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The autosomal dominant spinocerebellar ataxias: emerging mechanistic themes suggest pervasive Purkinje cell vulnerability

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Abstract

The spinocerebellar ataxias are a genetically heterogeneous group of disorders with clinically overlapping phenotypes arising from Purkinje cell degeneration, cerebellar atrophy and varying degrees of degeneration of other grey matter regions. For 22 of the 32 subtypes, a genetic cause has been identified. While recurring themes are emerging, there is no clear correlation between the clinical phenotype or penetrance, the type of genetic defect or the category of the disease mechanism, or the neuronal types involved beyond Purkinje cells. These phenomena suggest that cerebellar Purkinje cells may be a uniquely vulnerable neuronal cell type, more susceptible to a wider variety of genetic/cellular insults than most other neuron types.

The autosomal dominant spinocerebellar ataxias (SCAs) are a genetically and clinically heterogeneous group of neurodegenerative disorders (tables 1 and 2). To date, 32 unique subtypes attributed to distinct genetic loci have been identified, comprising a collective global prevalence of ~4/100 000, with evidence of regional increases in prevalence of some SCAs due to the founder effect.[1–4] All subtypes share the common end point of cerebellar and predominantly Purkinje cell degeneration.[5] For 22 of the 32 subtypes, specific genetic defects have been identified (tables 3 and 4).[5–31] The known genetic causes include CAG repeat expansions encoding expanded polyglutamine repeats in unrelated proteins,[6–10121321] untranslated repeat expansions,[1415173128] and conventional mutations in critical genes (figure 1).[111618–202325–2730]

CLINICAL FEATURES OF THE SCAS

The autosomal dominant SCAs have been clinically classified into three groups, autosomal dominant cerebellar ataxia (ADCA) types I, II and III.[32] ADCAI represents mixed cerebellar ataxias, that is, involving other neurological symptoms in addition to cerebellar ataxia.

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ADCAII is specifically limited to cerebellar ataxias that include retinopathy, of which there is only one, SCA7. ADCAIII contains the pure cerebellar ataxias, in which cerebellar ataxia is the only or predominant neurological manifestation of disease. As more causative genes and disease mechanisms have been identified, no definitive correlation between phenotype and gene or mechanistic class has been delineated. Presently, although the division is not always homogenous within genotype, the autosomal dominant SCAs are typically classified as either mixed or pure. Key clinical features of the SCAs are summarised in tables 1 and 2.[22232628303133–37]

While patients with any of the mixed cerebellar ataxias may exhibit essentially pure cerebellar features, typically they develop additional neurological deficits, such as extrapyramidal symptoms, arreflexia, seizures, sensory deficits and cognitive deficits early in the course of the disease. These SCAs include SCA1–4, 7, 8, 10, 12–14, 17–21, 23, 25, 27–29, 32, 35 and 36.[33–35] SCA7 is the mixed ataxia associated with progressive blindness due to a retinal rod-cone dystrophy that was originally identified as ADCA II. Genetic loci, neuroradiological findings and causative genes with mutation type (if known) of the mixed SCAs are listed in table 3.

The pure cerebellar ataxias are distinguished by exclusive cerebellar ataxia without other neurological symptoms, and include SCA5, 6, 11, 15/16, 26, 30, 31 and 34.[33–35] However, rare reports for some of these predominantly pure cerebellar ataxias have noted involvement of other systems, resulting in pyramidal symptoms, peripheral neuropathy and movement disorders.[76] Genetic loci, neuroradiological findings and causative genes with mutation type (if known) for the pure cerebellar ataxias are indicated in table 4.

GENETICS AND DISEASE MECHANISMS OF THE REPEAT EXPANSION-ASSOCIATED SCAS

Polyglutamine expansion ataxias

The mixed ataxias SCA1–3, 7 and 17, as well as the pure ataxia SCA6, are caused by expansions of CAG repeats encoding polyglutamine tracts within several unrelated genes and, as with other repeat expansion disorders, there is an inverse correlation between repeat length and age of onset.[72139414677] The expanded polyglutamine tracts impair native protein folding, function, DNA-protein or protein–protein interactions of the mutant protein, often leading to dysregulation of their function in transcription. The group is thus often considered part of a larger group of disorders called transcriptionopathies.[34] Several of the polyglutamine ataxias are associated with the formation of cytoplasmic or intranuclear aggregates in affected tissue. While originally believed to be deleterious, the aggregates may actually represent protective sequestration of the misfolded protein.[78]

SCA1 is caused by an expanded CAG repeat in the gene, *ATXN1,* that encodes an N-terminal polyglutamine tract in the widely expressed ataxin-1 protein[7] (normal range 6–39, pathological ~39–83).[67] Borderline alleles also become pathological when interrupting CAT sequences normally present in the non-disease-associated CAG repeat sequence are absent

and are unable to provide a stabilising effect during DNA replication and prevent repeat expansion.[7]

Ataxin-1 has been studied intensely, and a comprehensive review is beyond the scope of this summary. In short, ataxin-1 is a chromatin-binding factor that suppresses Notch signalling in the absence of Notch.[79] Ataxin-1 is phosphorylated on a key residue, S776, that regulates nuclear translocation through its interaction with Capicua.[68081] The polyglutamine expansion increases complex formation with the RNA-binding RBM17 protein.[82] Alterations in calcium homeostasis,[83] nuclear transcription,[81] and protein aggregation[84] have all been implicated in the pathogenesis of SCA1.

SCA2 is caused by an expanded CAG repeat in the gene, *ATXN2,* resulting in an N-terminal polyglutamine tract in the widely expressed ataxin-2 protein (normal 13–31, pathological 32–79 repeats, superexpansions >100, incomplete penetrance 32–34).[8985] Repeat expansions in the *ATXN2* gene of up to 500 repeats have been identified in patients presenting with a fatal infantile encephalopathy.[86] Recent studies have also suggested that intermediate expansion lengths (27–33) also confer increased susceptibility to amyotrophic lateral sclerosis (ALS).[87] Ataxin-2 is thought to be involved in RNA processing based on sequence homology to other RNA binding proteins.[39] There is some evidence for the role of altered calcium homeostasis.[88]

SCA3 is caused by a CAG repeat expansion in the gene *ATXN3* resulting in a C-terminal polyglutamine tract in the ubiquitously expressed ataxin-3 protein (normal 44 or less, pathological 52–86, incomplete penetrance 45–51).[41] Small expansions (45–59) tend to manifest initially with predominantly neuropathic features and sleep disorders, developing ataxia later; modest expansions (≥60, average 73–76) present with an ataxia predominant syndrome; and large expansions (≥60, average 80) present with severe dystonia.[41]

The function of ataxin-3 has not been fully clarified,[10] but it has demonstrated deubiquitinase activity, with a predilection for longer ubiquitin chains.[4189] Several mechanisms have been postulated for the molecular pathogenesis of SCA3, including toxic effects of a proteolytic fragment of the expanded ataxin-3 protein; altered protein-protein interactions leading to transcriptional dysregulation; or perturbation of axonal transport.[419091] Several groups have also implicated mitochondrial dysfunction,[9293] or altered calcium homeostasis.[88]

SCA6 is caused by expansion of a small CAG repeat in the *CACNA1A* gene. The expanded polyglutamine tract, the smallest in the SCA family, (normal 4–18 repeats, pathological 19–33 repeats),[77] appears in two proteins encoded by this gene: within the C-terminus of some splice variants of the a1A subunit of the voltage-gated P/Q-type calcium channel, and within a separate transcription factor protein, a1ACT.[1294]

The α1ACT transcription factor was recently discovered to be the product of an internal ribosome entry site within the *CACNA1A* gene, and is important for neural and Purkinje cell development. The polyglutamine expanded α1ACT loses transcription factor function, leading to cell death in cultured cells and cerebellar atrophy and clinical ataxia in transgenic mice.[94]

SCA7 is caused by an expanded CAG repeat in the gene, *ATXN7,* resulting in a polyglutamine tract in the ataxin-7 protein (normal 7–17, pathological 38–150).[1346] Longer repeats (100–150) correlate to the most severe infantile form of the disease, while shorter repeats (36–43) correspond to a milder form of the disease with adult onset. The typical disease involves 50–55 repeats, and symptoms begin in adolescence or adulthood.[1346] The protein ataxin-7, a transcription factor, is a component of the STAGA complex involved in chromatin remodelling via histone acetylation and deubiquitination.[344695] Polyglutamine-expanded ataxin-7 may exert its deleterious effects through a combination of gene dysregulation in retinal cells and protein aggregation within neurons.

SCA17 is caused by an expanded repeat of CAG and CAA in the gene, TATA-box binding protein (TBP), encoding the ubiquitously expressed transcription factor TBP (normal 25–44, pathological 47–63, incomplete penetrance 45–46).[2196] TBP performs well-known transcriptional functions, although the effect of the polyglutamine expansion on Purkinje cells is still an area of active research.

Ataxias caused by non-coding repeat expansions

The mixed ataxias SCA8, 10, 12 and 36 as well as the pure ataxia SCA31 are caused by non-coding repeat expansions, that is, expanded repeat tracts identified outside of the recognised protein coding regions, such as in introns or 5′ UTRs. SCA8, which presents as either a pure or spastic ataxia, is believed to exert its deleterious effects through a non-coding CTG triplet repeat expansion within the *ATXN8* gene (normal 16–37, pathological 107–127),[14] with several examples of incomplete penetrance reported.[48] Bidirectional transcription of the trinucleotide repeat expansion occurs, resulting in an untranslated CTG expansion in the *ATXN8* opposite strand (*ATXN8OS*) RNA transcript and a translated CAG repeat (C-terminal polyglutamine) expansion in the *ATXN8* strand.[97] The pathogenesis of the 5′ UTR CTG repeat in *ATXN8OS* has been most well studied, and leads to RNA toxicity through toxic gain of function, seen as RNA foci co-localising with MBNL1.[98]

Recent studies in SCA8 have uncovered a novel molecular mechanism of gene expression, known as repeat-associated non-ATG (RAN) translation, which may also contribute significantly to disease. In RAN translation, expanded repeat sequences within mRNA, triplet and otherwise, are the site of initiation of protein translation downstream from the 5′ capped mRNA and initial ATG start codon, and in the case of triplet expansions leading to production of homopolymeric proteins in all three reading frames.[99100] This was initially demonstrated for SCA8, but has now also been shown for other neurological disorders, including myotonic dystrophy type 1, fragile X tremor ataxia syndrome and C9ORF72 ALS with frontotemporal dementia.[100] For repeat expansion diseases including SCA8, this discovery raises the question of whether the deleterious effects of the repeat expansion are exerted through RNA, protein, or both. In vitro SCA8 polyserine and polyalanine homopolymeric proteins have been identified, and antibody to these polypeptides detected polyserine and polyalanine deposits in postmortem SCA8 brain specimens. The role of these RAN translation products in SCA8 disease pathogenesis is currently under study.

SCA10 is caused by an untranslated pentanucleotide repeat (ATTCT) expansion, 800–4500 repeats, in the *ATXN10* gene (normal 10–29),[15] although there is some evidence for

incomplete penetrance.[101] It has recently been demonstrated that the pathologically expanded RNA sequesters heterogeneous nuclear ribonucleoprotein K (hnRNP K) within mouse neurons, triggering release of protein kinase (PK) C5 and activating apoptosis, suggestive of a gain of toxic RNA function.[102]

SCA12 is caused by a non-coding triplet CAG expansion in the 5′ UTR of the brain-specific regulatory subunit of the serine/threonine protein phosphatase PP2A, PPP2R2B, (normal 9–28, pathological 55–78.)[17] Within a *Drosophila* SCA12 model it has been demonstrated that the CAG repeat expanded homologue gene results in mitochondrial dysfunction and increased oxidative stress, shortening the organism's lifespan.[103]

SCA31 has been attributed to an intronic pentanucleotide (TGGAA) expanded repeat insertion in brain-expressed, associated with NEDD4 (BEAN), (pathological insertion 2.5–3.8 kb).[28] Most normal controls in the Japanese population demonstrated no such insertions; the incidence of non-pathogenic uninterrupted pure expansions in control individuals may be somewhat higher in other populations.[29] The repeat-expanded RNA was demonstrated to localise to centromeres in vivo, suggesting a role in heterochromatin or chromosomal structure,[28] with unknown function in Purkinje cells.

SCA36 has been attributed to an intronic hexanucleotide (GGCCTG) repeat expansion in NOP56 (pathological repeat length 1500–2000).[31] NOP56 is predicted to function in an early pre-rRNA processing step[104] with unknown effect on Purkinje cell function. With the detection of RAN translation in an increasing number of neurodegenerative diseases caused by non-coding repeat expansions it is likely that there will be additional evidence for this mechanism in other ataxias.

GENETICS AND DISEASE MECHANISMS OF SCAS CAUSED BY CONVENTIONAL MUTATIONS IN CRITICAL GENES

While the identification of coding and non-coding repeat expansions provided initial hope of identifying common molecular mechanisms, the subsequent demonstration that many SCAs are caused by missense mutations in critical proteins promised to reveal common pathogenic themes and key Purkinje cell vulnerabilities. The SCAs attributed to such conventional mutations in critical genes include the mixed cerebellar ataxias SCA13, 14, 19/22, 23, 27, 28 and 35, as well as the pure cerebellar ataxias SCA5, 11, 15/16 and 26.

Although a common downstream outcome for missense mutations in critical proteins may simply be protein misfolding and aggregation, there are some recurring themes of protein function and dysfunction that point to key areas of Purkinje cell vulnerability. The most common theme relates to disturbances of ion channel function either by direct mutation of an ion channel protein or genetic disruption of a pathway that plays a role in modulating ion channel function (SCA13, 15/16 and 19/22) and neuronal excitability (SCA5, 14 and 27).

SCAs due to mutations in ion channel genes

SCA13 is directly attributed to ion channel dysfunction, via a mutation in the widely expressed voltage-gated potassium channel, *KCNC3*.[18105106] Three point mutations have

been associated with the disease to date, F448L, R420H and R423H. The first (F448L) shifted the activation curve of the channel and slowed channel closing.[18] The latter two are located in the voltage-sensing domain and resulted in a dominant negative loss of channel function,[18] leading to Purkinje cell degeneration by an unknown mechanism.

SCA15/16 has been associated with deletions or missense mutations in the *ITPR1* gene which encodes the type 1 inositol triphosphate receptor.[20] SCA15/16 stands alone in implicating a haploinsufficiency mechanism, as some *ITPR1* deletions have been demonstrated to result in lower levels of ITPR1 protein.[20] Homozygous loss-of-function *ITPR1* mutations in mice cause severe ataxia and heterozygous mutations cause motor incoordination.[107]

SCA19/22 has recently been associated with several point mutations in *KCND3,* encoding the voltage-gated potassium channel $K_V4.3$.[22] These point mutations lead to a misfolded potassium channel subunit that is retained in the ER.[22] It is unclear whether the protein misfolding or loss of channel function is responsible for Purkinje cell degeneration.

SCAs affecting neuronal excitability or excitotoxicity

Several SCAs have implicated disruption in neuronal excitability and signalling. SCA5, a pure cerebellar ataxia, has been attributed to a series of mutations in *SPTBN2,* encoding (β-III spectrin.[11] The defective (β-III spectrin fails to stabilise the glutamate transporter, EEAT4, at the membrane, possibly producing degeneration through glutamate toxicity.[11] Loss of (β-III spectrin has been demonstrated to stunt development of normal Purkinje cell morphology, specifically of dendritic spines.[11]

SCA14 has been attributed to a variety of point mutations in the widely expressed PKCγ protein,[1954] Suggested gain-of-function mechanisms from PKCγ mutations include mutant protein aggregation,[108] altered calcium homeostasis[109] and impaired signalling.[110111]

SCA27 is caused by a point mutation, F145S, in the widely expressed fibroblast growth factor 14 (FGF14) protein.[26112] This leads to a loss of FGF14 function in its role of regulating Purkinje cell excitability and plasticity, possibly impairing neuronal signalling.[113114]

Other mutations

SCA23 has been attributed to several distinct mutations in the neuron-specific prodynorphin (PDYN), the precursor for several opioid neuropeptides.[23] Three mutations are located in DynA, a peptide with opioid and non-opioid activities, resulting in increased DynA production and excessive toxicity in cultured cells.[23] A fourth mutation is located in the PDYN domain and affects protein expression patterns in the opioid and glutamate system, potentially pointing to a downstream glutamate toxicity effect.[23]

SCA11 has been attributed to frameshift mutations in the widely expressed t tubulin kinase 2 (TTBK2).[16] These mutations have been demonstrated to promote TTBK2 expression while inhibiting its kinase activity and increasing nuclear localisation,[115] although the link to

Purkinje cell death has not yet been found. Homozygosity for the mutation in mice is notably embryonic lethal.[115]

SCA26 was recently attributed to a proline to histidine change at residue 596 in the eukaryotic elongation factor 2 protein found in a single kindred.[25] In a yeast model of SCA26, P596H eEF2 has been demonstrated to result in an increased rate of frameshifting during protein translation, disrupting proteostasis and rendering yeast more susceptible to unfolded protein response-inducing stressors.[25]

SCA28 has been attributed to a series of mutations in the widely expressed ATPase family gene 3-like 2 (*AFG3L2*), encoding the catalytic subunit of the m-AAA protease.[27] The AFG3L2 protein is an ATP-dependent protease located in the inner mitochondrial membrane known to degrade misfolded proteins and assist in ribosome assembly.[116] The disruption of AFG3L2 function has been linked to both dominant-negative and loss of function mechanisms for disrupting mitochondrial function.[116]

SCA35 was recently attributed to point mutations in *TGM6,* the non-neuron specific transglutaminase 6, specifically L517W and D327G,[30] but little else is known at this time. Likewise little is presently known about SCA20, which has been mapped to chromosome 11p13-q11. A putative copy number variant has been implied between markers rs4963307 and rs10897193, although this has not yet been demonstrated to be causative.[61]

CONCLUSION

While a unifying theme in SCA pathology seems elusive, a few trends have emerged—polyglutamine expansions leading to transcriptional dysregulation, RNA toxicity and the novel RAN translation products from expanded RNA repeats, as well as channel dysfunction and signalling disruption. While simple correlations between genetic defect and cell types affected or clinical phenotype seem elusive, the common end point is that these heterogeneous genetic defects predominantly result in a gain-of-toxic function to which Purkinje cells are especially susceptible, either exclusively or in advance of other neuronal cell types.

Several features that distinguish Purkinje cells might contribute to their vulnerability. The Purkinje cell is one of the largest neuronal cell types with a high metabolic activity and a massive dendritic arbour receiving extensive excitatory inputs. It has been demonstrated that impaired proteostasis affects Purkinje cells before other neuronal types in mice[119–122] and in human disease.[123] Proteostasis, the balance of protein synthesis and degradation, is crucial for synaptic signalling and neuronal function, but is best studied in spherical cells in which all machinery is confined to a limited cytosolic space. The unique Purkinje cell vulnerability to proteostatic insult may be due to an imbalance of synthesis and degradation machinery within its extensive dendritic arbour outside the soma. For example at synapses, protein synthesis regularly occurs, but lysosomes, which are instrumental in autophagic degradation of protein aggregates, are restricted to the soma.[124] It seems plausible that some of the common cellular pathways for combating protein misfolding, as well as altered

transcription, DNA damage or disrupted ionic gradients, are less well adapted to the size and morphological complexity of the Purkinje cell.

The mechanistic themes that have emerged (transcriptional dysregulation by polyglutamine expanded tracts, RNA toxicity and channel/signalling dysfunction) may represent areas of crucial Purkinje cell function, which when disturbed are more likely to activate the common defence mechanisms. Identification of which intracellular repair or protective pathways might be overwhelmed, such as calcium buffers, DNA repair, the ubiquitin-proteasome system or autophagy may suggest common pathogenic mechanisms or therapeutic strategies. Currently therapy is limited to symptomatic management with as yet no neuroprotective strategies to alleviate the progressive nature of the SCAs. Looking to the future of therapeutics for SCA, emphasis on early diagnosis through genetic testing will be key, as well as further honing in on the aspects of Purkinje cells that renders them so uniquely susceptible to cellular perturbations and how to combat the diverse genetic insults that cause the SCAs.

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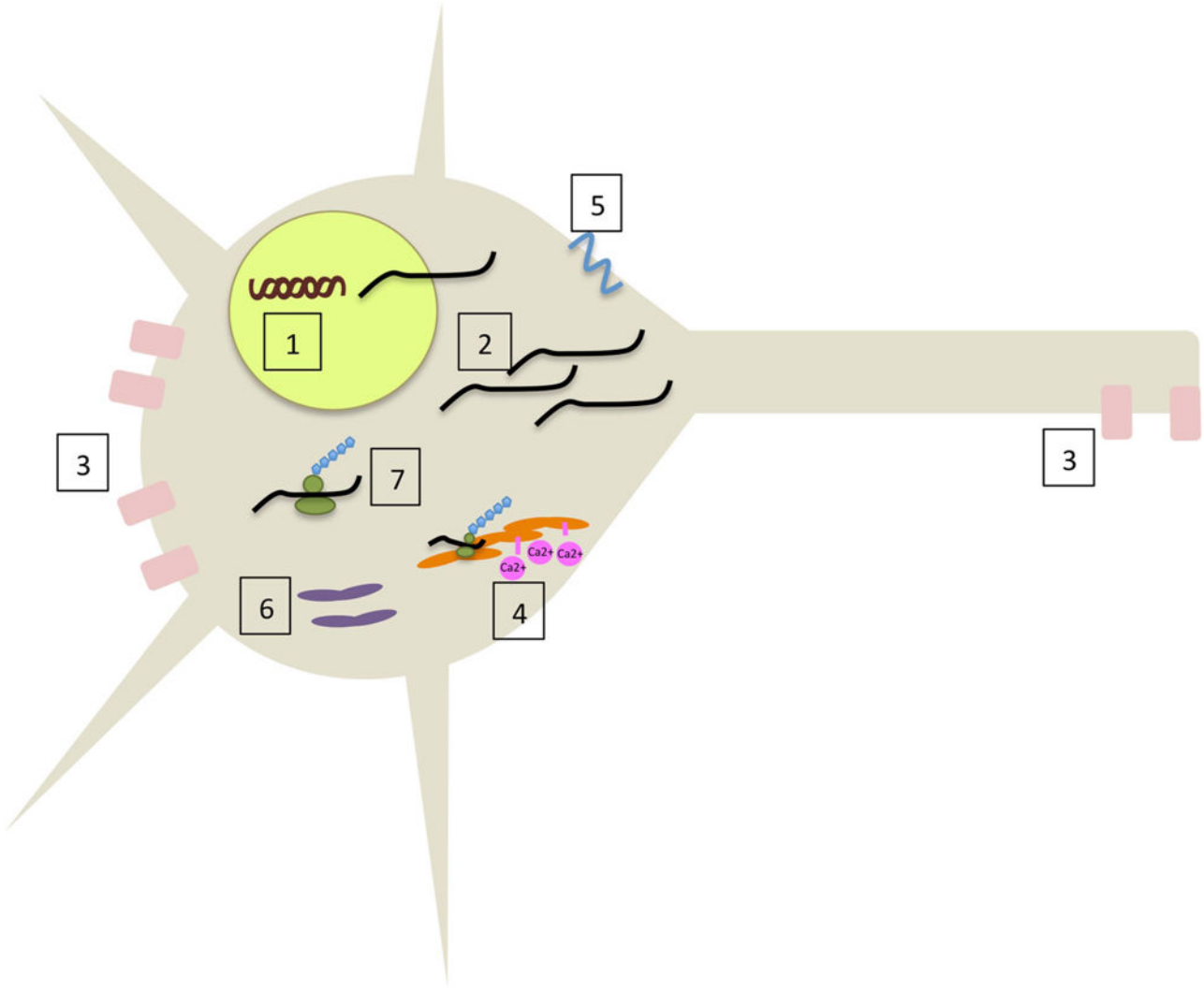

Figure 1.

Overview of the spinocerebellar ataxia (SCA) disease mechanisms. 1: Transcriptionopathies (SCA1, 2, 3, 6, 7, 17). 2: Non-coding repeat expansions/RNA toxicity (SCA8, 10, 12, 31 36). 3: Voltage-gated potassium channel dysfunction (SCA13, 19/22). 4: ITPR1 loss (SCA15/16). 5: β3-Spectrin dysfunction (SCA5). 6: Mitochondrial dysfunction (SCA28). 7: Individual protein dysfunction (SCA11, 14, 23, 26, 27, 35).

Table 1

The mixed spinocerebellar ataxias

SCA	Phenotype	Age of onset: mean (range)	Predominant geographical distribution[5]
Mixed			
SCA1	CA/spasticity/ophthalmoplegia[6]	33 (4–74)[738]	South Africa, India, Japan, Italy, Australia
SCA2	CA/dystonia/parkinsonsism/arreflexia/loss of saccades[39]	32 (1–65)[3940]	USA, Spain, India, Mexico, Italy
SCA3	CA/dystonia/spasticity/peripheral neuropathy/sleep disorders[41]	36 (5–70)[1041]	Most common worldwide
SCA4	CA/motor and sensory neuropathy[42]	39 (19–72)[43]	USA,[44] Germany[45]
SCA7	RP/CA[46]	18–41 (0–70)[1346]	Finland, Mexico, South Africa, UK, Belgium, France, Germany, Japan
SCA8	CA/EP/spasticity[47]	40 (1–73)[4748]	USA/Finland
SCA10	CA/seizures[49]	36 (10–49)[4950]	Mexico, Brazil
SCA12	CA/EP[51]	35 (8–55)[5152]	India
SCA13	Variable[18]	Childhood (0–45)[1853]	France, Philippines
SCA14	CA/axial myoclonus/dystonia[19]	34 (5–70)[1954]	UK, France, The Netherlands, USA, Japan, Australia
SCA17	Variable/EP/psychosis[42]	33 (3–55)[55]	Japan, Portugal, USA
SCA18	CA/sensorimotor neuropathy[56]	15 (12–25)[56]	USA[56]
SCA19/22	Variable[42]	34 (10–46)[225758]	The Netherlands,[57] China,[58] France[59]
SCA20	CA/palatal tremor/dysphonia[60]	47 (19–64)[6061]	Australia
SCA21	CA/cognitive deficits/EP[62]	18 (7–30)[62]	France[62]
SCA23	CA/sensory neuropathy[63]	50 (43–56)[63]	The Netherlands
SCA25	CA/sensory neuropathy[24]	? (1–39)[53]	France[64]
SCA27	CA/cognitive deficits[26]	? (15–20)[26]	The Netherlands
SCA28	CA/hyper-reflexia[65]	19 (12–36)[27]	Italy, France, UK
SCA29	Congenital non-progressive ataxia[66]	Congenital[66]	Canada,[67] Australia[66]
SCA32	CA/cognitive deficits/azoospermia[68]	Childhood to 60s	US[68]
SCA35	CA/torticollis[30]	44 (40–48)[30]	China
SCA36	CA/motor neuron disease[31]	53 (48–57)[31]	Spain, Japan
SCA37	CA/impaired vertical eye movements[37]	48 (38–64)[37]	Spain[37]

Clinical phenotypes, average age of onset (if reported in the literature) and predominant geographical distribution.

CA, cerebellar ataxia; EP, extrapyramidal or Parkinsonian features; RP, retinopathy; SCA, spinocerebellar ataxia.

Table 2

The pure spinocerebellar ataxias

SCA	Phenotype	Age of onset: mean (range)	Predominant geographical distribution[5]
Pure			
SCA5	Pure CA[69]	30 (10–68)[6970]	USA, Germany, France
SCA6	Pure CA[71]	43–52 (19–71)[71]	USA, Germany, Australia, Taiwan
SCA11	Pure CA[72]	25 (15–43)[1672]	UK, France, Germany
SCA15/16	Pure CA[60]	31 (7–66)[60]	UK, France
SCA26	Pure CA[36]	42 (26–60)[36]	USA[36]
SCA30	Pure CA[73]	52 (5–76)[73]	Australia[73]
SCA31	Pure CA[42]	52–62 (8–72)[2974]	Japan
SCA34	Pure CA, erythrokeratodermia[75]	Skin—childhood; ataxia—>40[75]	Canada[75]

Clinical phenotypes, average age of onset (if reported in the literature) and predominant geographical distribution.

CA, cerebellar ataxia; SCA, spinocerebellar ataxia.

Table 3

The mixed spinocerebellar ataxias

SCA	Locus	Neuroradiological findings[117]	Gene	Cause
Mixed				
SCA1	6p23	OPCA[38]	*ATXN1*	PolyQ-encoding CAG repeat expansion
SCA2	12q24	OPCA, spinal/cortical atrophy	*ATXN2*	PolyQ-encoding CAG repeat expansion
SCA3	14q24.3-q31	OPCA, enlarged 4th ventricle	*ATXN3*	PolyQ-encoding CAG repeat expansion
SCA4	16q22.1	CA		
SCA7	3p21.1-p12	OPCA	*ATXN7*	PolyQ-encoding CAG repeat expansion
SCA8	13q21	CA	*ATXN8, ATXN8os*	Non-coding CTG×CAG repeat
SCA10	22q13	CA	*ATXN10*	Non-coding pentanucleotide repeat
SCA12	5q31-q33	CA+cerebral atrophy	*PPP2R2B*	Non-coding CAG expansion (5′UTR)
SCA13	19q13.3-q13.4	OPCA	*KCNC3*	Multiple missense mutations
SCA14	19q13.4	CA (vermis)	*PRKCG*	Multiple missense mutations
SCA17	6q27	CA±general atrophy	*TBP*	PolyQ-encoding (CAG or CAA repeat expansioi
SCA18	7q22-q32	CA		
SCA19/22	1p21-q21	CA±cerebral atrophy	*KCND3*	Multiple missense mutations
SCA20	11p13-q11	CA		
SCA21	7p21.3-p15.1	CA		
SCA23	20p13	OPCA[118]	*PDYN*	Multiple missense mutations
SCA25	2p21-p13	CA		
SCA27	13q34	CA	*FGF14*	Missense mutation F145S
SCA28	18p11	CA[27]	*AFG3L2*	Multiple point mutations
SCA29	3p26	Cerebellar hypoplasia[66]		
SCA32	7q32-q33	CA[68]		
SCA35	20p13	OPCA[30]	*TGM6*	Multiple point mutations
SCA36	20p13	CA[31]	*NOP56*	Intronic hexanucleotide repeat expansion
SCA37	1p32	CA[37]		

Mapped locus, predominant neuroradiological findings, gene (if known) and mutation type (if known).

CA, cerebellar atrophy; OPCA, olivopontocerebellar atrophy; SCA, spinocerebellar ataxia.

Table 4

The pure spinocerebellar ataxias

SCA	Locus	Neuroradiological findings[117]	Gene	Cause
Pure				
SCA5	11q13	CA	*SPTBN2*	Missense or in-frame deletions
SCA6	19p13	CA	*CACNA1A*	PolyQ-encoding expansion
SCA11	15q15.2	CA	*TTBK2*	Various mutations
SCA15/16	3p26-p25	CA (vermis)	*ITPR1*	Large genomic deletions
SCA26	19p13.3	CA[36]	*eEF2*	Missense mutation P596H
SCA30	4q34.3-q35.1	CA[75]		
SCA31	16q21	CA	*BEAN*	Intronic pentanucleotide repeat expansion
SCA34	6q12.3-q16.2			

Mapped locus, predominant neuroradiological findings, gene (if known), and mutation type (if known).

CA, cerebellar atrophy; OPCA, olivopontocerebellar atrophy; SCA, spinocerebellar ataxia.