Spinocerebellar ataxia

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Abstract | The spinocerebellar ataxias (SCAs) are a genetically heterogeneous group of autosomal dominantly inherited progressive disorders, the clinical hallmark of which is loss of balance and coordination accompanied by slurred speech; onset is most often in adult life. Genetically, SCAs are grouped as repeat expansion SCAs, such as SCA3/Machado–Joseph disease (MJD), and rare SCAs that are caused by non-repeat mutations, such as SCA5. Most SCA mutations cause prominent damage to cerebellar Purkinje neurons with consecutive cerebellar atrophy, although Purkinje neurons are only mildly affected in some SCAs. Furthermore, other parts of the nervous system, such as the spinal cord, basal ganglia and pontine nuclei in the brainstem, can be involved. As there is currently no treatment to slow or halt SCAs (many SCAs lead to premature death), the clinical care of patients with SCA focuses on managing the symptoms through physiotherapy, occupational therapy and speech therapy. Intense research has greatly expanded our understanding of the pathobiology of many SCAs, revealing that they occur via interrelated mechanisms (including proteotoxicity, RNA toxicity and ion channel dysfunction), and has led to the identification of new targets for treatment development. However, the development of effective therapies is hampered by the heterogeneity of the SCAs; specific therapeutic approaches may be required for each disease.

Ataxia means 'absence of order' and it denotes a clinical syndrome of incoordination. The term ataxia is also used to refer to a specific group of degenerative diseases of the nervous system in which progressive ataxia is the prominent clinical manifestation[1]. The ataxias comprise diseases of both genetic and non-genetic origin and, of the ataxias with a genetic origin, the spinocerebellar ataxias (SCAs) represent the autosomal dominantly inherited diseases. SCAs are heterogeneous, and there are >40 genetically distinct subtypes of SCA. Each subtype is named SCA followed by a number; the numbers are progressive and represent the chronological order in which the disease locus or causative gene of the subtype was identified. The term spinocerebellar was chosen to represent the concomitant involvement of the spinal cord and the cerebellum in these diseases. However, the spinal cord is unaffected in many SCAs, and pathological changes occur in other regions of the nervous system, including peripheral nerves and the brainstem and basal ganglia. Nevertheless, SCA is still generally used to denote the autosomal dominant ataxias, irrespective of disease pathology in the nervous system. The SCA nomenclature is further complicated by the fact that a number of autosomal recessive and X-linked ataxias are also referred to as SCA, with the addition of an R (SCAR) or X (SCAX), respectively[2,3].

The clinical hallmark of all SCAs is a progressive loss of balance and coordination accompanied by slurred speech. Onset of ataxia in mid-adulthood is most usual, but manifestation in childhood and old age can occur[4]; thus, the possible range of ataxia onset almost covers the entire lifespan. The mobility and communicative skills of individuals with an SCA are restricted, which strongly impairs quality of life (QOL), and many SCAs lead to premature death[4–6].

Genetically, the SCAs fall into two major groups: those caused by dynamic repeat expansion mutations (repeat expansion SCAs) and those caused by non-repeat mutations (TABLE 1 and Supplementary Table 1). Repeat expansions are also a major cause of non-SCA inherited neurological diseases; these diseases share common features such as anticipation (that is, the tendency for disease symptoms to worsen from generation to generation) (BOX 1).

There are at least 12 repeat expansion SCAs (FIG. 1). Six of these diseases — SCA1, SCA2, SCA3/Machado–Joseph disease (SCA3/MJD; note that SCA3/MJD refers to a single disease that has been called both SCA3 and MJD in the literature), SCA6, SCA7 and SCA17 — are caused by translated CAG repeat expansion mutations that encode stretches of pure glutamine in the respective disease proteins; these diseases are thus referred to as polyglutamine SCAs[7]. A further disorder caused by a translated CAG repeat, dentatorubral-pallidoluysian atrophy (DRPLA), is classed as an SCA given its clinical features[8]. Of note, although a CAG repeat is the disease mutation underlying SCA12, it is not thought to encode polyglutamine because the repeat is located in the 5′ untranslated region of the gene[9]. However, this possibility has not been formally ruled out. Alternatively,

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the repeat might affect the expression of the gene product of *PPP2R2B*, a brain-specific regulatory subunit of protein phosphatase 2A[10]. The CTG repeat expansion in SCA8 is transcribed in both directions[11], and transcription of the antisense strand of DNA results in a CAG repeat. Although SCA8 is not a polyglutamine disorder, its antisense strand can be translated via repeat associated non-ATG (RAN) translation[12] to generate a

Table 1 | **Genetics and phenotype of selected SCAs**

SCA[a]	Gene (type of mutation)	Protein (wild-type protein function)	Neuropathology	Clinical phenotype
SCAs due to repeat mutations				
SCA1	*ATXN1* (translated CAG repeat)	ATXN1 (gene transcription)	Cerebellum, brainstem and spinal cord	Ataxia, spasticity, ophthalmoplegia, bulbar symptoms and sensory symptoms
SCA2	*ATXN2* (translated CAG repeat)	ATXN2 (RNA repair, ribosomal translation)	Cerebellum, brainstem, substantia nigra, spinal cord and polyneuropathy	Ataxia, slow saccades and sensory symptoms
SCA3/MJD[b]	*ATXN3* (translated CAG repeat)	ATXN3 (deubiquitinase)	Dentate nucleus, basal ganglia, substantia nigra, spinal cord and polyneuropathy	Ataxia, ophthalmoplegia, spasticity, basal ganglia symptoms, sensory symptoms, amyotrophy including facial atrophy and fasciculations
SCA6	*CACNA1A* (translated CAG repeat, missense)	α_{1A}-Subunit of voltage-dependent calcium channel of P/Q-type (neuronal excitability)	Cerebellum	Pure cerebellar ataxia and downbeat nystagmus
SCA7	*ATXN7* (translated CAG repeat)	ATXN7 (subunit of histone acetyltransferase complexes)	Cerebellum, brainstem, basal ganglia and retina	Ataxia, visual loss, ophthalmoplegia and spasticity
SCA8[c]	*ATXN8* (CTG repeat in 3′ untranslated region)	ATXN8, also antisense strand ATXN8OS (unknown)	Cerebellum	Ataxia, spasticity, sensory symptoms, cognitive and mood changes
SCA10	*ATXN10* (intronic ATTCT repeat)	ATXN10 (unknown)	Cerebellum	Ataxia and epilepsy
SCA12	*PPP2R2B* (CAG repeat in 5′ untranslated region)	Brain-specific regulatory subunit of protein phosphatase 2A (serine/threonine phosphatase involved in cell cycle and transcription)	Cerebellum and polyneuropathy	Ataxia and tremor
SCA17	*TBP* (translated CAG repeat)	TATA-box-1-binding protein (gene transcription)	Cerebellum	Ataxia, spasticity, basal ganglia symptoms, psychiatric disorders and dementia
SCA31	*BEAN1* (intronic TGGAA repeat insertion)	Brain-expressed protein associating with NEDD4 homologue (binding partner of NEDD4)	Cerebellum	Pure cerebellar ataxia
SCA36	*NOP56* (intronic GGCCTG repeat)	Nucleolar protein 56 (RNA maturation)	Cerebellum	Ataxia, amyotrophy and hearing loss
SCA37	*DAB1* (intronic ATTTC repeat)	Disabled homologue 1′ (intracellular adaptor in reelin signalling pathway)	Cerebellum	Ataxia and abnormal vertical eye movements
SCAs due to conventional mutations				
SCA5[d]	*SPTBN2* (deletion, missense)	βIII-Spectrin (cytoskeletal protein that stabilizes membrane proteins, including glutamate receptors)	Cerebellum	Pure cerebellar ataxia
SCA13	*KCNC3* (missense)	Subunit K_v3.3 (neuronal excitability)	Cerebellum and brainstem	Ataxia and intellectual disability
SCA14	*PRKCG* (missense)	Protein kinase Cγ (serine/threonine kinase)	Cerebellum	Ataxia and myoclonus
SCA15/SCA16[b]	*ITPR1* (large deletion, missense)	Inositol 1,4,5-triphosphate receptor type 1 (intracellular inositol-triphosphate-gated calcium channel)	Cerebellum	Pure cerebellar ataxia
SCA19/SCA22[b]	*KCND3* (missense, deletion)	Subunit K_v1.3′ (neuronal excitability)	Cerebellum	• SCA19: ataxia, cognitive impairment and myoclonus • SCA22: pure cerebellar ataxia
SCA28	*AFG3L2* (missense)	AFG3-like protein 2 (part of m-AAA protease complexes in the inner mitochondrial membrane)	Cerebellum	Ataxia, spasticity, ophthalmoplegia and ptosis

ATXN, ataxin; DRPLA, dentatorubral-pallidoluysian atrophy; MJD, Machado–Joseph disease; SCA, spinocerebellar ataxia. [a]The table shows all known SCAs caused by repeat mutations and the most prevalent SCAs caused by conventional mutations. An expanded table showing this information for all currently known SCAs, including DRPLA, is included as Supplementary Table 1. [b]Refers to a single disease that has been called both names in the literature. [c]In SCA8, penetrance of *ATXN8* mutation is incomplete. [d]In SCA5, homozygous *SPTBN2* mutations cause infantile-onset SCA and psychomotor delay (SCAR14; also known as SPARCA1).

Box 1 | **Non-SCA repeat expansion diseases**

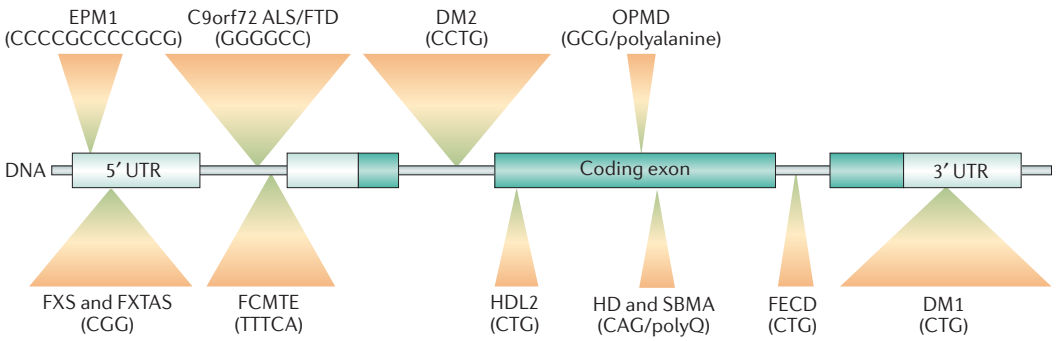
The most common spinocerebellar ataxias (SCAs) are caused by expansions of short tandem repeat sequences. Repeat expansions also cause inherited neurological diseases beyond SCAs and Friedreich ataxia, and these repeat expansions can occur in the 5′ untranslated region (UTR), introns, exons or 3′ UTR of the disease gene (see the figure)[40]. The following genetic diseases are caused by repeat expansions: C9orf72 expansion-mediated amyotrophic lateral sclerosis and frontotemporal dementia (C9orf72 ALD/FTD), myotonic dystrophy types 1 and 2 (DM1 and DM2), Fragile X syndrome (FXS) and fragile X-associated tremor/ataxia syndrome (FXTAS; both are diseases of heritable intellectual disability), Fuchs endothelial corneal dystrophy (FECD; also known as corneal dystrophy), oculopharyngeal muscular dystrophy (OPMD), Huntington disease (HD), Huntington disease-like 2 (HDL2), progressive myoclonic epilepsy 1 (EPM1; also known as Unverricht–Lundborg disease), familial cortical myoclonic tremor with epilepsy type 1 (FCMTE; also known as benign adult familial myoclonic epilepsy (BAFME)) and spinobulbar muscular dystrophy (SBMA).

Repeat expansion diseases share several general features that reflect the dynamic nature of repeat sequences. Disease-causing expansions arise from polymorphic short tandem repeats that normally exist throughout the genome. Expansions are typically unstable and can change in size (most often increasing) in patients from generation to generation. As a consequence, repeat expansion diseases show remarkable phenotypic heterogeneity owing to the phenomenon of anticipation: disease tends to become more severe and have an earlier onset in successive generations[40].

Why a particular expansion causes a specific disease depends on factors such as the function of the gene, the site in the gene where the repeat expansion resides, the size and sequence of the expansion and whether the expansion occurs in protein-coding or non-coding regions of the gene.

The CGG repeat expansion underlying FXS is a compelling example of the importance of repeat size. Full-blown expansions essentially silence expression of the synaptic functional regulator FMRP, a protein crucial for brain development, resulting in intellectual disability[243]. By contrast, a smaller pre-mutation expansion in FMRP in the grandfathers of males with FXS permits expression of the gene encoding FMRP and causes the degenerative brain disease FXTAS later in life[244]. Thus, different-sized expansions of the same repeat sequence cause distinct diseases through different mechanisms.

Given the range of repeat expansions occurring in different locations in genes of different function, the disease mechanisms of repeat expansion diseases are thought to vary greatly. For example, similar to SCA1, SCA2, SCA3/Machado–Joseph disease (MJD), SCA6, SCA7 and SCA17, HD is principally thought to be caused by polyglutamine expansion in the disease protein, leading to a dominant-toxic effect[7]. In DM1 and DM2, expansion at the RNA level sequesters critical splicing factors to disrupt the balance in the expression of splice isoforms of critically important genes in muscle and in the brain[245]. The smallest repeat expansion known to cause a repeat expansion disorder, which occurs in OPMD, modestly lengthens a polyalanine stretch in polyadenylate binding protein nuclear 1, a protein essential for proper gene regulation[246]. Furthermore, the hexanucleotide expansion in *C9orf72* likely acts through multiple mechanisms, including the production of deleterious dipeptide repeat proteins through repeat associated non-ATG mediated (RAN) translation[247]. A new hurdle in understanding the complex disease mechanisms of repeat expansion diseases is the recognition that many disease-linked repeats are subject to transcription from both the sense and the antisense strands.



polyglutamine-containing protein. At least four SCAs — SCA10, SCA31, SCA36 and SCA37 — are caused by repeat expansions in introns. These expansions, which are located outside of traditional open-reading frames, tend to be much larger than the translated CAG expansions. For example, the intronic mutation causing SCA10 may comprise up to 4,500 ATTCT repeats[13], whereas the mutations underlying the polyglutamine SCAs typically do not exceed 100 CAG repeats. The intronic repeat mutations may primarily cause disease at the RNA level. All remaining SCAs are due to conventional non-repeat mutations (that is, missense mutations, nonsense mutations, insertions or deletions).

A frequently updated account of the genetic and clinical features of SCAs can be found under the Ataxia sections of the Neuromuscular Disease Center run by Washington University, St. Louis, MO, USA.

Ataxia results from damage to the cerebellum and interconnected regions of the nervous system, in particular, the spinal cord. Although ataxia is common to all SCAs, the exact neuropathological findings associated with each SCA varies; this variation is unsurprising given the genetic heterogeneity of these diseases. Neuropathological studies have mainly been performed in patients with a common polyglutamine SCA; neuropathological data for other SCAs are scarce. Loss of

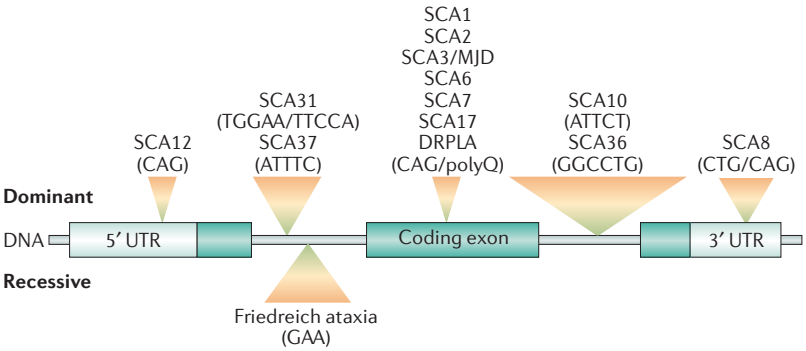


Fig. 1 | **Repeat expansions that cause ataxia.** A schematic of a gene indicating the disease, repeat sequence and location of the repeat within the ataxia-causing gene is depicted. Spinocerebellar ataxias (SCAs) and dentatorubral-pallidoluysian atrophy (DRPLA) are dominant ataxias (shown above the gene); Friedreich ataxia is the only recessive repeat expansion ataxia (shown below the gene). Apart from the CAG repeat in SCA12, the CAG repeats in the ataxia shown occur in the protein-coding region of the gene and encode polyglutamine (polyQ) in the disease protein. All other repeats shown are untranslated and may cause disease through one or more mechanisms at the transcriptional or post-transcriptional level. For simplicity, repeats are shown oriented to transcription from the sense strand. Transcription in the antisense direction, however, also likely occurs for many repeats, and this is best documented in SCA8 (as indicated by CTG/CAG). MJD, Machado–Joseph disease; UTR, untranslated region.

cerebellar Purkinje neurons is characteristic of SCA1, SCA2 and SCA6 (REFS[14,15]), and Purkinje neuron degeneration has also been described in some cases of non-polyglutamine SCAs at autopsy[16,17]. The loss of Purkinje neurons is typically accompanied by retrograde degeneration of inferior olive neurons. In SCA1 and SCA2, but not SCA6, there is also degeneration of pontine nuclei in the brainstem. By contrast, in SCA3/MJD, neuronal loss occurs less in the cerebellar cortex and more in the dentate nucleus and basal ganglia[18,19]. However, loss of dopaminergic neurons of the substantia nigra is an overlapping feature of SCA2 and SCA3/MJD[19,20].

In this Primer, we discuss the epidemiology of SCAs before providing an overview of the pathophysiology and diagnosis of these diseases. Intense research has expanded our understanding of the pathobiology of many SCAs and has led to the identification of new targets for treatment development. However, as we discuss in the Management section, there is currently no treatment that can slow or halt any of the SCAs.

Epidemiology

Determining the prevalence of each SCA subtype has been challenging owing to the limited number of population-based epidemiological studies and the heterogeneity of genes tested in clinical centres worldwide. Most reports describe the frequency of SCAs on the basis of the number of patients diagnosed in specialized ataxia centres, in which the only genetic tests performed are for polyglutamine SCAs. Polyglutamine SCAs share a common type of genetic mutation that can be detected by diagnostic tests that are available in ataxia centres worldwide. However, the genetic diagnosis of SCA subtypes caused by untranslated repeats or conventional mutations requires advanced molecular techniques that are available only in a few, resource-rich clinical centres. The difference in the availability of diagnostic screening procedures among disease centres could bias our estimation of the prevalence of SCAs[21].

In a 2014 systematic review providing a global overview of the distribution and prevalence of hereditary cerebellar ataxias, the prevalence of SCAs assessed in population-based studies ranged from 0 to 5.6 cases per 100,000 individuals, with an average of 2.7 cases per 100,000 individuals[22]. Currently, polyglutamine SCAs (SCA1, SCA2, SCA3/MJD, SCA6, SCA7, SCA17 and DRPLA) are the most commonly recognized genetic forms of SCAs[5]. A summary of the distribution and prevalence of polyglutamine SCAs, according to published data, follows.

SCA3/MJD is the most common SCA worldwide (20–50% of families with SCA), followed by SCA2 (13–18%) and SCA6 (13–15%)[23]. The relative frequency of the different SCA subtypes shows marked geographical and ethnic variability, often owing to founder effects[24,25] (FIG. 2). Founder effects, which can result when a chromosome from an individual carrying a disease allele is introduced into a population by migration or by a de novo mutation, can explain the presence of high-frequency rare Mendelian diseases in some populations. On the basis of haplotype analyses, the SCA3/MJD mutation may have arisen from two distinct events, the first occurring in Asia and the second occurring in the Portuguese population; however the worldwide spread of the mutation is attributed to Portuguese emigration[26,27]. This fact may explain why SCA3/MJD is very frequent in Portugal (58–74% of families with SCA) and in particular on the Azores Islands, of which the highest prevalence occurs on Flores island (1 in 239 individuals)[28]. SCA3/MJD is also frequent in Brazil (69–92% of SCA families), China (48–49%), the Netherlands (44%), Germany (42%) and Japan (28–63%). By contrast, SCA3/MJD is less frequent in the USA and Canada (21–24% of SCA families), France (20%), Mexico (12%), Australia (12%) and India (5–14%). It is very rare in South Africa (4% of SCA families) and Italy (1%)[29].

A founder effect has also been described for SCA2 in Holguin province in Cuba, where a frequency of 40 cases per 100,000 individuals was estimated for persons of Spanish ancestry[30]. SCA2 accounts for ~10–25% of autosomal dominant familial cases in ethnically and geographically diverse populations. The SCA2 genotype is particularly frequent in Mexico (43% of families with SCA), Korea (31%), India, Italy and Spain (15–27%) and is rare in the Japanese population (5%)[31]. SCA6 is the third most common SCA genotype worldwide and represents 10–30% of families with SCA in Germany, the Netherlands, the United Kingdom, Taiwan, Australia, the USA and Japan[24,32]. SCA1 is the cause of SCA in ~3–16% of families with a history of SCA in North America and in Europe[5]. The highest prevalence of SCA1 is found in Poland (68% of families with SCA), Russia (41%), South Africa (41%), Serbia (34%), Italy (25%) and India (22%). Of the polyglutamine SCAs, SCA7, SCA17 and DRPLA have the lowest prevalence worldwide (0–3% of families with SCA)[23]. A significant proportion of DRPLA cases are found in Japan (3–16% of families with SCAs)[33], in Portuguese and Spanish families (5–17%)[22,34] and in ~3% of Korean and Venezuelan families with SCA[24,25].

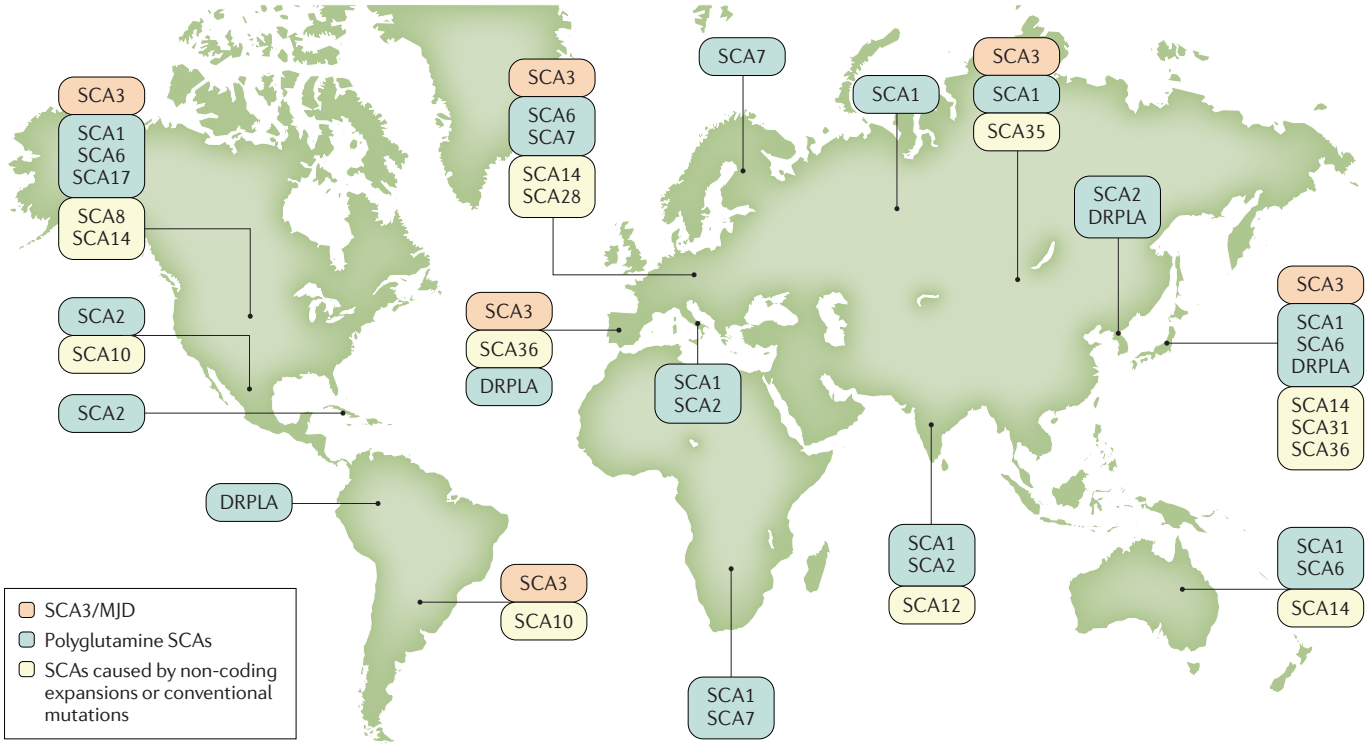


Fig. 2 | **Geographical distribution of SCAs.** Schematic representation of the global prevalence of spinocerebellar ataxia (SCA) subtypes. Polyglutamine SCAs (blue rectangles) are more frequent than SCAs caused by other expansions or by conventional mutations. SCA3/Machado–Joseph disease (MJD) is the most common polyglutamine SCA worldwide, accounting for 20–50% of families with a dominant ataxia (red rectangles). Owing to the lack of systematic studies, the prevalence and geographic distribution of SCAs caused by non-coding expansions or conventional mutations (yellow rectangles) are still fragmentary[5,22,24]. DRPLA, dentatorubral-pallidoluysian atrophy.

SCA7 frequency is high in Scandinavia (~50% of families with SCAs)[35], South Africa (22%)[36] and Mexico (7%)[37], and its frequency is associated with local founder effects. In the past 10 years, an increasing number of SCAs caused by untranslated repeat expansion mutations or by conventional mutations have been recognized. These subtypes account for a small percentage of cases ranging from 3% to 6% of families with SCA in different populations[4,23]. Reports from specialized centres indicate that SCA12 is frequent in India (7–16% of families with SCA)[38], SCA31 is frequent in Japan (8–17%) and SCA36 is frequent in both Spain (6%) and Japan (9%)[23,31]. SCA10 also accounts for multiple families with SCA in South and Central America[39]. Among the SCAs due to conventional mutations, the most frequent forms are SCA14 and SCA28 (REF.[4]). SCA14 has a frequency of 1–4% of families with SCA, and it has been diagnosed in families from Europe, North America, Japan and Australia. SCA28 was diagnosed in 1–3% of families in European cohorts of patients[23] (FIG. 2). Prevalence studies are relatively scarce for SCA10, SCA14 and SCA28, and figures could be misleading as screening for SCAs caused by untranslated repeats and conventional mutations is not routinely carried out worldwide.

Currently, the epidemiology of polyglutamine SCAs seems well-defined worldwide, whereas, for most of the other SCA genotypes, the frequency of families with autosomal dominant ataxia remains uncharacterized. Although >40 SCA genetic subtypes have been identified thus far, the genetic defect has not been identified in a large percentage of patients with SCA (30–48%), suggesting that SCAs have a broad genetic heterogeneity and that causative genes have yet to be identified[4,22].

Mechanisms/pathophysiology

Pathologically, SCAs are remarkably heterogeneous, which is not surprising given that each SCA has a distinct genetic cause. The pathology of SCAs ranges from relatively pure cerebellar involvement, as observed in patients with SCA6, to broader degeneration involving other parts of the brain, the spinal cord and peripheral nerves, as observed in patients with SCA1, SCA2 or SCA3/MJD. For many SCAs, clinical features can vary greatly even within a family, partly because the most common SCAs are due to dynamic repeat expansions[40]. These expansions can vary in size between individuals within an affected family, and they often change in size between generations. Furthermore, as longer repeats tend to cause disease with greater severity and an earlier onset than shorter repeats, and disease-causing repeats tend to lengthen upon transmission, disease symptoms often worsen from generation to generation in a family; this phenomenon is known as clinical anticipation. Clinical anticipation occurs in the most common SCAs, such as SCA1, SCA2 and SCA7, and in many other repeat expansion disorders[40] (BOX 1). For several repeat expansion SCAs, there is marked parental bias in the extent of anticipation. In SCA7 and DRPLA, for

example, repeat expansion upon paternal transmission is much greater than repeat expansion upon maternal transmission[41,42].

The first SCA-causing mutations identified were CAG repeat expansions, followed closely by the identification of other repeat expansions that underlie these diseases. However, the advent of next-generation sequencing revealed that a still-growing number of conventional mutations cause rarer SCAs. As a rule, the dominant pattern of SCA inheritance implies that they are caused by a dominant-toxic or dominant-negative pathogenic mechanism, or, in some cases, by a combination of these mechanisms. In individuals with SCA1, an enhanced wild-type activity of the disease protein appears to contribute to disease; this hypermorphic mechanism represents a dominant action of the mutation if not a dominant-toxic effect. It is also conceivable that some SCAs result from haploinsufficiency, although this has yet to be firmly established for any SCA.

Although the precise underlying molecular mechanism is unknown for any SCA, the growing range of genetic causes reveals that SCAs have common pathophysiological themes (FIG. 3) that could be targeted by disease-modifying therapy. Furthermore, as many SCAs are likely to be caused by interrelated pathophysiological mechanisms that result from the causative mutation, crosstalk is likely to occur between the molecular mechanisms underlying SCAs that are discussed here.

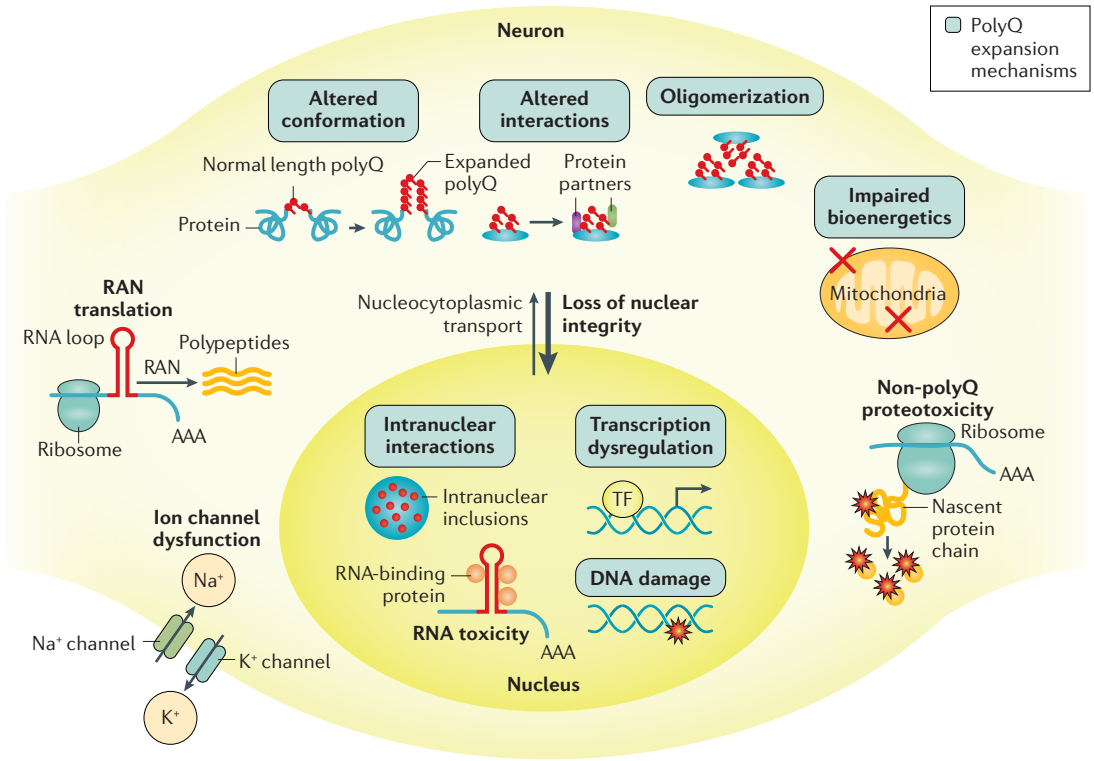


Fig. 3 | **Common disease mechanisms underlying SCAs.** Spinocerebellar ataxias (SCAs) share multiple pathophysiological mechanisms. At least seven dominantly inherited ataxias are caused by polyglutamine (polyQ)-encoding CAG repeat expansions, which contribute to disease pathogenesis via several mechanisms. Expanded polyglutamine may adopt conformations that alter protein structure and function, cause disease proteins to differentially engage with their interacting proteins (which has deleterious consequences for neurons), are prone to oligomerization and form aggregates in the form of intranuclear inclusions that sequester other proteins. In addition to proteotoxicity caused by polyglutamine expansion, non-polyglutamine SCA disease-causing proteins containing missense mutations may fold incorrectly, leading to non-native protein structures that alter protein function and promote aggregation. At least four SCAs are caused by large non-protein-coding repeat expansions that bind to, and sequester, RNA-binding proteins, often within intranuclear RNA foci and resulting in RNA toxicity owing to perturbed splicing. In the cytoplasm, expanded repeats can engender repeat associated non-ATG mediated (RAN) translation, leading to aggregate-prone polypeptides. RAN translation may even occur with some of the expanded CAG repeats underlying polyglutamine diseases. Many SCAs are directly caused by mutations in genes encoding ion channels or ion-channel-associated regulatory proteins that lead to ion channel dysfunction. Other SCAs, particularly polyglutamine SCAs, are indirectly associated with changes to channel function or expression. At least one SCA disease protein directly, and other SCA disease proteins indirectly, impairs mitochondrial function, leading to impaired bioenergetics. Polyglutamine disease proteins tend to concentrate within neuronal nuclei, which could reflect altered nucleocytoplasmic transport (as described for the polyglutamine disorder Huntington disease) and lead to a loss of nuclear integrity. Finally, emerging evidence suggests that DNA damage, altered chromatin acetylation and major transcriptional changes may contribute to disease pathogenesis in numerous SCAs, including polyglutamine SCAs. Note that established polyQ expansion mechanisms may also occur in SCAs that are not caused by polyQ expansion. TF, transcription factor.

Polyglutamine expansion. SCA1, SCA2, SCA3/MJD, SCA6, SCA7, SCA17 and DRPLA belong to the class of polyglutamine diseases along with Huntington disease and the motor neuron disorder spinobulbar muscular atrophy[43]. Although the disease mutations in polyglutamine diseases are expanded CAG repeats, the abnormally long polyglutamine tracts encoded by the repeat in the respective disease proteins are believed to drive pathogenesis[7,43]. More is known about polyglutamine SCAs than any other type of SCA, and, although proteotoxicity is thought to contribute to the pathogenesis of this class of SCAs, studying this group of SCAs has shed light on other recurring pathophysiological mechanisms of SCAs (see below).

A common pathological hallmark of polyglutamine disease is the accumulation and aggregation of the disease protein in intraneuronal deposits, most often within the nuclei of neurons[14]. Whether neuronal aggregates are directly toxic or a protective effort by the cell to segregate abnormal proteins is debated[44]. Some disease models and neuropathological evidence suggest that inclusions themselves are protective. Indeed, the formation of inclusions in cultured neurons expressing mutant polyglutamine protein offered a survival advantage[45]; neurodegeneration in some mouse models is dissociated from the presence of inclusions[46], and many surviving neurons in the end stage of human diseased brain have inclusions. By contrast, the aggregation of polyglutamine disease proteins in neuronal processes can disrupt crucial cargo trafficking[47–49] and trap other proteins, potentially compromising various cellular processes and cellular homeostasis[50,51]. Confusion in the literature about the role of polyglutamine aggregation in disease is understandable[52]. This confusion stems from the fact that aberrant proteins transition through a complex pathway, from the formation of oligomers to the formation of diffusible (small) and then sedimentable (large) aggregates; structurally diverse species, which may be neurotoxic or neuroprotective, are generated along the pathway[53–55].

Regardless of the role of inclusions or aggregates in polyglutamine diseases, the chronic production of a polyglutamine disease protein that fails to adopt its native, functional conformation must place a bioenergetic burden on neurons. Studies of polyglutamine disease proteins containing different-sized polyglutamine tracts show that the tendency of disease proteins to aggregate coincides with the repeat length threshold for human disease (that is, the shortest repeat length that results in human disease), which varies for each polyglutamine-tract-containing protein[56–58]. Moreover, in vitro, cellular and animal models of disease have shown that proteins with longer polyglutamine tracts tend to aggregate more robustly than proteins with shorter polyglutamine tracts[59]. The correlation between protein aggregation and repeat length threshold for a disease suggests that the abnormal conformation and aggregation of a disease protein underlie disease pathogenesis.

Despite this shared feature, polyglutamine disease proteins are structurally and functionally unrelated. Apart from SCA6, all of these proteins normally reside in the cytoplasm or nucleus as soluble proteins. The SCA6 disease protein is a cell surface transmembrane protein that constitutes the pore-forming subunit of a voltage-dependent P/Q-type calcium channel[60]. Perhaps related to the cellular location of SCA6, at only 20–33 repeats, the SCA6 expansion is the smallest polyglutamine-disease-causing expansion. By contrast, disease repeat lengths in other polyglutamine ataxias are much larger; for example, SCA1, SCA2 and SCA3/MJD are caused by polyglutamine repeats of 38–85, 36–100 and 60–87 repeats, respectively. These data on repeat length underscore how the distinctive clinical and pathological features of each polyglutamine SCA are attributed to the specific protein in which the mutation resides[61,62]. The relatively selective loss of Purkinje cells in patients with SCA6 as compared with patients with other polyglutamine SCAs may also reflect that the expression of SCA6 is more restricted than the expression of other polyglutamine disease proteins.

In addition to promoting aggregation, polyglutamine expansions within disease proteins can alter protein–protein interactions and, consequently, the function of the protein in which they reside. In this respect, the SCA1 disease protein ataxin 1 (ATXN1; also known as SCA type 1 protein) is particularly well-characterized (note that ataxin proteins have been referred to using ATXN throughout this article with the gene name in italics (*ATXN*)). ATXN1 is a transcription cofactor that interacts with numerous other proteins implicated in gene expression. The expansion in ATXN1 favours its interaction with the transcriptional repressor protein capicua homologue (capicua) over its interaction with the RNA-binding protein and spliceosome component RBP7; this shift in ATXN1 binding disrupts gene expression and splicing events in vulnerable neurons[63]. Studies in mouse models and in induced pluripotent stem cells derived from patients with SCA1 suggest that the increase in ATXN1–capicua drives toxicity in the cerebellum through a gain-of-function mechanism[64]. The toxicity of mutant ATXN1 also depends on its phosphorylation at serine 776, an amino acid that is distant to the polyglutamine expansion[65]. ATXN1 engineered to lack serine 776 is no longer toxic, despite still harbouring a polyglutamine expansion[65]. Moreover, genetically or pharmacologically inhibiting protein kinase A, the kinase that principally phosphorylates ATXN1 at serine 776, ameliorates disease in a mouse model for SCA1 (REF.[66]). In short, studies of ATXN1 underscore that, although the polyglutamine expansion in ATXN1 is essential for disease, other motifs within the protein as well as the function of the protein itself influence the toxicity elicited by the polyglutamine mutation. The same principle will likely prove to be true for other, less well-characterized, SCA polyglutamine disease proteins.

The glutamine repeats in each SCA disease protein are usually polymorphic in the general population; non-disease forms of these proteins may contain glutamine stretches because, even when within the normal range, glutamine repeats favour conformational flexibility[67]. This flexibility may allow the protein to engage in a wider range of protein interactions to achieve its full range of functions. Indeed, most polyglutamine disease proteins have regulatory functions that depend on their interaction with multiple proteins, as exemplified

by ATXN1. When the repeat is expanded, the polyglutamine protein loses this flexibility[68], with deleterious consequences for neurons.

Polyglutamine expansion tends to drive polyglutamine disease proteins, some of which are normally concentrated in the cytoplasm, into the nucleus of neurons[7]. The SCA3/MJD disease protein ATXN3 (also known as SCA type 3 protein and Machado–Joseph disease protein 1) illustrates this point well. In healthy individuals, ATXN3 is present throughout the cell or predominantly in the cytoplasm, depending on the cell type. In patients with SCA3/MJD and in numerous animal models, ATXN3 is concentrated in the nuclei of neurons, where, particularly in brainstem neurons, it forms large inclusions[69]. Similarly, in SCA1, SCA7, SCA17 and DRPLA, the disease protein becomes heavily concentrated within neuronal nuclei in susceptible brain regions, including the cerebellum and brainstem[14,70]. The accumulation of mutant protein in nuclei may be directly toxic or may cause toxicity by preventing the nuclear protein from shuttling between the nucleus and cytoplasm. For example, in the case of ATXN3, which is a deubiquitylating enzyme that normally participates in ubiquitin-dependent quality control, the loss of its action in the cytoplasm could be deleterious. Marked changes in gene expression profiles have been described in the brains of patients with most polyglutamine SCAs[71], which may reflect the aberrant nuclear concentration of disease proteins that regulate gene expression.

Although polyglutamine-mediated toxicity is thought to be a principal component of disease pathogenesis, the repeat could also be toxic at the RNA level (see below)[72]. Moreover, the recently described phenomenon of RAN translation may occur in some of the polyglutamine SCAs[12]. Although protein translation typically begins at an ATG start site encoding methionine, CG-rich repeat sequences can lead to non-canonical RAN translation from the repeat itself. RAN translation across a CAG repeat can produce homopolymeric peptides in the three different reading frames, therefore encoding polyserine and polyalanine in addition to polyglutamine. Compelling data suggest that CAG repeats are subject to RAN translation in Huntington disease[73], but the evidence is more limited for the polyglutamine SCAs[74]. It is well-established that the CUG repeat expansion in SCA8 supports RAN translation[75,76] and, because the antisense (CAG) strand of this gene can encode polyglutamine, SCA8 may even share pathogenic elements with the polyglutamine SCAs.

In summary, in polyglutamine SCAs, the disease protein has a propensity to adopt abnormal conformations, engage differently with normal binding partners, concentrate in the nucleus and form intraneuronal aggregates. The myriad downstream consequences are likely to differ for each disorder and to depend on the protein sequences surrounding the polyglutamine repeat and the normal functions, subcellular location and brain expression pattern of the disease protein. Given this complexity, the earliest steps in the pathogenic cascade of polyglutamine SCAs seem the most attractive targets for disease-modifying treatments.

Proteotoxicity. The expanded polyglutamine disorders include the best examples of proteotoxicity in the SCAs; the disease proteins in these disorders form intraneuronal oligomers and aggregates that may be toxic themselves or may exert toxic effects by sequestering protein quality control components, such as the proteasome and molecular chaperones[7]. Even if the polyglutamine protein aggregates are not directly toxic, they will place a continual burden on the proteostasis machinery of neurons that, over time, likely compromises cellular integrity[77,78]. In support of a central role for proteotoxicity in the pathogenesis of polyglutamine SCAs, overexpressing specific molecular chaperones in animal models can mitigate toxicity[79].

Proteotoxicity is also likely to contribute to several SCAs that are not caused by polyglutamine repeats. Among the SCAs caused by conventional mutations, some mutant proteins have been directly implicated in protein fidelity, for example, the disease proteins eukaryotic elongation factor 2 (EF2; in SCA26)[80] and transglutaminase 6 (TG6; in SCA35)[81]. The single amino acid change in EF2 in patients with SCA26 is thought to reduce the fidelity of protein translation, leading to potentially deleterious translational frameshifting[80]. In patients with SCA35, various mutations cause TG6 to accumulate in insoluble perinuclear deposits, which induces the unfolded protein response[81]. In other SCAs, pathogenic mutations in the disease-causing protein can promote its misfolding and aggregation; for example, the disease-causing protein in SCA14, protein kinase Cγ, undergoes accelerated amyloid fibril formation when mutated[82]. In SCA5, mutations in *SPTBN2*, the gene encoding βIII-spectrin (also known as SCA type 5 protein), alter cytoskeletal dynamics, which perturbs the delicate and dynamic architecture of distal processes and lessens the stability of glutamate receptors in Purkinje cells[83,84]. As additional SCAs are studied, we anticipate that other disease proteins with a proteotoxic mechanism will be identified.

RNA toxicity. At least four SCAs (SCA10, SCA31, SCA36 and SCA37) are caused by moderate-to-large pentanucleotide or hexanucleotide expansions within non-protein-coding introns[85]. In all four cases, the expanded repeat-containing transcripts accumulate in RNA foci within neurons[86–88]. These foci sequester key RNA-binding proteins and, as a result, splicing or other RNA-dependent processes are perturbed[89]. As is the case for the repeat expansion disease myotonic dystrophy, this perturbation in RNA homeostasis is likely to drive cytotoxicity[85]. Indeed, studies in *Drosophila melanogaster* and murine models of several SCAs support the hypothesis that toxic RNA underlies several repeat expansion SCAs[89–91]. That being said, increasing evidence suggests that RNA toxicity may also negatively influence protein homeostasis; thus, a clean separation of repeat expansion SCAs into RNA-based and protein-based diseases may not capture the complexity of the underlying disease mechanisms. In addition, even when expanded repeats are not translated into proteins via the conventional mechanism, they might represent sites for RAN translation, adding another route to proteotoxicity for SCAs[12].

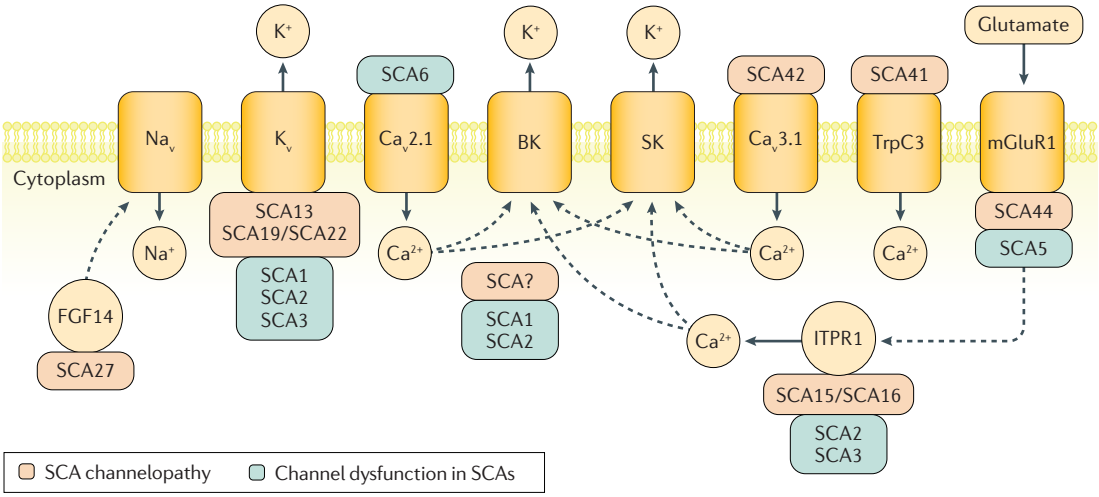


Fig. 4 | **Ion channel dysfunction associated with SCAs.** Various ion channels and signalling molecules important for cerebellar physiology and circuitry are depicted. Spinocerebellar ataxias (SCAs) that have been directly associated with channelopathies (that is, mutations in channels themselves) and polyglutamine (polyQ) SCAs that have been associated indirectly with impaired ion channel function are shown in red and blue rectangles, respectively. Although a mutation in *KCNMA1*, encoding calcium-activated potassium channel subunit-α1 (also known as BK channel) has been reported[248], it has not been associated with a specific SCA, as indicated by the question mark. Impaired stability of metabotropic glutamate receptor type 1 (mGluR1) has also been reported for SCA5, but channel dysfunction has not been investigated in most non-polyQ SCAs. Dashed lines signify a protein–protein or calcium–protein interaction. Solid lines signify the direction of ion movement upon channel activation. BK, large conductance calcium-activated potassium channel; Ca_v, voltage-gated calcium channel; FGF14, fibroblast growth factor 14; ITPR1, inositol 1,4,5 trisphosphate receptor type 1; K_v, voltage-gated potassium channel; Na_v, voltage-gated sodium channel; SK, small conductance calcium-activated potassium channel; TrpC3, transient receptor potential cation channel type 3. Adapted with permission from REF.[93], Elsevier.

Channel dysfunction. The coordination of movement involves the complex and highly regulated neuronal circuitry connecting the cerebellum, brainstem and spinal cord. The intrinsic autonomous firing of cerebellar Purkinje neurons and the neuronal inputs to Purkinje neurons are regulated by various ligand-gated and voltage-dependent ion channels. Evidence suggests that channel dysfunction helps drive neuronal dysfunction, and possibly neurodegeneration, in several ataxias[92–96]. In the past decade, research into at least 11 SCAs has revealed pathogenic mutations in the genes encoding, or changes in the expression and/or function of, ion channels and signalling pathway components that regulate channel activity (FIG. 4). SCAs caused by mutations in the genes encoding specific ion channels include SCA6 (*CACNA1A*, encoding voltage-dependent P/Q-type calcium channel subunit-α1A)[97], SCA13 (*KCNC3*, encoding potassium voltage-gated channel subfamily C member 3)[98], SCA19/SCA22 (*KCND3*, encoding potassium voltage-gated channel subfamily D member 3; note that SCA19/SCA22 refers to a single disease that has been called both SCA19 and SCA22 in the literature)[99], SCA15/SCA16 and SCA29 (*ITPR1*, encoding inositol 1,4,5-trisphosphate receptor type 1; note that SCA15/SCA16 refers to a single disease that has been called both SCA15 and SCA16 in the literature), SCA41 (*TRPC3*, encoding short transient receptor potential channel 3)[100], SCA42 (*CACNA1G*, encoding voltage-dependent T-type calcium channel subunit-α1G)[101] and SCA44 (*GRM1*, encoding metabotropic glutamate receptor 1)[102]. SCA6 is caused by a CAG repeat expansion in the last exon of the longest isoform of *CACNA1A*[60]. Missense mutations altering the calcium channel-encoding sequence in *CACNA1A* can cause progressive ataxia with a phenotype similar to that of SCA6 (REF.[103]), but these mutations are also associated with episodic ataxia type 2 and familial hemiplegic migraine[104]. Although specific *CACNA1A* mutations tend to segregate with a particular phenotype (for example, episodic ataxia versus hemiplegic migraine), the phenotype may even vary among patients within one family with SCA6 (REF.[103]). Although these channel-linked SCAs are clinically distinct disorders with a range of phenotypes, SCAs caused by mutations in ion channels or regulatory pathways associated with them tend to manifest as slowly progressive or even non-progressive ataxia[101,102,105,106]. However, depending on the mutation and on how it affects the associated channel, symptoms can have relatively pure cerebellar involvement or they can be associated with myoclonus, episodic symptoms and even cognitive impairment. With the exception of SCA6, there is typically less neurodegeneration in SCA channelopathies than in polyglutamine SCAs, and some SCA channelopathies, such as SCA13, SCA27 and SCA29, can manifest early in life with a neurodevelopmental component.

Another exciting development is the recognition that channel dysfunction or perturbed cerebellar circuitry indirectly contributes to the pathogenesis of various polyglutamine SCAs and possibly other SCAs[93–96]. Channel function also appears to be indirectly affected in the non-polyglutamine SCA, SCA5, in which mutations in βIII-spectrin destabilize glutamate receptors[83]. In animal models of various SCAs, including SCA1, SCA2 and SCA3/MDJ, compounds or gene delivery

strategies that modulate specific glutamate receptors, calcium channels or potassium channels have alleviated motor deficits[107–110]. Accordingly, in patients with ataxia, channel modulators such as specific potassium channel activators represent an attractive route to symptom-modifying and disease-modifying therapy.

Impaired bioenergetics. An extensive literature supports a role for impaired bioenergetics, and particularly mitochondrial dysfunction, in Huntington disease; by extension, impaired bioenergetics might also have a role in other polyglutamine disorders[43]. However, the evidence that impaired bioenergetics contributes to polyglutamine SCAs is less robust, and little is known about the role of impaired bioenergetics in non-repeat expansion SCAs. Cellular and animal models of SCA3/MJD have revealed that a truncated form of mutant ATXN3 can induce mitochondrial fission and oxidative stress, leading to deficits in mitochondrial complex II, and an increase in the number of common mitochondrial DNA deletions was observed in individuals carrying mutated *ATXN3* (REFS[111–113]). Furthermore, mouse models of SCA1 have deficits in oxidative phosphorylation in the cerebellum owing to impaired mitochondrial function due to alterations in mitochondrial morphology, the mitochondria proteome and energy production; mitochondrial function can be corrected with antioxidant treatment[114,115]. The SCA2 disease-causing protein ATXN2 (also known as SCA type 2 protein) appears to induce the expression of the key mitochondrial quality control protein PINK1, although the implications of this induction are unknown[116].

Among the SCAs, the best example of impaired bioenergetics due to mitochondrial dysfunction is SCA28. This ataxia is caused by missense mutations in *AFG3L2*, which encodes a critical component (AFG3-like protein 2) of the mitochondrial m-AAA protease that helps maintain mitochondrial protein quality control, organelle morphology and oxidative phosphorylation. Mice harbouring a disease-causing mutation in *AFG3L2* develop impaired mitochondrial bioenergetics, presumably as a result of mitochondrial proteotoxicity[117].

The bioenergetics landscape of neurons is, of course, much more complex than that of mitochondria alone. Cellular pathways from gene transcription and ribosome biogenesis to ubiquitin-dependent pathways and autophagy influence mitochondrial function. Given the involvement of polyglutamine disease proteins in transcriptional dysregulation, impaired proteostasis and autophagy, SCA disease proteins might not need to directly affect mitochondria to aberrantly affect mitochondrial bioenergetics. Although numerous studies have shown that boosting energy production and reducing oxidative stress can be beneficial in model systems of polyglutamine diseases[114,118,119], clinical trials to boost such pathways in patients with SCA have not been performed.

Loss of nuclear integrity. Evidence suggests that nuclear functions are disrupted in numerous SCAs, and particularly in the polyglutamine disorders[7,120]. In polyglutamine diseases, in addition to the proteinaceous inclusions and RNA foci that tend to form in the cell nucleus, the disease-causing proteins themselves tend to concentrate within neuronal nuclei. These features may help to explain the large-scale changes in gene expression profiles that have been documented in model systems of numerous SCAs. A compelling example of altered nuclear integrity in an SCA is provided by the SCA7 disease protein ataxin 7 (ATXN7; also known as SCA type 7 protein), which is a component of the SAGA histone acetyltransferase complex. Polyglutamine expansion disrupts the activity of the SAGA histone acetyltransferase, resulting in aberrant chromatin acetylation and marked changes in gene expression[121]. The SCA17 disease protein, the TATA-box-binding protein, is a key component of the basal transcription machinery in neurons and other cells; therefore, polyglutamine expansion in this disease protein is likely to perturb the transcriptome in the brain of patients with SCA17 (REF.[122]).

DNA repair pathways are also thought to be impaired in some SCAs. For example, the activity of the DNA end-processing enzyme polynucleotide kinase 3′-phosphatase is inhibited by ATXN3 in vitro and in mouse models of SCA3/MJD, and the protein products of multiple DNA repair and DNA damage response genes modify the onset of polyglutamine SCAs[121,123–126]. In a cell culture model, nuclear DNA damage was one of the earliest adverse consequences of expressing a polyglutamine disease protein[55]. The fact that DNA repair pathways have been implicated in some SCAs is intriguing given that mutations in DNA repair genes directly cause several autosomal recessive ataxias, including ataxia telangiectasia, ataxia with ocular apraxia type 1 and ataxia with ocular apraxia type 2. CAG repeat-containing RNAs might also disrupt activity in the nucleolus, resulting in the reduced transcription of ribosomal RNA, nucleolar stress and the induction of apoptosis[127].

Finally, the transport of proteins across the nuclear membrane is disrupted in numerous neurodegenerative diseases, including Huntington disease and other polyglutamine diseases[128,129]. Given that pathological alterations to nuclear form and function occur in various SCAs, it is unsurprising that perturbations in neuronal integrity contribute to disease processes. Moreover, links between cytoplasmic protein quality control pathways and the nucleus are increasingly being recognized. Perturbations in one of these subcellular domains likely influence what happens in the other domain; indeed, impaired autophagy has been shown to cause nuclear breakdown through nucleophagy[130].

Diagnosis, screening and prevention

Pre-ataxia stage. Disease onset in SCAs, which is retrospectively assessed in most studies, has traditionally been defined as the onset of ataxia and equated with the time the patient first noticed gait difficulties[131]. However, two large observational studies showed that symptoms begin several years before the onset of manifest ataxia. The European multicentre RISCA study enrolled 276 first-degree non-ataxic relatives of patients with SCA1, SCA2, SCA3/MJD or SCA6, each of which had a 50% risk of carrying the disease-causing mutation[132]. Compared with individuals not carrying the

mutation, patients carrying a mutation in the SCA1 or SCA2 disease gene performed worse in coordination tests. Furthermore, the prevalence of gaze-evoked nystagmus was increased in patients carrying a mutation in the SCA3/MJD disease gene, and the prevalence of muscle cramps was increased in patients carrying a mutation in the SCA1 or SCA2 disease gene[132]. In a monocentric prospective study of 40 Cuban patients carrying a mutation in the SCA2 disease gene, muscle cramps and sensory disturbances were more frequent than in controls and showed worsening over time[133]. MRI studies of a subset of patients in the RISCA and Cuban SCA2 cohort revealed mild cerebellar and brainstem volume loss in patients carrying the disease mutation; volume loss was more pronounced in the individuals closest to the expected onset of ataxia[132,134]. The results of these studies require the view that the polyglutamine SCAs start with the manifestation of ataxia to be revised. Instead, manifest ataxia in these disorders is preceded by a pre-ataxia period of several years that is characterized by mild coordination deficits, manifestation of non-ataxia symptoms and the start of atrophy of posterior fossa brain structures[135]. Although similar studies have not been performed in patients with non-polyglutamine SCAs, these conclusions are likely to apply to all SCAs.

The pre-ataxia stage is of particular research interest as, given that the manifestation and progression of ataxia are associated with irreversible brain degeneration, the initiation of treatments at the pre-ataxia stage may be more effective than the initiation of treatments at the stage of manifest disease. This assumption is supported by experiments in a conditional mouse model of SCA1, in which inhibiting expression of the disease gene before the manifestation of ataxia (at 6 weeks) prevented the disease, inhibiting expression at an intermediate age (12 weeks) led to partial recovery from SCA1 and inhibiting expression at a late age (32 weeks) had no benefit[136]. However, the methodology to perform preventive trials in patients with SCAs needs to be developed.

Age of onset. For most SCAs, the onset of ataxia occurs in the third or fourth decade of life, but there is variation between genotypes, within genotypes and even within families. In general, the age of onset of SCAs due to conventional mutations is earlier than that of polyglutamine SCAs. Specifically, the average age at ataxia onset was 25 years in a group of patients with SCA caused by conventional mutations affecting genes encoding ion channels, compared with 41 years in patients with ataxia caused by CAG repeat expansions[92]. Childhood onset occurs in some SCAs caused by conventional mutations (for example, SCA5, SCA12, SCA13, SCA21, SCA25, SCA29 and SCA47 (REF.[137])) but also in patients with very large CAG repeat expansions[138]. By contrast, SCA6 and SCA31 typically start in later adulthood with an average onset in the sixth decade[60,139–141]. Given the large variation in the age of ataxia onset, this information is usually not helpful in selecting the appropriate genetic test to diagnose SCAs.

In SCAs caused by repeat expansions, the age of ataxia onset inversely correlates with the length of the expanded repeat, as measured in peripheral blood leukocytes[4,5]. However, in a Dutch–French cohort of 802 patients with CAG repeat expansion SCAs, the length of the expanded repeat explained only 44–75% of age at onset variance, suggesting that other factors also help determine this in these SCAs[142]. Genetic factors that might modify the age of onset include the size of the normal allele of CAG repeat-containing genes that are associated with other polyglutamine diseases and genetic variants in DNA repair pathway genes[143,144]. Genetic variants of genes, the protein products of which are involved in DNA repair, may promote the somatic expansion of CAG repeats and thereby affect age of ataxia onset. However, the patterns of somatic mosaicism in SCA1 and SCA3/MJD do not correlate with neuronal vulnerability[145,146]. The effects of non-genetic factors on the age of onset for SCAs have not been systematically studied.

Clinical features. The prominent clinical feature of SCAs is progressive ataxia. The ataxia in patients with SCA is mainly of cerebellar origin, but afferent and vestibular ataxia contribute to the full spectrum of symptoms. In most cases, the first abnormality recognized by patients is unsteadiness of gait. As ataxia progresses, the coordination of the extremities deteriorates, resulting in difficulties with writing and the loss of fine motor skills. Almost all patients with an SCA also experience speech and swallowing problems. On clinical examination, many patients with SCA have oculomotor abnormalities owing to cerebellar dysfunction. These abnormalities, which are not recognized by patients, include disturbed pursuit eye movements (broken-up smooth pursuit), difficulties in eccentric gaze holding (gaze-evoked nystagmus) and inaccuracy of fast saccadic eye movements (dysmetric saccades); however, some patients do complain of double vision[147]. The clinical presentation of SCAs is complicated by the frequent occurrence of non-ataxia symptoms, including motor symptoms (namely, weakness, spasticity and amyotrophy), movement disorders (such as parkinsonism, dystonia and chorea)[148], oculomotor abnormalities related to brainstem dysfunction (such as slowing of fast saccadic eye movements or gaze palsy), sensory symptoms, epilepsy, myoclonus, cognitive and intellectual dysfunction and urinary symptoms[147]. Visual loss due to retinal degeneration is a characteristic feature of SCA7 (REF.[149]). Sleep disorders are also frequent in patients with SCAs and include restless leg syndrome, rapid eye movement sleep behaviour disorder, excessive daytime sleep, insomnia and sleep apnoea[150].

Non-ataxia symptoms are particularly prominent in the polyglutamine SCAs SCA1, SCA2, SCA3/MJD, SCA7, SCA17 and DRPLA, whereas SCA6 is the prototype of an SCA with a purely ataxic phenotype[5]. Although each polyglutamine SCA has a characteristic spectrum of non-ataxia symptoms, there is considerable overlap between them. In exceptional cases, non-ataxia symptoms may occur before ataxia or even be the predominant manifestation of the disease. For example, in SCA7 patients with expansions >59 repeats, visual loss is often the initial symptom[151]. Interrupted repeats with a length of <39 repeats in the SCA2 gene are associated

with parkinsonism rather than ataxia[152,153]. Furthermore, intermediate-length expansions (27–33 repeats) of the SCA2 gene confer an increased risk of amyotrophic lateral sclerosis (ALS)[154] and are associated with shorter survival times in ALS patients[155]. SCA17 may present initially with psychiatric symptoms and chorea[156], and the phenotypical spectrum of DRPLA includes progressive myoclonus epilepsy, choreoathetosis and dementia[157].

Although intellectual symptoms are not part of the typical clinical spectrum of SCAs, neuropsychological testing reveals subtle abnormalities in executive functions, visual–spatial processing, linguistic function and affective regulation[158]. These symptoms, which are designated cerebellar cognitive affective syndrome, are thought to be due to dysfunction of the cognitive part of the cerebellum, mainly lobules VI and VIIA, which are connected to the frontal cortex via the dentate nucleus and thalamus[159]. Cognitive decline resulting in manifest dementia is rare but may occur in polyglutamine SCAs, mainly SCA17 and DRPLA[156,157]. Intellectual disability is a feature of several SCAs caused by conventional mutations[92].

Depression affects 17–26% of SCA patients[160,161], and it has a strong negative impact on the functional status and QOL of patients with SCAs[161,162]. The relationship between depression, neurodegeneration and disease severity is complex. Although depressive symptoms worsen with disease progression, they are not simply the consequence of motor disability in SCAs[161,163].

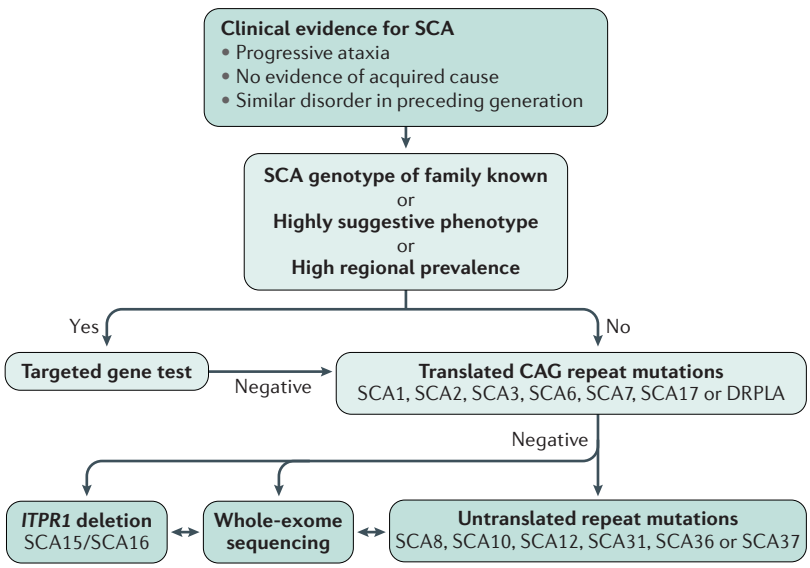


Fig. 5 | **Flowchart of molecular genetic diagnosis of SCAs.** If there is clinical evidence for a diagnosis of a spinocerebellar ataxia (SCA), molecular genetic testing should be initiated. A targeted gene test is recommended only if the SCA genotype of the family is known, if the phenotype is highly suggestive of a certain SCA or if there is a high regional prevalence of a certain SCA. If none of these factors are present, or if the targeted gene test is negative, a systematic approach to diagnosis, starting with tests for translated CAG repeat mutations, is recommended. There is currently no consensus on the appropriate order for performing genetic tests when tests for translated CAG repeat mutations are negative. However, a specific test for the deletion in *ITPR1* that causes SCA15/SCA16 deletion is dispensable if whole-exome sequencing with a specific search for deletions is performed. DRPLA, dentatorubral-pallidoluysian atrophy.

Diagnosis. Patients with SCAs are diagnosed on the basis of a clinical presentation with progressive ataxia and no evidence for an acquired cause, a history of a similar disorder in the preceding generation and a positive genetic test for an SCA genotype. As the overlap in clinical features between different SCAs is considerable, knowledge of these clinical features can guide the selection of the molecular genetic test only in exceptional cases, such as in patients with ataxia and visual loss, which are usually due to SCA7. Other diagnostic procedures, such as MRI, nerve conduction studies and autonomic and cognitive testing, can help identify clinical manifestations and rule out certain conditions, but they do not usually inform the selection of the molecular genetic test.

If a specific SCA genotype is known to be present in the family of an individual with ataxia, a targeted genetic test is possible. Targeted testing can also be considered, in exceptional cases, on the basis of the presence of key clinical features (for example, visual loss in SCA7) or the prevalence of SCAs in the region from which the patient originates (for example, SCA2 in Cuba). In all other cases, a systematic approach is recommended for the diagnosis of SCAs (FIG. 5), although there is currently no consensus on the order in which genetic tests should be performed. This lack of consensus is not surprising given that procedures for molecular genetic diagnosis are rapidly changing owing to technological progress. In addition, the resources available for genetic testing are limited in many health-care systems, which often dictates the test that is selected. With this in mind, we suggest first testing patients suspected to have an SCA for the SCAs caused by translated CAG repeat mutations given their high prevalence. If CAG repeat mutations are not detected, testing can proceed via several routes. For example, whole-exome sequencing (WES) is becoming increasingly available and, in a mixed population of patients with ataxia in which common repeat mutations had been ruled out, WES yielded a definite or probable diagnosis in 22.6% of patients[164]. WES data can also be reanalysed, in cases in which the SCA genotype was not identified, at later time points when new ataxia genes have been identified. However, it is important to note that WES does not detect repeat mutations. To assess for all of the genetic causes of SCAs, additional tests for untranslated repeat mutations (namely, SCA8, SCA10, SCA12, SCA31, SCA36 and SCA37) must be carried out. Genetic testing of SCA8 also warrants specific consideration as it is debated if expansions in *ATXN8* are involved in ataxia[165]. Although linkage, haplotype and experimental data show that expansions in *ATXN8* cause SCA8, these expansions show reduced penetrance compared with expansions in other SCA disease genes[166]. Thus, some individuals carrying an expansion in *ATXN8* never develop ataxia[165]. The large deletion in *ITPR1* that causes SCA15/SCA16 can be detected using WES performed with the intention of identifying deletions. However, as this type of WES analysis is not routinely carried out by diagnostic laboratories, it may be necessary to carry out a specific search for deletions in *ITPR1*. In sum, we suggest that clinicians first test for the presence of CAG repeat expansions; once these have been ruled out, each

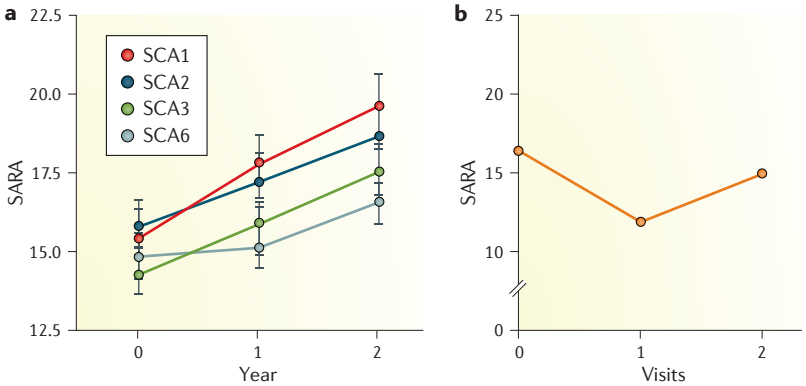


Fig. 6 | **The use of SARA scores in assessing the progression of SCAs. a** | Scale for the Assessment and Rating of Ataxia (SARA) scores in patients with spinocerebellar ataxia (SCA) were assessed over time in patients with SCA1, SCA2, SCA3/Machado–Joseph disease (MJD) or SCA6. The graph shows the 2-year follow-up data from the EUROSCA study. SCA1 has the fastest progression rate, SCA2 and SCA3/MJD have an intermediate progression rate and SCA6 has the slowest progression rate. **b** | Patients were assessed for the long-term improvement of SARA score due to coordinative training. The graph shows the mean SARA score of 14 ataxia patients at baseline (0), 4 weeks after coordinative training (1) and at long-term examination after 1 year (2). The improvement seen after 4 weeks was partially maintained after 1 year. Part **a** adapted from Jacobi, H. et al. The natural history of spinocerebellar ataxia type 1, 2, 3, and 6: a 2 year follow up study. *Neurology* **77** (11), 1035–1041 (2017) https://n.neurology.org. Data in part **b** from REF.[198].

clinician and diagnostic laboratory can decide in which order the genetic tests are performed.

Genetic testing for polyglutamine SCAs is relatively easy to perform and widely available worldwide, and the cost of WES is continuously falling, increasing the availability of this technique. However, the other tests discussed here are not routinely performed in many countries, despite the increasing availability and falling costs of genetic testing, as the genetic diagnostic process for SCAs is time consuming and expensive, especially if the initial tests for CAG repeat mutations are negative. Owing to the lack of systematic studies, it is unknown how many patients with an autosomal dominantly inherited ataxia have undergone the entire genetic diagnostic process but evaded a genetic diagnosis. In the future, the complex genetic testing strategy discussed here is likely to be replaced by whole-genome sequencing (WGS) with long read sequencing technology. WGS is currently used in research and is effective in identifying new disease mutations[167,168]. However, it is not routinely used for diagnostic purposes.

A diagnosis of SCA must also be considered in patients with sporadic ataxia and without a family history of SCA; these patients might have an SCA owing to novel mutations, reduced penetrance of the mutation or misattributed paternity. In patients without a family history of SCA, a careful diagnostic work-up, including MRI and laboratory tests, is essential to assess for non-genetic causes of ataxia[169]. If this work-up is negative, molecular genetic testing of patients for SCAs is justified. Genetic screening studies in individuals with sporadic adult-onset ataxia from the USA and Europe yielded mutations of SCA disease genes in 15–24% of patients[170–173]. Among polyglutamine SCAs, SCA6 is the most likely genotype of patients with sporadic SCA6 owing to its late onset; the parents transmitting SCA6 could have died before ataxia manifested in the patient[60,139,140].

In families with a known causative mutation of SCA, predictive genetic testing similar to that used to screen for Huntington disease can be offered to at-risk individuals. Children of patients with SCA have a 50% risk of having the disease. The testing procedure includes clinical examination, extensive counselling and psychological support in addition to the relevant molecular test. Utilization of predictive testing for SCAs varies between countries. Worldwide, the number of predictive genetic tests performed for SCAs is much lower than the number performed for Huntington disease. For example, a consortium of ten French centres performed 712 predictive genetic tests for Huntington disease but only 46 predictive genetic tests for SCAs[174]. However, in countries in which there is a high prevalence of a certain SCA, such as Cuba (SCA2), Brazil (SCA3/MJD) and Portugal (SCA3/MJD), large testing programmes have been established[175,176]. There have been only a few studies into predictive testing for SCAs and, according to these studies, the majority of tests are performed on women[174]. Of note, individuals being screened for SCAs often do not complete the screening programme, which includes post-test psychological evaluation. There have also been reports of serious events, mainly suicide attempts, following the disclosure of the result of the genetic test[174,177].

As long as there is no preventive treatment available for SCAs, early diagnosis through predictive testing has no positive impact on the health of individuals. However, predictive testing is useful because it provides relevant information for family planning and the preimplantation genetic diagnosis of embryos. Therefore, families need to be carefully informed about the option of predictive testing of at-risk individuals, and decisions should be made on an individual basis.

Disease progression. All SCAs are progressive disorders that often lead to disability and premature death[6,131]. However, there is an enormous degree of variability in progression rate both between and within the different SCAs. A number of cohort studies, including a large European natural history study called the EUROSCA study, longitudinally assessed the progression rates of the most common polyglutamine SCAs, SCA1, SCA2, SCA3/MJD and SCA6, by repeated administration of the Scale for the Assessment and Rating of Ataxia (SARA)[178–184]. SARA is a clinical scale based on a semi-quantitative assessment of ataxia on an impairment level. SARA underwent rigorous validation and is now widely used for both observational and interventional studies worldwide[185]. These studies have consistently found that, of the most common polyglutamine SCAs, SCA1 has the fastest progression rate, SCA2 and SCA3/MJD have an intermediate progression rate and SCA6 has the slowest progression rate[178–180,182] (FIG. 6a). However, the absolute progression rates differed between the various cohorts; specifically, the annual SARA increase in cohorts from Taiwan and Japan[181,182] was higher than that in cohorts from Europe, the USA and Brazil[178–184]. Global studies involving patients from different parts of the world are

presently lacking. In patients with SCA1, longer CAG repeat expansions are associated with faster disease progression, whereas CAG repeat length was not found to influence disease progression in other polyglutamine SCAs[178]. SCAs caused by mutations other than CAG repeat mutations tend to have slower progression and to take a more benign course[186]. For example, disease duration was markedly longer in a group of 412 patients with SCAs caused by conventional mutations (in genes coding for ion channels) than in a group of patients with polyglutamine SCAs, although the patients were enrolled in the study at similar functional stages of disease[92]. As data on disease progression are limited to the most common polyglutamine SCAs, natural history studies in patients with each subtype of SCA are required before future interventional trials can be carried out. Owing to the rarity of most SCAs, this goal can be achieved only through a global initiative.

Management

Pharmacological treatments for SCAs. The path to effective therapies for SCAs is hampered by their heterogeneity; specific therapeutic approaches may be required for each genotype. However, in the past decades, several pharmacological treatments were tested in clinical trials for their efficacy towards ataxia[187,188]. Some encouraging results were reported in a few randomized, double-blind, placebo-controlled studies, with drugs including riluzole, valproic acid, varenicline and lithium carbonate, but no definite evidence of benefit was established[189–192].

Riluzole, a drug licensed for the treatment of ALS, was reconsidered for the treatment of patients with ataxia owing to its ability to inhibit presynaptic glutamate release and activate calcium-activated potassium channels. In 55 patients with different types of genetic ataxias (SCAs and Friedreich ataxia), riluzole decreased SARA scores by 1.02 points in patients, compared with a mean increase in SARA score of 1.66 in the placebo group[189]. Although a change of 1.0 point in SARA score is thought to be clinically relevant[193], larger studies in patients presenting more homogenous genetic forms of ataxia are needed to define the effectiveness of riluzole in clinical practice. In fact, the data on the change in SARA score in the EUROSCA study suggest that the score of this scale is greatly influenced by the genetic subtype, the length of CAG expansion and the age of the patient at enrolment[178].

The anticonvulsant valproic acid has been proposed as a pharmacological treatment in SCA3/MJD for its neuroprotective properties as a pan-histone deacetylase inhibitor. Valproic acid was assessed in 12 patients with SCA3/MJD that were randomly assigned to receive high-dose valproic acid, low-dose valproic acid or placebo for 12 weeks[190]. The mean change in total SARA score after 12 weeks was significantly greater in the patients receiving a high dose (a 2.05 decrease in SARA score; $P = 0.021$) than in patients in other treatment groups. Although this study indicated that a high dose of valproic acid has a positive effect on ataxia symptoms, the small number of subjects in the study and the short period of treatment did not allow conclusive statements.

Lithium carbonate was evaluated in 62 ambulatory patients with SCA3/MJD for 48 weeks, but no difference was seen in mean scores of the neurological scale for ataxia[191].

Varenicline is a partial agonist of the α4β2 neuronal nicotinic acetylcholine receptor that is used to aid the cessation of smoking. Varenicline was anecdotally reported to have beneficial effects in patients with ataxia that were taking it as part of a smoking cessation programme[194]. This drug was subsequently tested in patients with SCA3/MJD, but its use was associated with a 40% dropout rate owing to side effects including nausea, insomnia, light headedness, depression and worsened unsteadiness[192].

Supportive treatments for SCAs. Currently, no pharmacological treatments are approved for routine use in patients with SCAs, the clinical management of which remains symptomatic and supportive for the maintenance of function[195]. General supportive management options include physiotherapy, occupational therapy and speech therapy. Different types of approaches and regimens have been tested in several studies and in several settings, including inpatient and outpatient settings, home-based programmes or a combination of these. The length of training undertaken by patients and the time to follow-up assessment were also very variable[196,197].

Physiotherapy focused on improving gait, balance, coordination, posture and muscle strength is often recommended. Interventions may include conventional physiotherapy exercises, computer-assisted training, treadmill training and biofeedback therapy[198–202]. In an intra-individual case–control design study, 14 patients with either cerebellar or sensory ataxia underwent intensive whole-body coordination training for 4 weeks[198]. After treatment, SARA scores decreased significantly ($P = 0.001$; −4.4 points on average) (FIG. 6b) and an improvement in motor performance and balance capacities was also observed using quantitative movement analysis based on a motion capture system[198]. This improvement was more substantial in patients with cerebellar ataxia than in patients with sensory ataxia, and the benefits persisted after 1 year in patients with cerebellar ataxia executing continuous training (that is, training for ~1 hour per day)[196]. In another study, 42 hospitalized patients, 20 of whom had SCA6, received 4 weeks of inpatient rehabilitation, including physiotherapy and occupational therapy, for 12 hours per week. Patients were instructed to maintain a similar level of activity at home after discharge[197]. Immediately after the rehabilitation period, SARA scores improved (specifically, SARA score decreased by 2.8 points on average). The effectiveness of the treatment was also evaluated using the Functional Independence Measure (FIM), which showed an improvement of 1.2 points[203]. Physiotherapy may improve daily life functions in ambulatory patients and in individuals with advanced disease. However, the improvement is more sustained in subjects with mild ataxia[200].

Three systematic reviews evaluating rehabilitation interventions for individuals with ataxia concluded that rehabilitation improves function and mobility in

Table 2 | **Treatments of non-ataxia neurological symptoms in SCA**

Symptom	Pharmacological treatments available	Non-pharmacological treatments available
Spasticity	Baclofen, eperisone, tizanidine, benzodiazepines and focal intramuscular botulinum toxin	Physiotherapy and stretching
Neuropathic pain and paraesthesia	Pregabalin, gabapentin, carbamazepine and duloxetine	Acupuncture
Parkinsonism	Levodopa and dopamine agonists	Not available
Chorea	Tetrabenazine and neuroleptic drugs	Not available
Dystonia	Benzodiazepines, trihexyphenidyl, biperiden and focal intramuscular botulinum toxin	Deep brain stimulation
Sleep disturbances	Benzodiazepines, zolpidem, melatonin, trazodone and mirtazapine	Not available
Restless leg syndrome	Benzodiazepines and pramipexole	Not available
Respiratory sleep apnoea	Not available	Non-invasive ventilation
Dysphagia	Not available	Logopaedic rehabilitation, dietary modification and percutaneous endoscopic gastrostomy
Urinary disturbances	Anticholinergic drugs, α1-selective α-blockers and β_3-adrenergic receptor agonists	Urinary catheterization
Seizures and myoclonus	Antiepileptic drugs and benzodiazepines	Not available
Depression	Selective serotonin reuptake inhibitors	Psychological support
Behavioural abnormalities	Selective serotonin reuptake inhibitors, mood-stabilizing antiepileptic drugs, benzodiazepines and neuroleptic drugs	Not available

SCA, spinocerebellar ataxia.

patients[188,196,197]. Thus, recommending that patients with ataxia regularly perform rehabilitative exercises and training appears to be important. Unfortunately, the accessibility, frequency and type of rehabilitating treatments, including physiotherapy, vary considerably between centres and countries and are highly dependent on economic resources.

Insufficient data exist on the use of speech and language therapy in patients with ataxia to draw conclusions[195]. Management of dysphagia in patients with ataxia, as for other types of neurological disorders, may require a dietician to suggest dietary modifications to optimize caloric intake and hydration. Speech therapists may be able to educate and train patients and their relatives by recommending supportive strategies and surveillance during swallowing to prevent respiratory infections. Aspiration pneumonia, insufficient cough and malnutrition are serious comorbidities in advanced stages of SCAs[204].

In addition to ataxia, non-ataxia neurological, intellectual and autonomic symptoms frequently occur in several forms of SCAs. Recognition of these symptoms and their adequate treatment following established guidelines, such as the guidelines of the UK patient organization (Ataxia UK), are mandatory.

The management of SCAs requires periodical neurological follow-up visits to evaluate disease progression and diagnose ataxia-associated symptoms that may contribute to ataxia or affect the general health of the individual. Possible pharmacological treatments targeting specific non-ataxia-associated symptoms or rehabilitation regimens for both ataxia and non-ataxia-associated symptoms should be discussed and started, as necessary, after each follow-up (TABLE 2).

It is also important to discuss prognosis, palliative care and advance care planning with patients with SCAs and their family members. Furthermore, monitoring disease progression and the quantitative assessment of signs and symptoms during the disease course help predict prognosis and can lead to patients being invited to participate in upcoming interventional clinical trials.

Quality of life

Although health-related QOL is undisputedly impaired in patients with SCA, our knowledge of the extent, variability and predictors of impairment is insufficient owing to the small number of meaningful studies and the absence of ataxia-specific QOL tools. In the EUROSCA study, which included 526 patients with SCA1, SCA2, SCA3/MJD or SCA6, QOL was assessed using EQ-5D[147]. EQ-5D is a generic instrument that was developed and validated by the EuroQuol Group in 1990, and it is available in validated translations for use as a questionnaire[205]. Compared with population controls, QOL was reduced in patients with SCA to a comparable degree to that reported for other chronic neurological diseases, such as epilepsy or Parkinson disease[162]. Almost all patients reported limitations in mobility, but some patients also reported pain and discomfort, depression and anxiety and problems with usual activities, including self-care. Determinants of QOL in patients with SCA were ataxia severity, the extent of non-cerebellar involvement and the presence of depressive syndrome, but these factors explained only 30% of the variance[162]. During an

observational period of 8 years, QOL measures in patients with SCAs steadily deteriorated in all genotypes[163]. A study of 80 patients with SCA that used the 36-item Short Form Health Survey (SF-36; another instrument to assess QOL that is not specific to ataxia) found that the presence of a caregiver was a strong determinant of QOL[206]. It is unknown at which time QOL begins to deteriorate in SCAs, although in the RISCA study, which compared carriers and non-carriers of SCA mutations on average 10 years before the onset of ataxia, there was no difference with respect to QOL, quality of sleep and depression between groups[132].

Outlook

Over the past two decades, knowledge of the epidemiology, pathophysiology and clinical manifestation of SCAs has increased enormously. In sharp contrast to this, there has been almost no progress in the development of therapies for SCAs. For trials of symptomatic treatment approaches, sufficiently validated clinical outcome measures are available. In order for early-phase trials of disease-modifying treatments to be performed, however, sensitive biomarkers that can indicate treatment efficacy in small groups of patients need to be identified before larger trials relying on clinical outcome measures can be initiated. It will be especially important to identify biomarkers for preventive trials, as clinical outcome measures for the severity of ataxia lack sensitivity in the pre-ataxia stage, when ataxia symptoms assessed by these scales are absent.

Clinical outcome measures and biomarkers for SCAs. SARA is currently the most widely used outcome measure in clinical studies and trials for SCAs (see above); its use can be complemented by performance tests that quantitatively assess coordination. The SCA Functional Index (SCAFI) is derived from the time it takes a patient with SCA to walk 8 m, the time it takes the patient to perform the nine-hole peg test and the number of syllables the patient can repeat in 10 seconds (REF.[207]). The Composite Cerebellar Functional Severity Score (CCFS) combines the results from a pointing task (specifically, a click test) and the nine-hole peg test[208]. Both SCAFI and CCFS, however, were less sensitive than SARA in detecting disease progression[186,193]. In a cross-sectional study, non-ataxic carriers of an SCA1 or SCA2 mutation performed worse in these performance tests than individuals without an SCA mutation[132]. Whether these tests can detect deterioration in the pre-ataxia stage is currently being studied. Similarly, quantitative movement analysis based on a motion capture system revealed differences in certain movement parameters between non-ataxic carriers of an SCA mutation and healthy individuals without an SCA mutation; however, how these parameters change over time in carriers of a mutation is unknown[209].

A biomarker is an objective and measurable feature that provides information on a biological process, and biomarkers may aid in the diagnosis and treatment of SCAs. For the diagnosis of SCAs, genetic tests provide highly reliable information on the presence or absence of the disease if the patient is affected by an SCA caused by a known mutation. MRI and biochemical biomarkers indicating the severity of the disease (that is, progression markers) and the efficacy of drugs (that is, pharmacodynamics markers) are under development. The identification of such markers is essential for future clinical trials, in particular for preventive trials in the pre-ataxia stage.

Structural MRI has been used to study brain morphological alterations in patients with SCA, in particular in the more common SCAs caused by translated CAG repeat mutations. The focus of most studies has been on the visualization and quantification of changes in volume in the cerebellum and brainstem. The different SCA genotypes are characterized by specific but overlapping atrophy patterns; specifically, isolated loss of cerebellar volume is characteristic of SCA6 and a number of SCAs caused by conventional mutations, whereas SCAs caused by CAG repeat mutations other than SCA6 typically have additional atrophy of the brainstem and basal ganglia[210,211]. Although not sufficiently studied, there is also evidence that spinal cord atrophy occurs in many SCAs, resulting from the degeneration of spinal fibre tracts[212–214]. Although there is only limited information on changes in longitudinal brain volume in SCAs, data suggest that the effect sizes are in the same range as, or higher than, those of clinical scales[215–217]. Finally, studies in non-ataxic patients carrying a mutation in SCA2 have detected loss of cerebellar volume, suggesting that this measure is a promising marker of progression in the pre-ataxia stage[132,134].

MRI markers other than brain volumes are under investigation for their use as markers of SCA progression. Diffusion tensor imaging (DTI) studies in patients with SCA1, SCA2 and SCA3/MJD revealed widespread microstructural damage in the white matter of the infratentorial and supratentorial brain regions[218,219]. As longitudinal data in large cohorts are rare, it is unknown whether DTI-derived measures are sensitive as progression markers of SCAs[218,219]. Magnetic resonance (MR) spectroscopy studies showed lower concentrations of *N*-acetylaspartate (NAA), a marker of neuronal integrity, as well as other neurochemical alterations in patients with different SCAs compared with healthy individuals[220,221]. In a recent MR spectroscopy study using a 7T scanner, neurochemical abnormalities were detected in non-ataxic carriers of SCA mutations[222]. MR spectra in patients with SCA2 changed over time[223], but the data do not allow the sensitivity of MR spectroscopy, in comparison to other potential progression markers, to be estimated.

In short, the development of biochemical markers for SCAs is still in its infancy. Given the current development of treatments that lower the concentration of the disease protein in polyglutamine SCAs, there is an urgent need for ATXN-specific bioassays. These bioassays will be indispensable as pharmacodynamic markers to demonstrate the efficacy of such treatments in early-phase clinical trials. Neurofilament light polypeptide (NF-L) is a nonspecific marker of neuronal damage. Preliminary data showing that serum levels of NF-L are increased in patients with SCAs suggest its potential as a progression marker of SCA[224], but the results need to be validated in larger studies that include repeated measurements.

Future SCA clinical trials. The search for symptomatic and disease-modifying therapies for SCAs has not yielded medications with clear benefits, but recent advances in our understanding of the disease mechanisms suggest promising avenues for both symptomatic and disease-modifying therapies. For example, the recognition that ion channel dysfunction contributes to many SCAs suggests that channel modulators could have symptomatic benefit and even alter the course of disease[93,107–110]. In fact, the small number of encouraging results in clinical trials to date include several ion channel modulators, such as riluzole[189], valproic acid[190] and 4-aminopyridine[225]. Ultimately, combination therapy that targets multiple points in cerebellar circuitry might be needed to achieve a robust beneficial effect in the treatment of SCAs.

Arguably, the most exciting recent therapeutic advance for SCAs is the variety of effective approaches for reducing or silencing disease genes[226,227]. As SCAs are caused by the dominant action of the mutant gene, silencing or reducing the expression of the implicated gene or its encoded transcript or protein is a compelling strategy for modifying these diseases. Co-opting the RNA interference pathway within cells of the central nervous system with virally delivered small interfering RNAs[228–230] or microRNA mimics[231] has shown promise in animal models of repeat expansion SCAs. Similarly, antisense oligonucleotides that target specific SCA genes have proved efficacious in animal models of several SCAs caused by repeat expansions, such as SCA2, SCA3/MJD and SCA36 (REFS[232–235]). Small molecules that selectively target repeat expansions represent another approach for treating SCAs, but these molecules have not yet been tested in animal models. In principle, any repeat expansion could be targeted with small molecules, as CG-rich and AU-rich repeat expansions have already been successfully targeted in various model systems, including the AUUCU repeat in SCA10 (REF.[236]). Results in human clinical trials of other neurodegenerative diseases, including Huntington disease, suggest that this strategy will be effective for treating SCAs[237]. Indeed, it is thought that nucleotide-based gene suppression strategies for several SCAs may move from the laboratory to clinical trials in humans within the next few years. Moreover, because these strategies target the earliest steps in the pathogenic cascade, they should be applicable to any SCA caused by a dominant-toxic RNA effect or a proteotoxic effect.

Similarly, the search is underway for compounds that, through a variety of pathways, can reduce the levels or toxicity of the gene products underlying specific SCAs. In SCA3/MJD, for example, unbiased compound screens have identified citalopram and aripiprazole as existing drugs that may reduce the levels, toxicity and/or aggregation of the disease protein[238,239]. It is currently unknown whether these compounds exert these effects through their canonical action on monoaminergic neurotransmission or by other yet-unidentified mechanisms[238,239]. Valproic acid can reduce the toxicity of the SCA3/MJD disease protein (ATXN3) by preventing the heat-shock-dependent nuclear transport of ATXN3 (REF.[240]). For the treatment of patients with SCA1, inhibiting protein-kinase-A-mediated phosphorylation of serine 776 in ATXN1 is a promising strategy to lessen toxicity[66]. Finally, given the frequent occurrence of protein aggregation and accumulation in the SCAs, strategies to rid the brain of toxic disease proteins by boosting protein degradation pathways or the autophagy–lysosomal system have been attempted with some success in animal models[241,242].

These advances offer hope that disease-modifying therapies may not be far off for the most common SCAs. This optimism is tempered, however, by the recognition that the SCA field still needs to establish biomarkers that can verify disease target engagement and document a slowing of disease progression.

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