalmoplegia, and cognitive impairment.[3] Onset is usually during the third or fourth decade of life, but can occur in childhood or old age. Atrophy of the cerebellum and brainstem are most often the prominent features, but other structures can be affected, leading to a substantial range of phenotypes.[4]

ADCAs were thought to be exclusively due to expansions of coding CAG repeats, as in the genes that underlie SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, and DRPLA (dentatorubro-pallidoluysian atrophy)—the so-called polyglutamine expansion SCAs. The polyglutamine expansion SCAs share a mutational mechanism with other polyglutamine expansion diseases, such as Huntington disease[5] and spinal bulbar muscular atropy,[6] and perhaps a pathogenic process, even though most of the proteins involved in polyglutamine expansion diseases have unknown or unrelated functions.[7] These disorders manifest above a threshold of CAG repeats that varies depending on the gene. When large and uninterrupted, the CAG repeats are unstable on transmission and result mostly in expansions, particularly during paternal transmissions.[8,9] Correlations between phenotype and genotype in the polyglutamine expansion SCAs have shown that differences in repeat size contribute to variation in disease progression and severity and to some of the clinical differences between patients. The same pathogenetic mechanism applies to SCA subtypes caused by more recently discovered expansions in non-coding regions of genes for SCA10,

SCA12, and SCA31—the so-called non-coding-expansion SCAs. The discovery of conventional mutations in some patients with ADCA—the conventional mutation SCAs—in addition to those with dynamic repeats, expands the variety of pathophysiological causes of ADCAs (table 1). Therefore, the different forms of dominantly inherited SCAs, which can no longer be grouped together as polyglutamine expansion disorders, need to be distinguished. This Review will focus on the clinical features of SCAs caused by polyglutamine expansions, non-coding expansions, and rare conventional mutations in SCA genes, and similarities and differences in the phenotypes and underlying pathophysiology between these SCA subtypes will be discussed.

Epidemiology of ADCA subtypes

Between one and three per 100 000 Europeans have ADCA. Polyglutamine expansion SCAs are more frequent than are other forms of SCA, and SCA3 is the most frequent subtype.[8] A mean of 44% (SD 25, ranging from 1% to 90% depending on geographical origin) of ADCA cases are still unaccounted for by the genes tested in many series (webappendix). However, in most series, only genes for SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17 were tested. There are founder effects in the genes for SCA2 (40/100 000 cases) in Cuba[10] and SCA3 in Portugal.[11,12] The relative frequency of SCA3 is high in Brazil (69% of cases),[13] Portugal (58%),[11,12] China (49%),[14] Japan (26–63%),[15–17] the Netherlands (28%),[18] and Germany (42%);[19] lower in France (20%),[20] Canada (24%),[21] and the USA (21%);[22] and rare in India (3%),[23] Norway (4%),[24] and Italy (1%).[25] In France, the most frequent mutations in 826 index cases were in genes for SCA3 (20%), SCA2 (10%), SCA1 (8%), SCA7 (6%), and SCA6 (2%; figure 1). Missense mutations in the genes for SCA14 (2%), SCA28 (2%), SCA13 (1%), and SCA5 (1%) were less frequent. SCA17 and SCA12 are very rare (<1%), and no cases of SCA10 or SCA27 were identified.[20] Heterozygous deletions were detected in patients with SCA15/16 (four of 76 cases), and a nonsense mutation was detected in a patient with SCA11 (one of

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	Gene	Mutations	Key symptom in addition to cerebellar ataxia
Polyglutamine expansions SCAs			
SCA1	ATXN1	CAG repeat	Early swallowing and respiratory signs
SCA2	ATXN2	CAG repeat	Slow eye movements
SCA3	ATXN3	CAG repeat	..
SCA6	CACNA1A	CAG repeat	..
SCA7	ATXN7	CAG repeat	Visual loss
SCA17	TBP	CAG repeat	Dementia
DRPLA	ATN1	CAG repeat	Epilepsy
Non-coding expansion SCAs			
SCA8	ATXN8 and ATXN8OS	CTG repeat	..
SCA10	ATXN10	ATTCT	..
SCA12	PPP2R2B	CAG repeat	..
SCA31=16qlinked	BEAN-TK2	TGGAA repeat	..
Conventional mutations SCAs			
SCA5	SPTBN2	Missense, in-frame deletion	..
SCA11	TTBK2	Frameshift	..
SCA13	KCNC3	Missense	Mental retardation
SCA14	PRKCG	Missense	Myoclonus
SCA15/16	ITPR1	Missense, deletion	..
SCA20	..	Duplication	Dysphonia
SCA27	FGF14	Missense, frameshift	..
SCA28	AFG3L2	Missense	Ptosis
Loci (test unavailable)			
SCA4	..	..	Sensory neuropathy
SCA18	..	..	Sensory neuropathy
SCA19	..	..	..
SCA21	..	..	Mental retardation
SCA22	Allelic to SCA19?	..	Mental retardation
SCA23	..	..	..
SCA25	..	..	Sensory neuropathy
SCA26	..	..	..
SCA30	..	..	..

SCA=spinocerebellar ataxia. ..=unknown.

Table 1: Genes and mutations that cause autosomal dominant cerebellar ataxias, according to locus and mutation type

77 cases) in a subgroup of negatively screened patients.[26] SCA10 is frequent in Brazil.[27]

Polyglutamine expansion SCAs

The polyglutamine expansion SCAs caused by translated CAG repeat expansions are the most well studied group of ADCAs. They share the same mutation, a CAG repeat, which manifests above a threshold of CAG repeats that varies according to the gene—usually above 37–40 repeats, but repeats are much smaller in the gene for SCA6 (>19)[28] and much larger for SCA3 (>51).[29]

Clinical features

Polyglutamine expansion SCAs are neurodegenerative disorders with diffuse neurological dysfunction, leading to death by brainstem failure. The mean age at onset of polyglutamine expansion SCAs is generally in the third or fourth decade of life, and is mainly, but not only, determined by the number of CAG repeats in the corresponding gene.[8] To become pathological, the number of CAG repeats has to reach a specific threshold, and the size of the CAG repeat and the age at onset are negatively correlated—ie, the longer the repeat the earlier the age at onset.[8,9] The pathological repeat size in SCA7 causes 88% of the variability in age at onset,[30] whereas in SCA2 the repeat size causes only 57% of the variability.[31] Small but important contributions of the normal polymorphic expansion on the unaffected allele have been identified in SCA1, SCA3, and SCA6.[32,33] Longer normal CAG repeats in non-causal genes can also have a minor role—eg, the gene for SCA6 contributes 5·8% of variance in age at onset in SCA2.[31] Somatic mosaicism—ie, tract length heterogeneity in the brain—plays a key part, as shown in SCA1[34] and SCA3.[35] In Huntington's disease, age at onset varied according to the different sizes of the CAG repeats in the cortex in two patients with identical CAG repeats in the peripheral blood.[36]

Gait disorders are the initial symptom in two-thirds of all patients with SCA.[37] Double vision, dysarthria, impaired handwriting, and episodic vertigo each precede ataxia in 4% of patients.[37] With disease duration, the clinical picture becomes increasingly complex, and this corresponds to the wide distribution of the underlying neuropathology.[4] As with age at onset, the clinical picture of polyglutamine expansion SCAs depends on the length of the CAG repeat expansion (table 2).[38] In DRPLA, for example, longer repeats are associated with a phenotype that is characterised by progressive myoclonus, epilepsy, and dementia, whereas smaller repeats result in a high frequency of choreic movements and psychiatric manifestations in adults.[39,40] In patients with SCA3, the frequency of pyramidal signs increases with the size of the expanded repeat, whereas the frequency of altered vibration sense decreases.[38,41] In patients with SCA7, the frequency of decreased visual acuity, ophthalmoplegia, and Babinski signs increases with the number of CAG repeats.[30]

Diverse abnormal eye movements are frequently associated with polyglutamine expansion SCAs. In SCA1, saccade amplitude is increased, resulting in hypermetria and decreased smooth pursuit gain; in SCA2, saccade velocity is substantially decreased and the percentage of errors in antisaccades is high; in SCA3, gaze-evoked nystagmus and hypometric saccades are often present, and smooth pursuit gain decreases greatly.[42] In SCA6, downbeat nystagmus is frequent,[43] and eye movements (gaze-evoked nystagmus, saccadic pursuit, hypometric saccades, and normal saccade velocity) are similar to those observed in patients with SCA3.[44]

With use of multinomial logistic regression analysis, hyper-reflexia and spasticity predicted 38% of patients to have SCA1, 33% SCA7, and 26% SCA3.[45] However, for other SCA types, the presence of pyramidal signs was a weak predictor of SCA2 (4%) and not a predictor of SCA4,

SCA5, SCA6, and SCA8.[45] In a large study in 17 centres of 526 patients with SCA1, SCA2, SCA3, or SCA6, pyramidal signs (67%) and brainstem oculomotor signs (74%) were most frequently associated with the cerebellar syndrome in SCA1, whereas peripheral nerve involvement was most frequent in SCA2 (68%). 24% of patients with SCA3 had dystonia.[46] In SCA7, a decrease in visual (83%) and auditory (24%) acuity was the predominant sign of the disease.[30] No clinical tests can accurately distinguish between the different polyglutamine expansion SCAs, but these forms of SCA can be distinguished from other SCA subtypes.[45]

Genetic anticipation

In dominant disease, the clinical observation of younger ages at onset and increasing severity in successive generations is referred to as genetic anticipation. Variability in age at onset, especially the anticipatory decrease in age at onset in successive generations, is regarded as a hallmark of polyglutamine expansion SCAs. The discovery that the CAG repeat length changes in size during transmission—ie, germline mosaicism—is the molecular explanation for this finding. Whereas normal alleles are transmitted to offspring without modification, pure expanded alleles are unstable and the number of CAG repeats tends to increase during transmission (eg, +0·5 CAG repeats in SCA3 and +12 CAG repeats in SCA7).[9] Paternal expansions are more likely to be unstable during transmission. This paternal bias is often attributed to the increased number of mitotic divisions preceding male gametogenesis, but could also be attributable to alterations in the activity and concentration of DNA repair proteins.[47]

Juvenile onset is associated with large expansions, and mostly with paternal transmission. The frequency of such expansions indicates the extent of intergenerational instability and consequently anticipation, and is 45% in DRPLA,[40] 43% in SCA7,[48] 35% in SCA2,[9] 30% in SCA17,[49] 15% in SCA1,[50] and 8% in SCA3.[51] No expansions have been recorded in SCA6.

Even in polyglutamine expansion SCAs, the anticipation observed is often greater than expected from the correlation between CAG repeat and age at onset. For example, the mean anticipation of 20 years recorded in 26 parent-child couples with SCA2 is larger than the 12-year anticipation expected from the observed mean increase of 3·7 CAG repeats, measured from the slope of the regression line.[52] Anticipation is most evident in DRPLA and SCA7, with a mean increase of 12 CAG repeats in SCA7.[9] In SCA7, de-novo expansions from large normal alleles have also been documented.[53–55] By contrast with polyglutamine expansion SCAs, the non-coding expansion subtype SCA10 is characterised by a younger age at onset, which is associated with smaller repeats.[56] Anticipation of age at onset is therefore the result of molecular instability, but is also an unavoidable source of observation bias. Because longer disease
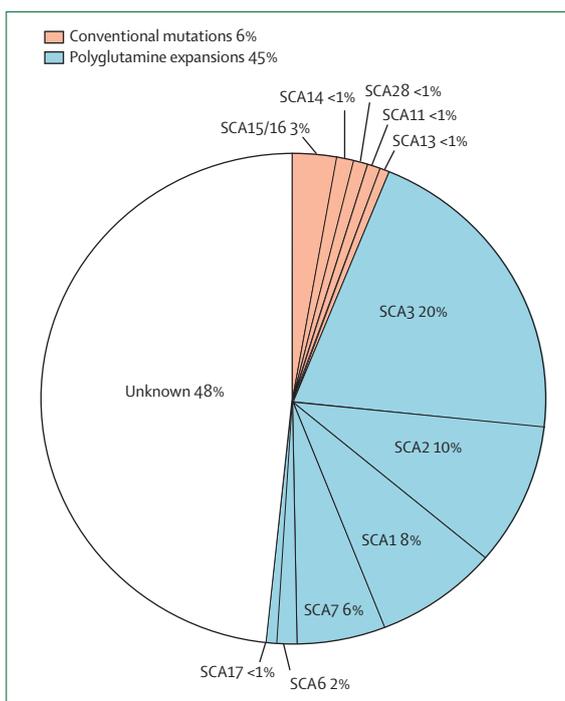

Figure 1: **Relative prevalence of SCA subtypes of autosomal dominant cerebellar ataxia**
826 index patients, mostly of French origin, were studied. Data from reference 20.

durations are associated with greater differences between the estimated age at onset in the patient and in offspring,[37] the presence of anticipation related to repeat expansions can be overestimated, as in the conventional mutation subtype SCA5.[57]

Non-coding expansion SCAs

In addition to the CAG repeat expansions, untranslated expansions can cause disease through a gain of function mechanism, triggered by the accumulation of transcripts containing expanded CUG or CCUG repeats. A gain in RNA function might have a role, but other mechanisms have also been proposed.[58]

SCA8 was the first ADCA caused by an untranslated CTG expansion to be described.[59] The phenotype is cerebellar ataxia with mild gait spasticity and global cerebellar atrophy.[60,61] Bidirectional expression of CUG and CAG expansions bring about the disease. Intranuclear inclusions were noted in Purkinje cells and pontine neurons in patients with SCA8, as in polyglutamine expansion SCAs.[62,63] The diagnosis, which is based on the CTG expansion, remains controversial because there is no correlation between repeat length and penetrance;[64,65] repeats have been noted in controls and patients with other diseases.[66–69] Therefore, genetic counselling of at-risk family members should take into account these uncertainties.

SCA10 is caused by expansion of an ATTCT pentanucleotide repeat in intron 9 of the *ATXN10* gene on chromosome 22q13.3. The pathological repeats range

	Small repeat	Medium repeat	Large repeat	Very large repeat
SCA1	..	Cerebellar ataxia, pyramidal syndrome	Amyotrophic lateral sclerosis-like disorders	Developmental delay
SCA2	Postural tremor	Cerebellar ataxia, decreased reflexes	Cerebellar ataxia, chorea, dementia	Myoclonus, dystonia, cardiac failure, retinal degeneration
SCA3	Axonal neuropathy, dopa-responsive parkinsonism	Cerebellar ataxia, diplopia	Dystonia, pyramidal signs	Rare cases, predominant dystonia
SCA6	Episodic ataxia	..	Few associated signs after 10-years of disease course	..
SCA7	Cerebellar ataxia without visual loss	Cerebellar ataxia, macular degeneration	Visual loss before cerebellar syndrome	Cardiac failure
SCA17	Huntington's disease-like phenotype, parkinsonism	Ataxia, dementia, chorea and dystonia, pyramidal signs	Ataxia, dementia, spasticity, epilepsy	Growth retardation
DRPLA	Chorea, ataxia, psychiatric manifestations	..	Progressive myoclonus, epilepsy, developmental delay, mild ataxia	Myoclonic epilepsy, chorea, cognitive impairment

..=unknown. SCA=spinocerebellar ataxia. DRPLA=dentatorubro-pallidoluysian atropy.

Table 2: Clinical features in polyglutamine expansion SCAs, according to size of CAG repeat

from 28 to 4500,[56] and the disease is characterised by slowly progressive ataxia, without brainstem involvement. Experiments on somatic hybrid cell lines have shown that the mutation does not interfere with the level of transcription or RNA processing.[70] This observation, which disproves a simple gain or loss of function mechanism, is supported by recent studies focusing on the genomic effect of the mutation; expansion of the pentanucleotide repeat causes DNA unpairing in yeast[71] and in human cell lines,[72] creating ectopic DNA replication origins and genomic instability.[73] Thus, SCA10 could be related to abnormalities in chromatin structure caused by the expansion, and not to an abnormal *ATXN10* or to haploinsuffiency.[74]

SCA12 is caused by a CAG repeat expansion in the non-coding region of the *PPP2R2B* gene.[75] It encodes Bβ2—a neuron-specific protein phosphatase 2A PP2A regulatory subunit. Dysregulation of mitochondrial morphogenesis is thought to be the underlying pathophysiological mechanism.[76] Ages at onset range from 8 years to 55 years. In most individuals, symptoms appear in the fourth decade of life, with tremor in the upper extremities, and progress over several decades to include head tremor, gait ataxia, dysmetria, dysdiadokinesis, hyper-reflexia, paucity of movement, abnormal eye movements, and dementia in the oldest patients. So far, SCA12 has been found exclusively in Indian people (webappendix).

SCA31 was previously called chromosome 16q22.1-linked ADCA.[77] An insertion consisting of a complex pentanucleotide repeat including a long (TGGAA)n stretch has been noted in introns of thymidine kinase 2 (TK2). In controls, shorter (1·5–2·0 kb) insertions without the (TGGAA)n repeat have been recorded. This cerebellar ataxia, which has a late age of onset (mean 60 years), is associated with hearing impairment. The Purkinje cells are predominantly affected. However, the relative frequency, with respect to the TGGAA repeat, has not yet been established.

Conventional mutation SCAs

The fastest growing group of known ADCAs is those attributable to conventional, often private, mutations in the associated genes. Screening of these genes is costly and time consuming. Furthermore, interpretation of the identified change and proof of its pathogenicity can be difficult. Only a few families have been identified with some of these mutations, so correlations between phenotype and genotype are difficult to generate.

In 1994, the gene for SCA5 was assigned to the centromeric region of chromosome 11 in one large American family.[57] The age at onset in families with SCA5 ranges from 10 years to 68 years, and patients who present with a slowly evolving cerebellar ataxia are still able to walk even after more than 20 years of disease. Patients with SCA5 have global cerebellar atrophy that affects both the cerebellar vermis and hemispheres, but does not affect regions of the brainstem and the cerebrum.[78] Three different mutations have been identified in the *SPTBN2* gene encoding β-III spectrin: a 39-bp deletion in exon 12 leading to an in-frame deletion in one of the spectrin repeat domains (Glu532_Met544del), a 15-bp deletion in exon 14 in the same spectrin repeat (Leu629_Arg634delinsTrp), and a 758T→C transition in exon 7 leading to a missense mutation (Leu253Pro) in the calponin homology domain.[79]

A large British family with SCA11 has been reported to carry a mutation in the *TTBK2* gene.[80] In these patients, there was a nearly complete loss of Purkinje cells, and tau pathological changes were visible in the basal ganglia, midbrain, and medulla. The phenotype was consistent with a slowly progressive, benign cerebellar syndrome, with mild hyper-reflexia and vertical nystagmus. Ages at onset ranged from 15 years to 70 years. After more than 20 years of disease duration, no patient was unable to walk and no dementia was noted.[81] An identical frameshift mutation was recorded in two unrelated families (1306_1307delGA), with an almost pure cerebellar syndrome and healthy life expectancy.[82]

Mutations in the voltage-gated potassium channel KCNC3 (Kv3.3) lead to SCA13.[83] Two different mutations, each segregating in a large family, have been identified. A 10767T→C (Phe448Leu) mutation segregated with affected individuals in a French family with early-onset ataxia has been identified.[83,84] The mutated protein is located at the cytoplasmic end of the channel pore and affects gating by increasing the relative stability of the open conformation. KCNC3 phenotypes range from developmental disorders to adult-onset neuro-degeneration, and there is a correlation between genotype and phenotype based on channel dynamics.[85] Of interest is the developmental phenotype, in which childhood-onset ataxia is associated with mild mental

retardation (IQ ranging from 62 to 76), seizures, and facial dysmorphia.[84]

The SCA14 locus was first mapped to chromosome 19q, and *PRKCG*—which encodes protein kinase Cγ (PKCγ)—was identified as the underlying gene.[86–88] PKCγ belongs to a subgroup of serine and threonine kinases. It is strongly expressed in the brain, particularly in Purkinje cells, and is thought to have an important role in signal transduction, cell proliferation, and synaptic transmission. The phenotype is associated with slowly progressive cerebellar ataxia, with a wide range of ages at onset. The cerebellar syndrome is variably associated with hyper-reflexia,[88,89] axial or peripheral myoclonus, focal dystonia, and cognitive decline.[90] So far, missense mutations, an in-frame deletion, and a possible splice-site mutation have been reported.

Deletions in the *ITPR1* gene, encoding the inositol-triphosphate receptor type 1, have been identified in SCA15 and SCA16. Deletions were reported initially in three families with SCA15, then in two Japanese families who were previously thought to have a distinct disease, SCA16;[91–93] a missense mutation was identified in another Japanese family.[91] Therefore, SCA15 and SCA16 are the same disease.[94] The phenotype in SCA15/16 families is a slowly progressive pure cerebellar ataxia.[26]

A 260-kb duplication has been noted within the region on chromosome 11q12 that was previously linked to SCA20. The phenotype is associated with dysphonia and palatal myoclonus that is similar to that noted in Alexander disease.[95] The age at onset of the disease ranges from 19 years to 64 years. Dentate nucleus calcification is a feature of this disease.[96]

A Dutch pedigree with ADCA was reported to carry a Phe145Ser mutation in the *FGF14* gene on chromosome 13q34.[97] A missense and a nonsense mutation in *FGF14* were previously linked to SCA27. The patients had childhood-onset postural tremor and a slowly progressive ataxia evolving from young adulthood. Moderate cerebellar atrophy and low IQ, memory deficits, and executive dysfunction characterise the phenotype. However, this *FGF14* mutation seems to be very rare.[98]

AFG3L2 has been identified as the causative gene for SCA28, previously linked to chromosome 18p11.22-q11.2.[99] *AFG3L2* is a mitochondrial metalloprotease that assembles in the m-AAA hexameric complex with the homologous protein paraplegin (SPG7). SCA28 begins in early to mid-life and is associated with cerebellar ataxia with hyper-reflexia of the lower limbs, ophthalmoplegia, and ptosis. A haploinsufficient mouse model of *AFG3L2*, with respiratory chain dysfunctions in Purkinje cells, mimics the disease.[100]

Polyglutamine expansion SCAs versus conventional mutation SCAs

Clinical features

ADCAs caused by conventional mutations (SCA5, SCA11, SCA13, SCA14, SCA15/16, SCA20, SCA27, and SCA28) are less frequent than are polyglutamine expansion

	Polyglutamine expansion SCAs	Conventional mutation SCAs
Age at onset	Variable (intrafamilial); anticipation	Variable (often in childhood); no anticipation
Disease progression	Progressive, often fatal and juvenile cases are more severe than late-onset cases	Slowly progressive, childhood onset is not associated with a more severe disease course
Clinical features	Multisystemic, neurodegenerative widespread lesions that increase with disease duration	Pure cerebellar, congenital features such as stable mental retardation
Neuropatholgy	Widespread neuronal loss	Predominant Purkinje cell loss
Cerebral imaging	Brainstem>cerebellar atrophy	Pure and global cerebellar atrophy

SCA=spinocerebellar ataxia.

Table 3: **Phenotypic differences between autosomal dominant cerebellar ataxias caused by polyglutamine expansions and conventional mutations**

ADCAs.[20] The overall phenotype of patients with conventional mutations differs from that of patients with polyglutamine expansions (table 3). Polyglutamine expansion SCAs can lead to substantial neurological dysfunction and are fatal, whereas lifespan is healthy in patients with conventional mutation SCAs. Onset is most often in childhood, but the disease is not as severe as would be expected in an infantile or juvenile patient with a polyglutamine expansion SCA (table 2). The disease progresses little if at all in these patients compared with those with polyglutamine expansion SCAs. This finding has been noted in SCA5,[57,78] SCA13,[84] and SCA14, in which only one of 14 patients needed support to walk after 22 years of disease.[90] Patients with SCA11 have a healthy life expectancy, with a mean age at death of 71 years; no patients using a wheelchair have been reported.[81] This finding contrasts with SCA7, for which the mean age at death is 42 years.[30] SCA15/16 is also very slowly progressive,[26] as is SCA27.[98] The most striking feature is the frequent childhood onset in all conventional mutation SCAs, but without rapid progression as recorded in extreme cases of juvenile onset in polyglutamine expansion SCAs (table 3).

In addition to slow progression and early onset, mental retardation without cognitive deterioration is noted in SCA13.[84] Developmental delay that improved during the first years of life has been described, suggesting a congenital disease course. This finding contrasts with the progressive subcortical dementia recorded in patients with large CAG repeats at the loci for SCA1, SCA2, and SCA7,[30,52,101] a finding that is independent of the size of the CAG repeat in the gene for SCA17.[49] Cerebellar involvement in cognitive function needs further study; of the pure cerebellar forms of SCA, cognitive impairment has been reported in SCA14 and SCA6, and this did not increase proportionally with severity of cerebellar atrophy.[90,102]

Imaging and pathology

Cerebellar atrophy is the hallmark of the cerebellar ataxias, but in polyglutamine expansion SCAs, vermian atrophy is often the only notable change in the cerebellum.

In polyglutamine expansion SCAs, pontine atrophy can predominate, especially in SCA1, SCA2, and SCA7.[103] In an MRI study, patients with SCA1 and SCA3 presented with severe atrophy throughout the entire brainstem (midbrain, pons, and medulla), cerebellar hemispheres and cerebellar vermis, putamen, and caudate nucleus.[104] Atrophy in the cerebellar hemispheres was less severe in SCA3 than in SCA1 and SCA6.[104] In conventional mutation SCAs, isolated cerebellar atrophy without brainstem involvement was reported for SCA5,[78] SCA11,[81] SCA13,[83,84] and SCA14.[90] The atrophy also spares the brainstem in SCA8[57] and SCA10,[27] and both the cortex and cerebellum in SCA12.[75] This finding is indicative of the underlying neuropathological lesions. All patients with polyglutamine expansion SCA have brainstem lesions;[4] Purkinje cells are affected, but not in SCA3 and DRPLA, and most patients have neuronal loss in the basal ganglia. The hallmark of polyglutamine expansion SCAs, intranuclear neuronal inclusions, is not seen in patients with conventional mutations.

Intranuclear inclusions are present in regions of the brain in which neuronal loss is not observed, suggesting that the pathogenetic effects of polyglutamine expansions are more widespread than was previously recognised. Cell loss is most widespread in SCA1, with predominant atrophy of cranial nerves and Purkinje cell loss in the cerebellum.[4] In SCA2, atrophy of the pons, the inferior olive, substantia nigra, and the cerebellum are key features, but cell loss in the cortex is also reported. In SCA3, lesions of the basal ganglia and the intermediolateral column and Clarke's column are severe.[4,33]

In conventional mutation SCAs, the brainstem seems to be spared. In SCA11, there is gross atrophy of the cerebellum due to severe loss of Purkinje cells, and a substantial loss of cerebellar granule cells. Neuro-fibrillary tangles, neuropil threads, and tau-positive neurites were visible in the medullary tegmentum, substantia nigra, midbrain tegmentum and tectum, and putamen, but not in the cerebellum.[80] In SCA23, there is neuronal loss in the Purkinje cell layer, dentate nuclei, and inferior olives, thinning of cerebellopontine tracts, and demyelination of posterior and lateral columns in the spinal cord, but no brainstem pathological changes are reported.[105]

A cerebral MRI study[104] showed that clinical dysfunction correlated best with the atrophy of the pons in SCA1, total brainstem atrophy in SCA3, and atrophy of the cerebellum in SCA6. The sagittal MRI scans in figure 2 show involvement of the cerebellum in polyglutamine expansion and conventional mutation SCAs. In conventional mutation SCAs such as SCA5, SCA13, and SCA14, the atrophy is more evident than in polyglutamine expansion SCAs, but remains limited to the cerebellum. By contrast, in the polyglutamine
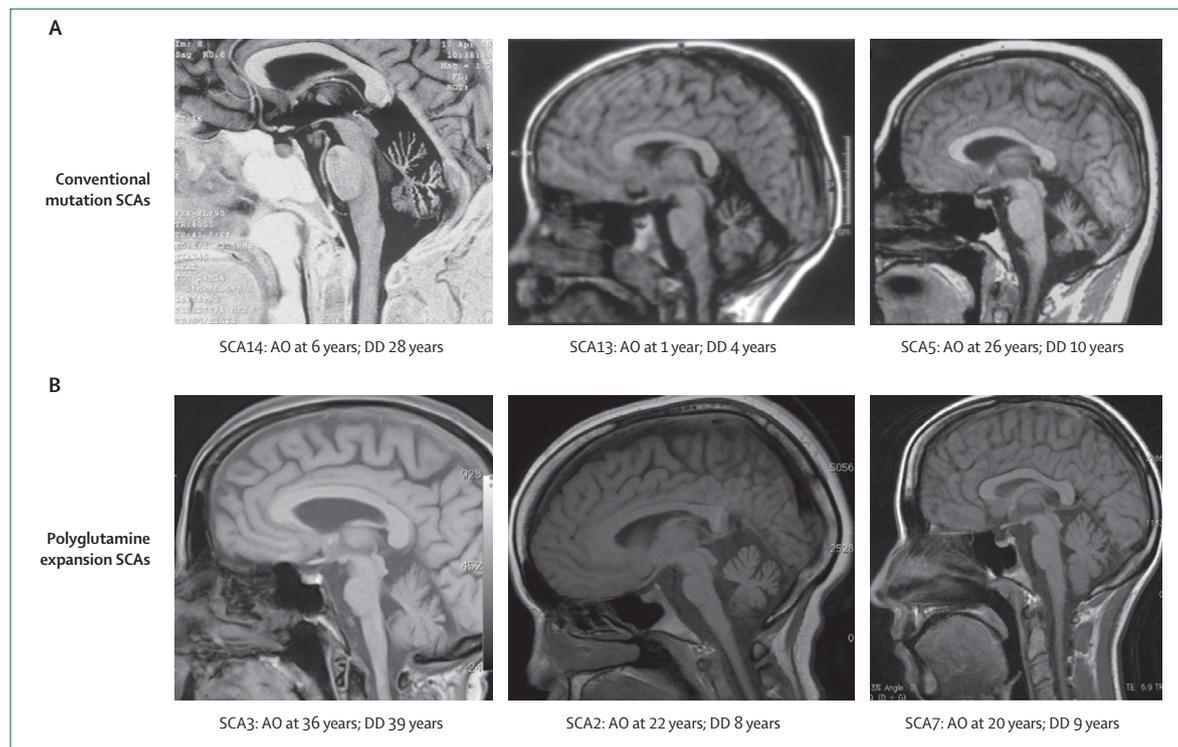

Figure 2: **Differences in cerebellar involvement on MRI between polyglutamine expansion SCAs and conventional mutation SCAs**
Sagittal MRI scans showing the involvement of the cerebellum only in conventional mutation SCAs (SCA5, SCA13, SCA14; A) and the brainstem with relatively minor involvement of the cerebellum in polyglutamine expansion SCAs (SCA2, SCA3, SCA7; B) in patients with comparable disease durations. SCA=spinocerebellar ataxia. AO=age at onset. DD=disease duration.

	Polyglutamine expansion SCAs	Non-coding expansion SCAs	Conventional mutation SCAs
Toxic accumulation of aggregates and intranuclear inclusions	SCA1/ATXN1, SCA2/ATXN2, SCA3/ATXN3, SCA7/ATXN7, SCA17/TBP, DRPLA/ATN1	SCA8/ATXN8	..
Transcription interference	SCA3/ATXN3, DRPLA/ATN1, SCA7/ATXN7, SCA17/TBP	..	..
Calcium homoeostasis	SCA2/ATXN2, SCA6/CACNA1A	..	SCA5/SPTBN2, SCA14/PRKCG, SCA13/KCNC3, SCA15/16/ITPR1, SCA27/FGF14
Glutamate transmission	SCA1/ATXN1, SCA3/ATXN3, DRPLA/ATN1, SCA7/ATXN7, SCA17/TBP	..	SCA5/SPTBN2
Mitochondrial dysfunction	SCA2/ATXN2, SCA6/CACNA1A, SCA7/ATXN7, DRPLA/ATN1	SCA12/PPP2R2B	SCA28/AFG3L2
RNA alterations	SCA1/ATXN1, SCA2/ATXN2, SCA7/ATXN7	SCA8/ATXN8, SCA31/BEAN-TK2	..
Chromatin structure abnormalities	SCA7/ATXN7	SCA10/ATXN10	..
Toxic accumulation of aggregates and RNA foci	..	SCA8/ATXN8, SCA10/ATXN10	..
Cytoskeletal abnormalities, axonal transport deficits	..	..	SCA5/SPTBN2
Tau phosphorlyation	..		SCA11/TTBK2
Potassium-channel dysfunction	..	..	SCA13/KCNC3

SCA subtypes and underlying genes are given. SCA=spinocerebellar ataxia.

Table 4: Pathophysiological mechanisms involved in autosomal dominant cerebellar ataxias

expansion SCA subtypes SCA2, SCA3, and SCA7, atrophy clearly predominates in the brainstem. Nevertheless there is some overlap—eg, SCA6 resembles conventional mutation SCAs, since it is not associated with early death or brainstem atrophy, and less often with non-cerebellar features.[44] SCA6 has the lowest threshold for pathological CAG expansions and involves a channel dysfunction as in the conventional mutation SCAs (such as in SCA13).

Pathophysiological links between polyglutamine expansion and non-polyglutamine expansion SCAs

Several types of dysfunction have been reported to cause SCAs, some of which are summarised in table 4. A link between the polyglutamine expansion and non-polyglutamine expansion SCAs is the formation of inclusions or aggregates. Coding CAG repeat expansions produce abnormally long tracts of glutamine residues with a toxic gain of function, whereas repeat expansions in untranslated regions might change the level of transcription of the gene or produce toxic RNA transcripts containing expanded ribonucleotide triplets.[7,58,106] Dysfunctional regulation of calcium homoeostasis has been described in the polyglutamine expansion subtypes SCA2[107] and SCA6[108] and the conventional mutation subtypes SCA14[109] and SCA15/16, the latter involving a gene encoding ITPR1 that is coupled to calcium channels. Defects in glutamate transmission are involved in SCA5 and SCA1, and perhaps other SCAs.[106] β-III spectrin is highly expressed in Purkinje cells and might play a part in stabilisation of the Purkinje cell-specific glutamate transporter *EAAT4* in the plasma membrane. This gene is also downregulated in the mouse model of SCA1. This downregulation is the earliest known effect of mutant ataxin-1, and occurs before any pathological changes are detectable.[110] Mitochondrial dysfunction is common in both groups. The gene underlying SCA28 encodes AFG3L2—a mitochondrial metalloprotease that is part of the m-AAA hexameric complex along with the homologous protein paraplegin.[99] Mitochondrial dysfunction is clinically evident in SCA7, in which cone-rod dystrophy and hearing impairment are associated with activation of the mitochondria-mediated apoptotic cascade.[111] In SCA2, the mitochondrial complex I gene polymorphism (10398G) is associated with early onset.[112] The similarities and differences in the pathophysiology of the groups of SCAs help to improve understanding of the features of the diseases, which are widespread in polyglutamine expansion SCAs, and more specific, mainly related to the cerebellum, in conventional mutation SCAs.

Conclusions

When should a patient with progressive cerebellar ataxia be tested for SCAs? The patient should have a family history of the disease before genes associated with ADCAs are tested. Repeat expansions in SCA1, SCA2, and SCA3 cause about 40–80% of autosomal dominant cerebellar ataxias, depending on the population (webappendix). These expansions can be searched for in sporadic cases, especially if the family history is unknown (eg, if the patient is adopted), the parents died before reaching the age at onset of the disease (censor effect), or if there is a phenotype of early-onset ataxia and macular degeneration (marked anticipation or neomutation in SCA7). Another indication is late onset of disease, since age at onset greater than 50 years was associated with SCA6 in 59% of patients.[106] Nevertheless, the experience of a diagnostic laboratory shows that only one of 346 sporadic cases had an expansion, whereas 28% of familial cases had abnormal

expansions in one of the polyglutamine expansion SCAs (Cazeneuve C, AP-HP, Salpêtrière Hospital, Paris, France, personal communication). Alleles with low repeat numbers have been identified in sporadic cases of SCA6 and SCA17.[1] In conventional mutation SCAs, mutations are scattered throughout the genes, so that direct mutational analysis can be very costly and time consuming. Further studies, with global techniques such as whole exome sequencing including all the genes that can be tested in sporadic cases, are awaited.

The phenotypic differences between polyglutamine expansion SCAs and conventional mutation SCAs are intriguing (table 3). The progression of the diseases clearly differs—a severe, disabling, life-threatening course of the disease in polyglutamine expansion SCAs contrasts with a slowly progressive course, despite an early onset, in conventional mutation SCAs. Therefore, the therapies offered to patients in the two groups will differ. These therapies should take into account the importance of the cerebellar lesions in the diseases, which are greater in conventional mutation SCAs than in polyglutamine expansion SCAs, in which the pathological changes are more diffuse.

Conflicts of interest
I have no conflicts of interest.

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