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Consensus Paper: Pathological Mechanisms Underlying Neurodegeneration in Spinocerebellar Ataxias

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Abstract

Intensive scientific research devoted in the recent years to understand the molecular mechanisms or neurodegeneration in spinocerebellar ataxias (SCAs) are identifying new pathways and targets providing new insights and a better understanding of the molecular pathogenesis in these diseases. In this consensus manuscript, the authors discuss their current views on the identified molecular processes causing or modulating the neurodegenerative phenotype in spinocerebellar ataxias with the common opinion of translating the new knowledge acquired into candidate targets for therapy.

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The following topics are discussed: transcription dysregulation, protein aggregation, autophagy, ion channels, the role of mitochondria, RNA toxicity, modulators of neurodegeneration and current therapeutic approaches. Overall point of consensus includes the common vision of neurodegeneration in SCAs as a multifactorial, progressive and reversible process, at least in early stages. Specific points of consensus include the role of the dysregulation of protein folding, transcription, bioenergetics, calcium handling and eventual cell death with apoptotic features of neurons during SCA disease progression. Unresolved questions include how the dysregulation of these pathways triggers the onset of symptoms and mediates disease progression since this understanding may allow effective treatments of SCAs within the window of reversibility to prevent early neuronal damage. Common opinions also include the need for clinical detection of early neuronal dysfunction, for more basic research to decipher the early neurodegenerative process in SCAs in order to give rise to new concepts for treatment strategies and for the translation of the results to preclinical studies and, thereafter, in clinical practice.

Keywords

Aggregation; Ataxia; Autophagy; Calcium; Cerebellum; Mitochondria; Neurodegeneration; Polyglutamine; Purkinje cell; Therapy; Transcription dysregulation; Neuronal death

Introduction

Some 20 years ago, the first genetic defect associated with a specific spinocerebellar ataxia (SCA) subtype, hence denoted as SCA1 (SCA type 1), was identified [1]. In addition to enabling unequivocal molecular diagnosis of the disease, this finding opened up multiple lines of basic scientific research aimed at understanding the biological functions of the gene products, the identification of the cellular and molecular pathways implicated, and the disease mechanisms of pathogenesis with the ultimate objective of identifying, developing and implementing effective treatments. These efforts have identified major etiological roles of transcriptional dysregulation, protein aggregation and clearance, autophagy, alterations of calcium homeostasis, mitochondria defects, toxic RNA gain-of-function mechanisms and activation of pro-apoptotic routes, amongst others, all leading to early synaptic neurotransmission deficits, progressive spinocerebellar dysfunction and, ultimately, neuronal and specifically cerebellar Purkinje cell demise (Fig. 1 and Table 1). The identification of the molecular targets influencing the critical pathways in the pathogenesis and, in particular, those triggering the onset of symptoms open the way for effective treatments by reversing the neurotoxic process during the early stages of neurodegeneration. Whilst the underlying mechanisms of pathogenesis are not yet well understood, the authors discuss their current interests and consensus views on the different basic mechanisms triggering neurodegeneration in SCAs and the ongoing and upcoming efforts to prevent them.

Cell Death in Spinocerebellar ataxias (Ivelisse Sánchez and Antoni Matilla-Dueñas)

Cerebellar cell degeneration and loss is a major neuropathological feature in spinocerebellar ataxias [2-4]. In fact, by the time the patients demonstrate ataxia, the most prominent motor symptoms of SCA, brain atrophy is already detected in most cases [3]. As disease progresses, substantial loss of the Purkinje cell layer and all four deep cerebellar nuclei is evident and the remaining neurons are atrophied and/or misplaced (heterotopy) within the cerebellum, as shown by neuroimaging and histological analyses [5-7]. However, the specific mechanisms leading to neuronal dysfunction and their eventual death in SCAs are

not well understood. With this in mind, many laboratories are currently focusing on identifying early preclinical measurable markers or clinical signs with prognostic value. This would allow effective treatment strategies to be applied prior to cell loss or the irreversible disruption of the neuronal circuitry. In addition to gaining an understanding of the possible mechanisms responsible for the disease symptoms from early biomarkers and clinical signs, the morphological features indicative of a specific type of cell death are also shedding light on the possible signalling routes involved. Therefore, these findings, together with functional studies, will reveal potential targets for treatment. The general morphological features based on histological and ultrastructural observations include cell shrinkage, nuclear condensation or DNA fragmentation, vacuolation, abnormal mitochondria and neurite morphology, and changes in neurite branching complexity or synaptic connections. Of these, changes in neurite morphology have been shown to be reversible to some extent in cell and animal models of several ataxias.

Few articles have been published describing the morphological features of Purkinje cell death process during disease progression in spinocerebellar ataxias, and for obvious reasons, most of the work has been done in animal models. The common morphological features described in several genetic mouse models resemble those of “dark cell degeneration” (DCD). During this form of cell death, neurons exhibit both apoptotic and necrotic features, including caspase activation, shrunken cell bodies, protein inclusions and initially swollen mitochondria and endoplasmic reticulum. However, the cardinal morphological feature of this form of cell death is the highly electron-dense cytoplasm. Interestingly, a morphologically similar cell death is detected in linker cells—specific gonad cells present in the male reproductive system of *Caenorhabditis elegans*—during male reproductive development [8, 9]. This cell death type was found to be independent of two essential players in apoptotic cell death, *ced-3* or *ced-4*. The human homologs of these two *C. elegans* proteins are the caspases and the apoptosis scaffold protein, apoptotic protease activating factor 1 (APAF-1), respectively [8, 9]. Similar to the DCD described in several polyglutamine (from here denoted polyQ) SCA models, dying linker cells do not show nuclear condensation and contain large numbers of single-membrane cytoplasmic vesicles [10-13]. These cytoplasmic vesicles may be responsible for the high electron density of the cytoplasm described in DCD. Likewise, caspase-3 or caspase-9 knockout mouse embryos have also shown the DCD form of cell death instead of the typical apoptosis, suggesting that DCD may be a default program in itself at least during development, or that in mammals it may exist as an alternative pathway [14]. It remains to be determined whether lack of the other caspases such as caspases 8 or 10 would elicit the same effect. Interestingly, a polyQ protein, pqn-41, was found essential for linker cell death in *C. elegans* [15]. Although it is not yet clear whether the *dark cell death* observed in polyQ SCAs or other SCAs are genetically and functionally similar to that of linker cells in *C. elegans*, these data suggest that polyQ SCA proteins may be in fact triggering a specialized cell death program [16, 17].

Interestingly, in addition to Purkinje cells from SCAs 2, 3, 7 and 28 mice, the ataxic Purkinje cell degeneration (Pcd) mutant mouse containing a mutation on the Zn carboxypeptidase Nna1 gene also showed similar cell death morphology [18]. Therefore, DCD may be a mechanism of cell death to which Purkinje cells are particularly sensitive. In fact, similar morphological features have been described in the cerebellum of models of AMPA-induced delayed excitotoxicity and of hypoxia [19, 20]. Purkinje neurons are highly innervated by excitatory input from granular cells in an environment containing Bergmann glia and other supporting cells which can serve to buffer glutamate levels at the synapses. It is then understandable that changes in the Ca^{2+} buffering capacity upon glutaminergic input due to extracellular or intracellular changes may cause or further enhance Purkinje cell dysfunction. It has been proposed that alterations in cellular functions directly or indirectly leading to Ca^{2+} signalling dysregulation are eventually responsible for DCD mitochondria-

mediated cell death [21]. Interestingly, in both SCA2 and SCA3, ataxins 2 and 3 respectively have been shown to interact with inositol 1,4,5-triphosphate receptor type 1 (IP3R1), inducing abnormal Ca^{2+} release to the cytoplasm and potentially inducing Ca^{2+} buffering defects by the mitochondria. In fact, suppression of inositol 1,4,5-triphosphate receptor-mediated calcium signalling by inositol 1,4,5-phosphatase (Inpp5a) enzyme (5PP) overexpression or treatment with dantrolene appeared to prevent DCD in SCA2 and SCA3 mouse models [10, 11, 22]. Similarly, mutant spinocerebellar ataxia type 7 (SCA7) expression in Bergmann glia cells was shown sufficient to interfere with their glutamate uptake functions, resulting in DCD of Purkinje cells [12]. On the other hand, the mutation underlying SCA28 is caused by haploinsufficiency of *Afg3l2* encoding for the inner mitochondria membrane m-AAA protease, directly resulting in respiratory chain dysfunction, increased oxidative stress and calcium buffering dysregulation [11]. It is then possible that the different mutated proteins in SCAs may ultimately trigger the same mode of cell death by exerting their effects at different levels in the signalling route.

Do these lines of evidence suggest that DCD is a common cell death mechanism in polyQ SCAs? This appears to be the case, but more scientific data are yet needed to support it. Furthermore, the temporal pattern of these morphological changes and the relationship of spinocerebellar ataxia causing mutations to the specific alterations in cellular functions leading to this specific form of cell death are not well understood. It is clear that DCD morphology has been detected in many SCAs and other polyglutamine disorders including the activation of caspases, which are key apoptotic players. However, the molecular mechanisms involved in the DCD of *C. elegans* and how these may relate to cell death mechanisms in mammals are just now being deciphered. Whilst it is clear that the time for therapeutic intervention should precede the late stages of the cell death pathway, we propose that dissecting the mechanisms leading to neuronal death in SCAs will yield important insights on shared signalling routes and potential early targets. Many questions still remain on what causes the defective excitatory input levels or its mismanagement as well as the Ca^{2+} and other signalling alterations in each of the spinocerebellar ataxias. Most importantly, understanding the critical early triggers to Purkinje cell dysfunction by each of the SCA genes should serve to propose rational therapy strategies. The most recent investigations pursuing all of these questions are herein addressed and discussed.

Dysregulation of Gene Transcription as a Trigger of Ataxia Pathogenesis (Antoni Matilla-Dueñas and Ivelisse Sánchez)

Transcriptional dysregulation in the brain has been implicated as a common generic molecular mechanism underlying pathogenesis in a myriad of spinocerebellar ataxias [23, 24]. Many transcription factors, such as the cAMP response element-binding protein TATA-binding protein (TBP) and Sp1, amongst others, contain polyglutamine regions within their primary sequence. These polyglutamine regions or domains appear necessary for their association with the chromatin in vivo and facilitate or prevent transcription, thereby acting as activators or repressors, respectively, depending on which promoter area they bind and the co-regulators with which they interact. There is already some experimental evidence suggesting that the function of polyQ could be to modulate protein–protein interactions. For example, the polyQ sequence in TBP modulates its interaction with TFIIB [25]. Further evidence has shown that mutations affecting polyglutamine expansions within ataxins in spinocerebellar ataxias interfere with transcription through different mechanisms, the most common being protein–protein or protein–DNA interactions, acetylation, phosphorylation and RNA interference, which would provide variable effects on gene expression. Among the 24 proteins directly responsible for spinocerebellar neurodegeneration in the SCAs identified to date (Table 1), most of them participate in the regulation of gene expression

either at the transcriptional or posttranscriptional levels or in the regulation of cellular and molecular events that somehow target transcription [26-31]. This is the reason why, at least in the case of polyQ ataxias, they are increasingly denoted as transcriptionopathies, in which neuronal toxicity would first arise from large-scale alterations of transcription. In these ataxias, dysregulation of gene expression occurs as a consequence of the direct effects of the respective mutations on transcription or RNA expression and/or by the indirect actions exerted by aberrant interactions participated by the mutated SCA gene products. The tissue-specific neurodegenerative nature of polyglutamine expansion spinocerebellar ataxias implies that their associated polyglutamine-expanded proteins affect a discreet set of regulatory factors and specific subsets of genes that are particularly vital for normal function in the affected neuronal cells and tissues. Most of the studies aiming to identify these genes and pathways dysregulated by transcription alterations in SCAs have been assessed by global transcriptome analyses either in cellular or animal models.

Sufficient evidence has been set forth to support a link between altered histone acetylation and altered gene expression in several polyglutamine expansion disorders [32]. As a result, histone deacetylase (HDAC) inhibitors have been tested as a therapeutic approach for the treatment of these disorders in laboratory models. Treatment with these drugs has been shown to reduce the expression of proteins involved in DNA synthesis, upregulate the expression of pro-apoptotic factors, promote cell cycle arrest and differentiation and, more generally, modulate the expression of a broad range of genes, which are amongst the main reasons why the wide application of these drugs to treat neurodegeneration has been limited to date (reviewed in [33]). However, focused research exploring specific regulators of transcription at different levels may provide new therapeutic approaches to treat neurodegeneration in spinocerebellar ataxias. This is thoroughly addressed in later sections in this manuscript.

Spinocerebellar Ataxia Type 1

SCA1 was the first ataxia with the gene identified and the associated protein characterized, and therefore there is a considerable amount of knowledge acquired relative to its pathogenic mechanisms (reviewed in [34]). The first suspicion linking ATXN1, the spinocerebellar ataxia type 1 protein, to transcription was provided by the fact that Atxn1 includes an AXH sequence identified first in the high-mobility group transcription activator HMG1 [35, 36]. The AXH domain has been shown to directly regulate transcription by interacting with at least one trans-activator, SP1 [26]. Determination of the AXH structure in Atxn1 has shown that it forms stable homodimers and contains an OB fold [37, 38], a structural motif found in many oligonucleotide-binding proteins, supporting the proposed role of Atxn1 in RNA binding [39]. Furthermore, the AXH module contains a cluster of charged surface residues that provide a surface for protein–protein interactions; many of them are crucial for the regulation of transcription [40]. Among the most characterised interactions regulating transcription include both co-activators and co-repressors such as ANP32A/LANP [41], ATXN1L [42], CBF1 [43], the Capicua homolog CIC [44], GFI-1 [45], HDAC3 [46], polyQ-binding protein 1 [47], RORα-Tip60 [48], SMRTER [46] and SP1 [26]. ATXN1 has also been shown to interact with at least two RNA-splicing factors: RBM17 [49] and U2AF65 [50]. All these interactions point to the relevant nuclear functions of ATXN1 as a co-regulator of transcription-related processes. Remarkably, some of these factors have been shown to modify the pathogenesis of SCA1 in mouse and fly models [44, 45, 48, 51-53]. For instance, *Ror*α haploinsufficiency results in enhanced pathogenesis [48] and partial Tip60 loss delays cerebellar degeneration during mid-stage disease progression in SCA1 transgenic mice [53]. Even though much of the genetic evidence suggests that SCA1 is mainly caused by a gain-of-function mechanism, additional data from studies with knockout and transgenic mice have revealed that both share common transcriptional and

molecular phenotypes. This highlights the contribution of the biological functions of ataxin-1 in SCA1 neurodegeneration, indicating the role of loss of ataxin-1 function in pathogenesis. Global microarray analysis of both knockout and transgenic mice revealed that ataxin-1 regulates genetic programs involved in cerebellar motor functions in mice through intracellular signalling [26, 27, 54]. Of these, the evolutionary conserved Wnt signalling pathway interacts with RA signalling to regulate multiple cell differentiation processes during embryonic and adult life, including neuron cell differentiation, neurite development, central nervous system (CNS) plasticity and nervous system development [55, 56]. Through the direct interaction with the transcription factor CBF1, Atxn1 acts as an integral component of the Notch signalling pathway [43]. Thus, more functions regulated by transcription are being assigned to ATXN1, which are highly relevant to understand SCA1 pathogenesis. Remarkably, modulating the transcriptional functions of ataxin-1 has been proven beneficial in transgenic mice, thereby opening new strategies to therapy [57]. Very recently, a previously undescribed function of ataxin-1 in the modulation of protein phosphatase 2a activity and the regulation of its holoenzyme composition has been described and found altered in the SCA1 mouse cerebellum [31]. Taken together, the evidence highlights that dysregulation of the biological functions of ataxin-1 underlies the early events in SCA1, further supporting the combination of both gain and loss of functions of ataxin-1 in SCA1 pathogenesis. This in turn is very relevant to the identification of therapeutic targets.

Spinocerebellar Ataxia Type 2

In SCA2, ataxin-2 has been linked to cellular RNA metabolism and endocytosis processes [58, 59] (reviewed in [60]). A role in transcription and translation regulation by ataxin-2 has been proposed through its interaction with poly(A)-binding protein 1, and the assemblage into polyribosomes suggests a role for ATXN2 in RNA metabolism [58, 61]. More recently, ATXN2 has been shown to interact with Krüppel-associated box-containing zinc finger repressor proteins [62]. Members of this family are involved in the transcriptional repression of RNA polymerase I, II and III promoters as well as in the binding and splicing of RNA, which result in crucial functions regarding the maintenance of the nucleolus, cell differentiation, and proliferation and apoptosis [63]. Thus, ATXN2 may as well act as a transcription co-regulator, together forming a multi-protein complex with ZBRK1.

Spinocerebellar Ataxia Type 3

Ataxin-3 (ATXN3), the disease protein in SCA3, interacts with several transcriptional components such as the TATA-binding protein-associated factor TAFII130 [64, 65], the cAMP response element-binding protein CBP [66, 67], the DNA repair protein RAD23 [68], the nuclear co-repressor receptor NCoR, and the histone deacetylases HDAC3 and HDAC6 [69] (reviewed in [70]). Normal ATXN3 is involved in the expression of genes implicated in stress response and extracellular matrix modelling, whereas mutant ATXN3 is associated with the upregulation of genes mainly involved in inflammatory reactions [71]. Studies have shown that ATXN3 modulates gene transcription through chromatin binding and recruitment of histone deacetylating complexes to target gene promoters [69]. In screenings for transcription factors specifically interacting with ATXN3, the forkhead box class O (FOXO) transcription factor 4 (FOXO4) was identified [72]. FOXO family transcription factors are involved in various cellular processes including regulation of cell cycle arrest, differentiation, cell death and resistance to cellular oxidative stress. ATXN3 interacts with and stabilizes the FOXO transcription factor FOXO4, and upon oxidative stress, they both translocate to the nucleus and activate manganese superoxide dismutase (SOD2) transcription, which in turn protects cells from oxidative damage. Thus, mutant ATXN3

associates with a significantly reduced capability to counteract oxidative stress, contributing to neuronal cell death in SCA3.

Spinocerebellar Ataxia Type 7

The SCA7 gene product, ataxin-7 (ATXN7), localises to the nucleus and has been shown to function as a component of the TATA-binding protein-free TAF-containing SPT3-TAF9-GCN5 acetyltransferase transcription complex [73]. ATXN7 is highly homologous to the yeast protein, Sgf73, which acts as a subunit of the SAGA chromatin remodelling and transcription complex which is made up of 21 proteins highly conserved from yeast to man. The SAGA modular complex includes, amongst others Spt, Ada, and Gcn5 acetylase and acts as a histone acetyltransferase complex like cAMP response element-binding protein (CBP) and also harbours histone deubiquitination activity (reviewed in [74]). In human and mammals, SAGA complex has multiple homologues: TATA-binding protein-free TAF complex, SPT3/TAF9/GCN5 acetyltransferase complex and the PCAF/GCN5 complex. These co-activator complexes are recruited by specific transcription factors to enhancer/promoter regions in target genes and induce the unwinding of DNA from nucleosomes via histone acetylation to upregulate transcription. In a polyQ–Atxn7 knock-in mouse model, transcription downregulation was demonstrated to be an early event leading to photoreceptor dysfunction, retinal degeneration and visual impairment [75]. SCA7 neuropathology has been linked to the functions of ATXN7-interacting proteins within the multicomponent complexes [75]. Thus, the presence of polyQ in ATXN7 would diminish the transcriptional co-activator functions of SAGA.

Spinocerebellar Ataxia Type 17

Of the nine polyglutamine diseases causing ataxia, spinocerebellar ataxia type 17 (SCA17) is caused by polyglutamine expansion (>43 glutamines) within the TATA box-binding protein (TBP) [76, 77], which is an essential transcription factor for the expression of most genes. The identification of the mutation in TBP as the direct responsible causative defect in SCA17 pointed to alterations in transcription as the main primary trigger of SCA pathogenesis. Like other polyglutamine diseases, SCA17 shows late-onset neurodegeneration that is particularly prominent in the cerebellum. Of all the identified polyglutamine proteins, TBP is the smallest and has been well characterised for its function. Thus, SCA17 has become an ideal disease model for understanding how polyglutamine expansion alters transcription and causes selective neuropathology. Although TBP associates with a myriad of transcription factors to regulate the expression of the vast majority of genes, global transcriptomics studies with transgenic SCA17 mice revealed no overt abnormalities of transcriptional profiling in the brain of these mutant mice [25], suggesting that polyglutamine expansion may selectively affect the function of specific transcription factors and their targets. In these studies, proposed negative effects of the mutant TBP on chaperone expression were uncovered. Chaperones are known to be protective against neuronal damage under cellular stress [78] and acute and chronic stresses which occur to neuronal cells in the brain over the course of ageing. Reduced levels of chaperones in the brain are expected to decrease the cellular capacity to refold polyglutamine proteins and to protect against oxidative stress during ageing, which can promote ageing-related neuropathological changes. Although improving chaperone function in neuronal cells has been proposed to reduce the toxicity of misfolded proteins [79-81], the complexity of chaperones has made it difficult to pinpoint specific targets for effective treatment. This highlights the need of deciphering the transcriptionally dysregulated pathways in SCAs for the identification of putative therapeutic targets.

Spinocerebellar Ataxia Type 36

Aberrant GGCCTG expansions are found in intron 1 of the *NOP56* gene in SCA36, but these expansions are not shown to alter the levels of *NOP56* RNA or protein expression. The NOP56 protein is a core component of the box C+D small nuclear ribonucleoprotein, which is required for ribosome biogenesis [82]. NOP56 and SRSF2 co-localise with RNA foci, and the transcription of MIR1292 decreases as the repeat was expanded, suggesting that a toxic RNA gain-of-function mechanism is responsible for SCA36 [83].

Dentatorubral-Pallidoluysian Atrophy

Dentatorubral–pallidoluysian atrophy (DRPLA) is a human polyQ ataxia caused by the expansion of a CAG stretch in the *atrophin-1* gene. The protein atrophin-1 (ATN1) takes part in several cellular processes and functions as a bimodal transcriptional cofactor that is recruited to regulatory elements by a number of transcription factors [84-86]. Several studies provide a role of ATN1 as a nuclear co-repressor (reviewed in [87]). Atrophin-1 was shown to interact with the transcriptional repressor ETO/MTG8 and to repress transcription in tissue culture cells [88]. *Drosophila* atrophin mutants show defects in multiple developmental processes and derepression of several genes [84]. Both human atrophin-1 and *Drosophila* atrophin repress transcription in vivo when tethered to DNA, and polyQ expansion in atrophin-1 reduces repression. A recent genome-wide transcriptional profiling focusing on primary events preceding neurodegeneration in flies led to prove that mutant polyQ-expanded atrophin represses the transcription of the *fat* tumour suppressor gene, the function of which in this system protects from degeneration and atrophin toxicity [89]. Remarkably, in *fat* mutants, neurons undergo progressive degeneration with autophagic hallmarks. These data uncover specific mechanisms of toxicity by examining the dysregulated transcription profiles exerted by the expanded mutation.

Transcription Regulation by Calcium Signalling

Calcium homeostasis is critical in neurons for establishing and maintaining the synaptic transmission properties, including long-term potentiation and depression, and intracellular signalling. Ca^{2+} is able to specify distinct genomic responses by the differential activation of transcriptional regulators that decipher the information contained in Ca^{2+} signals. It triggers electrical activity-dependent gene expression, and one of the earliest genomic consequences is the induction of immediate early genes, many of them have been identified, including transcription factors, protein kinases, synaptic vesicle proteins and neurotrophins. Many immediate early genes encode transcription factors such as c-*fos*, *fosB*, c-*jun* and *zif268*, which in turn regulate the expression of late response genes the products of which contribute to the structural and functional changes underlying neuronal plasticity. Others, such as the neurotrophin brain-derived neurotrophic factor (BDNF), act directly. BDNF promotes neuronal survival, acts as a neurotransmitter eliciting postsynaptic action potentials and modulates synaptic transmission by enhancing neurotransmitter release.

A few SCAs are caused by the dysregulation of neuronal calcium homeostasis. Mutations causing insufficiency in the smooth endoplasmic reticulum calcium channel IP3R1 in humans are directly responsible for ataxia in SCAs 15 and 16. However, abnormal neuronal Ca^{2+} signalling may also play an important role in the pathogenesis of other ataxia subtypes, such as in SCAs l, 2, 5, 6 and 14. There is evidence supporting this. Microarray analyses of the SCA1 transgenic mouse models have revealed early-altered calcium signalling impairment [90]. These mice express significantly reduced levels of the calcium buffers calbindin and parvalbumin, ITPR1, type 1 inositol phosphate 5-phosphatase, endoplasmic reticulum (ER) calcium transporter SERCA, glutamate transporter EAAT4, EAAT4

stabilizer β-spectrin III, T-type voltage-gated calcium channels and transient receptor potential type 3 calcium channels [54, 90]. A calcium-mediated pathway that influences transcription involves the mitogen-activated protein kinase (MAPK/ERK) cascade, which transduces the information from the site of calcium signal generation at the plasma membrane to the nucleus [91]. Nuclear signalling of the MAPK cascades catalyses the phosphorylation of transcription factors, but also regulates gene expression more globally at the level of chromatin remodelling. These data point to the convergence of calcium intrasignalling pathways in the regulation of transcription.

MicroRNAs in Spinocerebellar Ataxias

Bilen et al. [92] provided the first evidence that microRNAs (miRNAs), including the anti-apoptotic miRNA *bantam*, limit the severity of polyglutamine repeat-induced neurodegeneration. These findings were further supported by other studies where a few microRNAs were identified on the basis of their central role in tuning the fine expression of polyQ disease-causing proteins in mammals, such as ataxins 1 and 3, and atrophin-1 and their modulatory roles of miRNA-mediated mechanisms in toxicity [93-95]. These studies extend the types of biological processes regulated by miRNAs to the long-term survival of neurons and the response and handling of toxic disease proteins. Identifying the miRNAs involved should address the nature and type of targets and the extent of the biological regulation of the occurring pathways.

The Role of Aggregation in the Neuropathogenesis of SCAs (Thorsten Schmidt, Jana Schmidt and Olaf Riess)

The accumulation of proteins is the hallmark of most neurodegenerative disorders. However, the localisation of these accumulations differs; that is, the Lewy bodies in Parkinson's disease (PD) or dementia with Lewy bodies can be found in the cytoplasm whereas plaques and tangles formed in Alzheimer's disease (AD) are cytoplasmic or even extracellular, and the aggregates in most spinocerebellar ataxias caused by polyglutamine expansions or Huntington's disease (HD) are found inside the nucleus and are therefore termed neuronal intranuclear inclusion bodies (NII) [77, 96-102]. However, there are contradictory reports in SCA2 describing the existence or the lack of nuclear aggregates [103, 104], whereas in spinocerebellar ataxia type 6 (SCA6), cytoplasmic but no intranuclear aggregates have been described so far [105]. Having in most cases the intracellular localisation of the aggregated protein in common (in the nucleus) whilst the normal localisation of the affected protein differs between polyQ diseases indicates that also the pathways leading to the nuclear import and thereby to the protein aggregation may differ.

Recent studies demonstrated that major misfolded proteins associated with neurodegenerative diseases like AD, PD, HD and amyotrophic lateral sclerosis (ALS) share seeded aggregation properties of prions, whereas in all these cases self-propagation is not clear so far (reviewed in [106]). Although a prion-like neuron-to-neuron transmission of aggregates [107] has not been shown for polyglutamine diseases yet, it was demonstrated that cultured cells are able to take up aggregated polyglutamines [108], which then may seed further aggregation and recruitment of proteins [109].

In SCAs, not only the altered proteins with expanded polyglutamine repeats but also repeat-containing RNA may accumulate. In SCA8 for instance, the occurrence of CUG-positive ribonuclear inclusions both in human SCA8 patients and in transgenic mice was described [110]. Comparable RNA foci were also found in SCAs 31 and 36, respectively [111]. On the protein level, widespread tau accumulations were described in SCA11 [112]. Due to the

limited postmortem neuropathological data about non-polyglutamine SCAs [111], we focus next on those SCAs caused by polyglutamine expansion.

Why are the polyglutamine-containing proteins aggregating at all? Nearly two decades ago, it was described that polyQ repeats may form β-sheet-like structures enabling polyglutamine proteins to accumulate via polar zippers [113]. This process may be favoured by the release of a polyglutamine-containing fragment out of the context of the affected protein. The data from transgenic mice present a clear picture: the use of a protein fragment containing an expanded polyglutamine gave rise to a phenotype stronger than the full-length protein [114-116]. The amino acids surrounding the polyglutamine repeat seem to modify, retard or even prevent the aggregation of the expanded protein. Interestingly, the polyglutamine repeat is located in all polyglutamine SCA tendentially at the N- or C-terminus rather than in the middle of the protein [117], thereby facilitating the release of such fragments. In this line, for several polyglutamine diseases, cleavage of the affected protein was observed [118-120]. As cleaving enzymes, both caspases and calpains were described [121-126]. Importantly, for SCA3, in vitro and in vivo data did reveal that even protein domains of ATXN3 outside of the polyglutamine repeat are able to aggregate [127-129], indicating that not only the polyglutamine-containing fragment but also the remnant of the protein contribute to the aggregation process.

In addition to the affected, expanded protein, intranuclear aggregates also contain the non-affected normal allele of the respective protein; and other SCA-associated proteins are recruited to the aggregates as well [130-132]. Besides that, several other proteins including ubiquitin, chaperones, proteasomal subunits and transcription factors were detected within the aggregates [130, 133-135], indicating that interference of the proteasomal function and transcriptional regulation are involved in the pathogenesis. Indeed, it has been shown that the ubiquitin–proteasome system (UPS) is not able to efficiently degrade polyglutamine aggregates [136] and that the UPS might even be functionally impaired by polyglutamine aggregates [137-139]. In PD, for alpha-synuclein, it was shown that its aggregates are not degraded by the proteasome but through autophagosomes [140]. These results suggest that this might also be the case for protein aggregates associated with spinocerebellar ataxias.

Whether protein aggregates in polyglutamine diseases are something bad or something good is a long and still ongoing discussion [141]. On one hand, the large accumulation itself and the recruitment of additional proteins into the aggregates may mix up the nuclear homeostasis. On the other hand, the separation of the missfolded and toxic expanded polyglutamine repeat could relieve the intracellular refolding and disposal system and thereby contribute to the restoration of a normal homeostasis. Although (large) protein aggregates are without a doubt a hallmark of polyQ-caused SCAs, their formation turned out to be no prerequisite for the development of a phenotype: protein aggregates have also been observed in brain regions which are mildly or non-affected by degeneration as well as even in peripheral tissues [99-101, 142]. Furthermore, several transgenic models developed neurological symptoms long before the first protein aggregates could be detected microscopically [143-146]. Novel techniques for the visualization of aggregates on the sub-microscopic level (like sophisticated variations of classical gel electrophoresis) [147] confirmed, however, that the formation of smaller, still soluble, accumulations precedes the onset of symptoms. This means that not the large protein aggregates itself but oligomers or microaggregates seem to be the (initial) toxic species [147-149] leading to, e.g., transcriptional dysregulation [149], whilst the larger macroaggregates could be even protective. This concept is supported by the observation that an improved solubility of polyglutamines (via upregulated chaperone activity) enhanced their toxicity, whilst intensified aggregation was beneficial [150]. For this reason, an increased disposal of the toxic proteins via the proteasome or autophagy appears to be a more promising approach

than the inhibition of aggregate formation in general. In fact, the induction of autophagy has turned out to be a promising therapeutic approach [151, 152], as is discussed in the following section.

Autophagy Upregulation as a Therapeutic Strategy for Certain Spinocerebellar Ataxias (Benjamin R. Underwood and David C. Rubinsztein)

Autophagy as a Cellular Process

The cellular process of macroautophagy, which we will call autophagy, was first described by the Nobel laureate Christian de Duve nearly 50 years ago, though it is only in the much more recent past that it has become the focus of intense research [153]. Autophagy is a process by which a variety of substrates, including large cargoes such as organelles, can be degraded. It can be stimulated by a wide range of physiological stimuli (like oxidative stress) or drugs (like rapamycin) [154, 155]. On initiation, autophagosomes form at random locations in the cytoplasm before moving towards the microtubule organising centre, where lysosomes are clustered. This brings them into proximity to lysosomes and facilitates autophagosome–lysosome fusion, after which the lysosomal hydrolases degrade autophagic contents. Work in the early 1990s identified the genes coding for essential autophagy proteins in yeast, and this was the first step towards elucidation of the cellular mechanisms underlying this process [156]. Whilst a detailed description of the molecular machinery of autophagy is beyond the scope of this manuscript, some elements are relevant and worth highlighting. Initiation of autophagy requires two large macromolecular complexes. The first of these contains ULK1/2, a phosphorylation substrate for the serine/threonine kinase mammalian target of rapamycin (mTOR). Phosphorylation of ULK1/2 by mTOR leads to inhibition of autophagy. Treatment with rapamycin results in inactivation of mTOR, decreased phosphorylation of ULK1/2 and subsequent induction of autophagy [157]. The second complex contains a number of proteins including Beclin-1 and the class 3 phosphoinositide 3 kinase (PI3K) Vps34. This is important since PI3K inhibitors such as 3-methyladenine are powerful inhibitors of autophagy and therefore useful tools for laboratory investigation of this process [158]. We discuss next how understanding of the machinery of autophagy has led to pharmacological interventions to both induce and inhibit the process.

Autophagy is not just regulated at initiation. Further important machinery is required for the expansion of the autophagosome. This includes two ubiquitin-like conjugation reactions, the second of which results in the incorporation of microtubule-associated protein 1 light chain 3 (LC3) to the autophagosomal membrane. This is important as LC3 is the only known specific marker of the autophagosome and, as a result, provides the basis for many autophagy assays [159]. Fusion is the last step of the process and again requires both specific molecular machinery and normal lysosomal physiology. Preventing normal acidification of the lysosome, for example with drugs such as the H^+ ATPase antagonist bafilomycin A1, prevents fusion and thus blocks autophagic flux, again providing an essential laboratory tool [160]. A much more detailed review of the current understanding of the molecular basis of autophagy can be found in [161].

Autophagy as a Therapeutic Strategy in Neurodegenerative Disease

Interest in autophagy and neurodegeneration has developed from two key observations. Firstly, autophagy is required for neuronal health. Mice deficient for essential autophagic proteins exhibit progressive neurodegeneration and intra-neuronal protein aggregation, features seen in many neurodegenerative diseases [162]. Loss of autophagy in the central nervous system causes neurodegeneration in mice [163]. Subsequently, dysfunctional or

abnormal autophagy has been found in a number of neurodegenerative disease models, including inborn errors of metabolism, Alzheimer's disease, Huntington's disease, Parkinson's disease and frontotemporal dementia [164-168]. Changes in autophagy have been reported in models of spinocerebellar ataxia. For example, mutant ataxin-3, the causative protein abnormality in SCA3, has been shown to enhance the autophagic degradation of parkin, which may in turn explain some of the parkinsonian features seen in this condition [169].

The second observation, which has linked the fields of autophagy and neurodegeneration, is that mutant aggregate-prone cytoplasmic proteins which underpin many of these diseases are autophagic substrates. This was first shown for mutant huntingtin, but has been subsequently expanded to show that mutant forms of tau, ataxin-3 and α-synuclein are similarly degraded by autophagy [155, 170-172]. These substrates probably have a high dependency on autophagy because their oligomeric and higher-order species cannot be degraded by the proteasome as they cannot access its narrow opening. These findings suggest the possibility of ameliorating conditions caused by such mutant proteins by upregulating autophagy. Subsequently, autophagy upregulation with a variety of different drugs has shown improvement in the phenotype of cellular, fly, zebrafish and mouse models of Huntington's disease [173, 174]. Similar results have been obtained in mouse models of Alzheimer's disease and Parkinson's disease, where autophagy has been upregulated by both drugs and via genetic upregulation of autophagy-inducing proteins [175-177]. Crucially, these findings in basic science and laboratory models of disease are beginning to be translated into potential therapies. Indeed, safety trials of autophagy-upregulating drugs have been initiated in Huntington's disease.

Autophagy and Spinocerebellar Ataxia

Given the similarity between Huntington's disease as a polyglutamine disorder and the wide involvement of autophagy in protein misfolding neurodegenerative disease, it is no surprise that autophagy has been investigated in the context of SCAs caused by polyglutamine expansions, where the mutant protein has a significant cytoplasmic residence time (nuclear proteins are inaccessible to autophagy). Genome-wide screens for modifiers of toxicity in SCA3 highlighted autophagy as an important pathway, where overexpression of key autophagy proteins suppressed toxicity in a *Drosophila melanogaster* model of SCA3 [178]. Similarly, ataxins 3 and 7 have been shown to be autophagy substrates in cell models, as have mutant proteins that lead to SCA but which do not exhibit polyglutamine expansions, such as mutant protein kinase c gamma which causes SCA14 [170, 179-181]. In these models, pharmacological induction of autophagy has been shown to decrease toxicity. The concept of ameliorating toxicity by inducing autophagy has been expanded to rodent models of SCA3, both using temserolimus, a rapamycin analogue, or by overexpression of beclin-1; in both cases, improvement in disease phenotype was seen [152, 182]. Given the body of evidence, both broadly in neurodegeneration and in several specific SCAs, and the identification of FDA-approved drugs which induce autophagy but have minimal side effects, there is now the real prospect of beginning trials of potential disease-modifying drugs in patient populations.

Ataxias as Channelopathies (Daniel R. Scoles and Stefan-M. Pulst)

Channelopathies are clinically definable syndromes that are caused by mutations affecting transmembrane channel functions. Transmembrane channels are important for the normal function of electrically excitable tissues including the heart, muscle, peripheral and central nervous system, and channelopathies can involve any of these tissues. Although the type of mutation and channel involved gives rise to significant phenotypic variability, channelopathies share some common phenotypic features: they are often associated with

episodic or paroxysmal dysfunction such as seizures, paroxysmal paralyses or movement disorders, or episodic ataxias. Next, we discuss ataxia disorders that arise from transmembrane channel mutations and the resultant physiology and patient phenotypes, not all of which are episodic.

Transmembrane channels fall into two main categories, including “selectively permeable” or “gated” ion channels (both voltage-gated and ligand-gated) and active transporters. Ion channels and active transporters have complementary functions: active transporters maintain ion gradients of physiologically relevant ions (Na^+, K^+, Cl^-, Ca^{2+}, H^+) in an energy-dependent fashion (usually ATP) and provide a driving force that moves ions through gated ion channels upon stimulation to open by voltage changes or ligand binding. Some electrogenic active transporters also utilize ion gradients to aid the movement of the transported ions, including glutamine, serotonin, norepinephrine and dopamine transporters [183, 184]. Mutations in these transmembrane channels disrupt electrical signals required for normal neuronal or muscle function, leading to clinically defined syndromes known as channelopathies (Table 2).

Voltage-Gated Ion Channels

Each of the voltage-gated ion channels (VGICs) has a pore-forming α-subunit that opens and closes at specific membrane potentials, resulting in a tightly timed passage of ions across the membrane. Voltage-gated sodium channels and voltage-gated calcium channels are typically closed at the resting potential and have active roles in neuronal depolarization, whilst voltage-gated potassium channels function in repolarization and repetitive firing. Defects in voltage-gated chloride channels are unrelated to ataxias, but cause renal failure and myotonia [185, 186]. There are five VGICs that when mutated give rise to ataxia disorders, including *CACNA1A*, *KCNC3*, *KCNN3* (*hSKCa3*), *KCNA1* and *KCND3*.

CACNA1A

CACNA1A encodes the α1a pore-forming subunit of the P/Q-type calcium channel Cav2.1. Distinctly different cerebellar diseases are caused by *CACNA1A* mutations, dependent upon the nature of the mutation.

SCA6 is an inherited progressive ataxia caused by CAG expansion repeat mutation in the *CACNA1A* gene [187]. The CAG repeat is located in a 3′-alternatively spliced exon and codes for a polyQ repeat. SCA6 patients have a relatively pure cerebellar phenotype and slow progression [187-189].

Episodic ataxia type 2 (EA-2) is caused most frequently by *CACNA1A* frameshift mutations or truncations as well as missense mutations that result in Cav2.1 loss of function [190-192]. Some patients will develop a progressive degenerative ataxia. Pace-making precision of Purkinje cells (PCs) is defective in mice harbouring a spontaneously occurring *CACNA1A* point mutation [193]. However, SCA6(84Q) knock-in mice had PCs with aggregated Cav2.1, but normal electrophysiological phenotype, suggesting that SCA6 is caused by an age-dependent partial toxic gain of function related to Cav2.1 aggregation [194].

Missense mutations in *CACNA1A* are also responsible for familial hemiplegic migraine type 1 (FHM1). These mutations have mixed effects on Cav2.1 channel function, commonly including channel activation at more negative potentials and either increases or decreases in channel current and speed of recovery or inactivation [195-199]. Of note is that some individuals with FHM1 may develop a progressive ataxia in late life.

KCNC3 (Kv3.3)

Spinocerebellar ataxia type 13 (SCA13) is caused by missense mutations in the voltage-gated potassium channel *KCNC3* (*Kv3.3*). Depending on the nature of the mutation, SCA13 can present as a dominant late-onset progressive ataxia [200] or a relatively stationary early-onset ataxia at times associated with mental retardation [201]. Initially, two *KCNC3* mutations were identified, including R420H in a Filipino and F448L in a French pedigree [202]. The R420H mutation changes a highly conserved amino acid that is localised inside the S4 transmembrane domain at the voltage-sensing region and leads to a dominant negative allele [202, 203]. The F448L mutation alters an amino acid just inside the S5 transmembrane domain and resulted in a gain-of-function allele [202]. More extensive studies of 260 familial ataxia patients in Europe and 327 sporadic and familial ataxia cases in the USA demonstrated that *KCNC3* mutations were relatively rare, but showed that the R420H and R423H mutations were recurrent [204, 205].

KCNN3 (hSKCa3)

Upon expression of a truncated dominant negative allele of the slow calcium-activated potassium channel, mice developed an ataxia that could be ameliorated with riluzole [206]. This led Figueroa and colleagues [207] to examine two polyglutamine tracts in hSKCa3 for mutations in 122 patients with autosomal dominant or sporadic ataxias. The study did not reveal any clear CAG expansion mutations, but showed a possible association of long normal *KCNN3* CAG alleles and the presence of ataxia. Further studies are needed to address the possible association of KCNN3 and ataxia in humans.

KCNA1

Episodic ataxia type 1 (EA-1) is a dominantly inherited disease caused by multiple missense mutations in the *KCNA1* gene, which encodes the alpha subunit of the Kv1.1 channel [190, 208]. The disease is characterised by myokymia and episodic skeletal muscle contractions [209]. Mutations in *KCNA1* cause loss of function and are associated with nerve hyperexcitability [210]. Some mutations cause impairment to both subunit tetramerisation and membrane targeting [211]. Rodent models utilizing Kv1 channel inhibitors demonstrated that normal Kv1 channels function to suppress PC hyperexcitability [212]. Consistent with this finding, a *Kcna1* V208A/+ mouse model of EA-1 demonstrated increased GABAergic inhibitory postsynaptic currents of PCs in electrophysiological recordings compared to wild-type mice [213]. Additionally, a *Kcna1* S309T/+ ENU mutagenized rat model of EA-1 with myokymia was characterised by motor incoordination and seizures [214].

KCND3

Recently, five groups in the Netherlands, France, US, Japan and Taiwan identified mutations in *KCND3* encoding Kv4.3, a Shal-related voltage-gated potassium channel that gives rise to a transient outward A-type K^+ current [215, 216]. Two of the five groups had independently mapped an ataxia locus to partially overlapping segments of human chromosome 1 in prior studies, but with designations of SCA19 and SCA22.

KCND3 mutations occurred worldwide and in individuals with different ethnic backgrounds. Two of the mutations were recurrent in different ethnic groups. Initial in vitro characterisation indicated that mutant alleles led to loss of function, although a dominant negative effect of these alleles has not yet been demonstrated.

Ligand-Gated Ion Channels

The ligand-gated ion channels share a common pore-forming architecture that consists of five protein subunits. These channels open after binding of a specific ligand, allowing passage of ions through the channel pore. Ligand/receptor pairs include nicotinic acetylcholine/nAChR, γ-aminobutyric acid (GABA)/GABAR, glycine/GlyR, serotonin/5-HT_3, inositol-3-phosphate (IP3)/IP3R, and glutamate/(NMDAR, AMPAR and kainate receptor). Ataxia is an uncommon manifestation of mutations in ligand-gated ion channels.

ITPR1

Spinocerebellar ataxia type 15 (SCA15, and also SCA16) [217] is caused by heterozygous gene deletions of the inositol 1,4,5-triphosphate receptor gene type 1 (*ITPR1*) [218, 219]. SCA15/16 is a dominantly inherited slowly progressing ataxia characterised by head tremor and cerebellar atrophy. The *ITPR1*-encoded channel IP3R is an intracellular ligand-gated Ca^{2+} channel located to the membranes of the endoplasmic or sarcoplasmic reticulum.

Active Transporters

The active transporters share a common function as transmembrane ion pumps powered by a nucleotide triphosphate, typically ATP that pumps specific ions against a concentration gradient. The classic example is the Na^+/K^+ ATPase that generates a negative charge inside the plasma membrane that supports neuron or muscle resting potentials by pumping three Na^+ ions out of the cell in exchange for two K^+ ions that are pumped in from the outside. Mutations in exchange transporters can result in changes in the ratio of ions that are exchanged and loss of electrogenesis, or complete loss of function. Active transporter types exist that can pump multiple ions including Na^+, K^+, H^+, Mg^{2+}, Cu^{2+} and Ca^{2+}, as well as amino acids, cholesterols, hormones and neurotransmitters. We discuss next syndromes associated with mutation in Ca^{2+} and glutamate transporters.

SLC1A3

SLC1A3 encodes a glutamate/aspartate transporter known as glutamate transporter excitatory amino acid transporter 1 (EAAT1), or glutamate aspartate transporter. EAAT1 has dual functions as a glutamate transporter as well as a ligand-gated anion channel [220]. Investigation on one patient with episodic ataxia, seizures, migraine and alternating hemiplegia identified the cause as a P290R missense mutation in the EAAT1 fifth transmembrane domain [221]. This mutation caused a dominant negative effect that lowered *SLC1A3* expression and the transport of glutamate by EAAT1. Another *SLC1A3* mutation, causing a V449C substitution in the hydrophobic C-terminal domain of EAAT1, resulted in loss of glutamate transport but no alteration on anion transport, demonstrating that the two functions are uncoupled [222].

ATP1A3

Mutation in the *ATP1A3* gene is well established as the cause of early-onset alternating hemiplegia [223] and rapid-onset dystonia Parkinsonism (RPD) [224]. Genetic analysis of two unique initially misdiagnosed paediatric cases of RDP with motor delay and episodic ataxia identified causative mutations in *ATP1A3* [225]. In one case, the mutation, a R756H substitution in the intracellular motif of the channel protein, was inherited, whilst the other mutation was a de novo D923N substitution that was previously shown to abrogate channel function by preventing binding of Na^+ [226].

ATP2B3

X-linked congenital cerebellar ataxia is caused by mutation in the *ATP2B3* gene encoding a calcium channel designated as plasma membrane Ca^{2+} ATPase 3 (PMCA3) [227]. PMCA3 functions to extrude Ca^{2+} from the cell and is inactivated by calmodulin binding. When intracellular Ca^{2+} rises, it binds calmodulin, releasing it from PMCA3 and activating the channel. The G1107D mutation in the calmodulin-binding domain of PMCA3 results in loss of function and abnormal elevation of intracellular Ca^{2+}.

Secondary Channel Abnormalities

In addition to direct mutations of channel proteins, voltage-gated and ligand-gated channels have been implicated as secondary mediators of polyQ pathology. These studies were conducted in transgenic animal models of SCAs examining spontaneous PC firing in cerebellar slice preparation [228-230]. Whereas the presence of mutant ataxin-3 results in depolarization block of PCs, mutant ataxins 1 and 2 lead to a slowing of PC spontaneous firing. Hansen and colleagues [228] showed that decline in motor performance closely mirrored the progressive slowing of PC firing frequency in a transgenic ATXN2[Q127] animal model.

As shown by reciprocal deletion/duplication syndromes such as Charcot–Marie–Tooth disease (CMT1A) and hereditary neuropathy with liability to pressure palsy [231], loss of tight dosage control can be pathogenic for some genes. Haploinsufficiency at the *ITPR1* locus causes SCA15/16, but functional activation of IP3R1 in the presence of mutant polyQ proteins is also involved in PC death. Using in vitro PC culture and animal models, the Bezprozvanny laboratory found that interaction of mutant ataxin 2 or 3 with the IP3R1 led to exaggerated Ca^{2+} release and subsequent PC death in culture and in vivo, which could be prevented by pretreatment with dantrolene [10, 11].

Therapeutics for Channelopathies

Channel proteins belong to a class of proteins in which the structure and function are extremely well understood. Thus, they offer great promise for the rational design of compounds that either up- or downregulate the function of the respective channel. Alternatively, downstream targets of signalling through the channel may be amenable to therapy. A challenge for these approaches is the abundant expression of channel proteins not only in different neuronal populations in the CNS but also in other tissues, thus increasing the potential for significant side effects. Direct modulation of gene expression in the CNS via viral gene delivery or use of antisense molecules may offer hope for targeted therapies in the future.

RNA Toxicity as an Underlying Mechanism of Spinocerebellar Ataxias (Karen N. McFarland and Tetsuo Ashizawa)

RNA toxicity in a number of spinocerebellar ataxias is proposed as a gain-of-function mechanism for neurodegeneration. In these cases, the mutation is the expansion of a microsatellite repeat sequence in non-coding regions of the mutated gene. Ataxic phenotypes result from CTG expansions in *ATXN8OS* in SCA8, ATTCT expansions in *ATXN10* in SCA10 [232], TGGAA expansions in *TK2*/*BEAN1* in SCA31 [233], GGCCTG expansions in the *NOP56* gene in SCA36 [83] and CGG expansions in *FMR1* in fragile X-associated tremor and ataxia syndrome (FXTAS) [234].

Numerous lines of evidence support a gain-of-function model at the RNA level, as we illustrate by example of spinocerebellar ataxia type 10 (SCA10). SCA10 results from the

expansion of a normally polymorphic ATTCT pentanucleotide repeat in intron 9 of the *ATXN10* gene on chromosome 22q13 [232]. With normal alleles ranging from 9 to 32 copies [235], the repeat expands up to 4,500 repeats in SCA10 patients [232]. The repeat expansion does not appear to cause a protein loss of function as mice heterozygous for an *Atxn10* null allele are pathologically and behaviourally normal [236]. Additionally, individuals with an ATXN10 haploinsufficiency, caused by a balanced translocation of chromosome 22, which disrupts one copy of *ATXN10*, are phenotypically normal [237].

Ataxin-10 (*ATXN10*) transcript levels are produced to levels similar to controls in fibroblasts isolated from SCA10 patients [236]. Furthermore, *ATXN10* pre-mRNA is processed normally with proper splicing of intron 9, which bears the repeat expansion [236]. Thus, the ATTCT expansion is transcribed into AUUCU RNA, which accumulates into RNA foci. The RNA foci are found in patient fibroblasts as well as in the brains of transgenic mice expressing untranslated AUUCU repeat expansions [238, 239]. The SCA10 RNA foci in these cells co-localise with the RNA-binding protein (RBP), heterogeneous nuclear ribonucleoprotein K (hnRNP K). We hypothesize that the normal functions of various RBPs are inhibited by binding and sequestration by the AUUCU RNA expansion, thereby resulting in a loss of function for the RBP.

hnRNP K is ubiquitously expressed and contains a nuclear-cytoplasmic shuttling “KNS” domain as well as three KH (K homology) domains, responsible for RNA and ssDNA binding [240, 241]. hnRNP K has multiple functions within the cell, including splicing regulation, translational control, chromatin remodelling, transcription regulation and mRNA stability, and is a component of stress granules [242]. hnRNP K also partners with diverse proteins including protein kinase C delta (PKCδ), which serves to phosphorylate hnRNP K [243, 244]. As our hnRNP K sequestration hypothesis suggests, preventing normal hnRNP K function by AUUCU binding will have a broad range of deleterious effects on cellular function (Fig. 2).

In support of this hypothesis, we find that the normal functions of hnRNP K are impaired in SCA10 fibroblasts as well as in SCA10 transgenic mouse models expressing untranslated AUUCU repeat expansions. Normal hnRNP K–PKCδ interactions are decreased, resulting in apoptosis triggered by the increased localisation of PKCδ to the mitochondria [238]. The function of hnRNP K as a regulator of alternative splicing is perturbed, as seen in altered levels of splicing isoforms of hnRNP K target genes in SCA10 patient fibroblasts [243]. Additionally, these molecular phenotypes are mimicked by knockdown of hnRNP K using small inhibitory RNA (siRNA) in normal fibroblasts [243].

Similar mechanisms are proposed for the other SCAs that are caused by non-coding repeat expansions. RNA foci are formed in SCA31 Purkinje cells and the RNA repeat sequence binds the RBPs, splicing factor arginine/serine rich 1 and SRFS9, in vitro [233]. Similarly, RNA foci form from the GGCCUG expansion in SCA36, and these foci co-localise with the SRFS2 protein in lymphoblastoid cell lines from patients [83]. Sequestration of RBPs Sam68/KHDRBS1, hnRNP G and MBNL1 by CGG-containing RNA foci occurs in FXTAS [245].

Loss of Function of RNA-Binding Proteins Leads to Spliceopathy

Loss of RBP function via sequestration of the RBPs by the repeat-containing RNA foci alters the regulation of alternative splicing and downstream dysfunction of these proteins. Such spliceopathies are a common underlying theme amongst numerous non-coding repeat expansion disorders, including not only the SCAs as discussed above but also the neuromuscular disorders myotonic dystrophy types 1 and 2 (DM1 and DM2). DM1

represents the archetypical non-coding repeat disorder. CUG-containing RNA foci form within the nucleus of DM1 cells and co-localise with proteins from the muscleblind family (MBNL1) in cardiac and skeletal muscle as well as neurons of DM1 patient cells [246, 247]. Altered splicing of insulin receptor pre-mRNA in skeletal muscles from DM1 patients correlates with a decreased response to insulin in culture [248]. Alterations in the levels of splice isoforms of cardiac troponin T (TNNT2) pre-mRNA are found in DM1 heart and skeletal muscles [249]. Aberrant ClC-1 pre-mRNA in DM1 cells causes a loss of ClC-1 protein function [250, 251]. Correcting the splicing patterns of ClC-1 can reverse the problems of chloride conductance, hyperexcitability and myotonia [252]. Thus, preventing the interaction between RNA expansion and their interacting RBPs may represent a universal therapeutic target for many of these disorders.

Repeat Interruptions as a Phenotypic Modifier

The nucleotide composition of the repeat expansion may hypothetically influence this disease mechanism. Repeat interruptions in SCA10 expansion dramatically influence repeat stability and alter canonical rules of genetic anticipation [253]. Furthermore, as RNA-binding proteins are known to interact in a sequence-specific manner, repeat interruptions within the expansions may differentially interact with a variety of RNA-binding proteins. Such a hypothesis may explain phenotypic differences that are observed for a single SCA disorder, as well as other repeat expansion disorders, and is evidenced in SCA1, SCA2, SCA10, SCA31 and DM1 [254-265].

Bidirectional Transcription

Antisense transcripts from microsatellite repeat expansions are increasingly recognised as potential auxiliary toxic agents in the pathogenic process. Antisense transcripts result from bidirectional transcription at the expansion, a concept first recognised in SCA8 [266] and subsequently found in other trinucleotide repeat disorder including myotonic dystrophy type 1 [267], SCA7 [268], Huntington's disease [269] and Huntington's disease like-2 [270].

In SCA8, a non-coding CTG expansion was first identified in the *ATXN8* gene in an ataxia patient [266]. Both CUG and CAG transcripts originate from the expansion and are found in patient tissue samples, indicating that transcription occurs from both strands of the microsatellite expansion [271]. CAG transcripts produce polyglutamine inclusions [272], whilst CUG transcripts result in RNA foci [110, 273]. As a result, understanding of the pathogenic mechanism in SCA8 is confounded by a gain of function at both protein and RNA levels.

Bidirectional transcription will likely become a more prominent mechanism in other ataxias that have long thought to be protein gain-of-function mutations. With the advent of next-generation sequencing technologies allowing for deep sequencing of RNA transcriptomes, an increasing number of coding trinucleotide repeat disorders (e.g. SCA1/*ATXN1*, SCA2/*ATXN2*, SCA3/*ATXN3*, SCA6/*CACNA1A*, SCA7/*ATXN7*, SCA17/*TBP* and DRPLA) are recognised as having natural antisense transcripts to varying degrees [274]. In addition, antisense transcripts to the *huntingtin* gene are produced in cells from the frontal cortex of HD patients and contain the CTG repeat [269].

Exact mechanisms downstream of the bidirectional transcription of repeat expansions have not been fully worked out. Antisense transcription can regulate gene expression through a variety of mechanisms, which may be perturbed by the repeat expansion [274]. Antisense transcripts to the CAG repeat expansion disorders could also follow the same downstream pathways described above (Fig. 2). Untranslated CUG and CAG repeat expansions can

separately trigger the formation of RNA foci and have similar effects on spliceopathy phenotypes caused by the loss of RBP function [275].

Repeat-Associated Non-ATG-Mediated Translation (RAN Translation)

A new mechanism for neurodegeneration in SCA8 was found when polyglutamine proteins were produced after the only ATG site upstream of the CAG expansion was mutated [276]. Further experimentation found that proteins were translated in all three frames—polyglutamine, polyalanine and polyserine—from constructs that lacked the traditional ATG translation start site. Such a phenomenon was dubbed repeat-associated non-ATG (RAN) translation and is dependent on repeat length as well as the formation of an RNA hairpin secondary structure. In vivo evidence for polyalanine proteins was found in the Purkinje cells of SCA8 postmortem cerebellum and in SCA8 transgenic mice. More recently, evidence of RAN translation is seen from the GGGGCC expansion in the c9orf72 locus of ALS-FTD [277]. Furthermore, indications for RAN translation are also found in cardiomyocytes and myoblasts from mouse models of DM1. Whilst RAN translation has not yet been shown to have disease-causing effects, it may represent a new pathogenic mechanism as many of the expansion-containing RNA molecules, both from sense and antisense transcripts, have the potential to become substrates in this pathway [278].

Expansion-containing RNA molecules, whether through their native sense or antisense transcripts, are important players in the pathways that lead to disease phenotypes. The degree of interplay (Fig. 2) between these pathways, which are described above, has yet to be determined and will complicate further understanding of pathogenic processes. Yet as many of these disorders share similar pathways, the development of therapeutic targets may benefit from exploiting these common features.

Mitochondria and Neurodegeneration in SCAs (Franco Taroni and Stefania Magri)

In the last 20 years, it has become quite evident that mitochondrial dysfunction may severely affect the proper function of the cerebellum and its afferent and efferent connections. The occurrence of ataxia in mitochondrial disorders related to defined primary mutations of mitochondrial DNA (mtDNA) is well known. This is the case with myoclonic epilepsy with ragged red fibers caused by the 8344A>G mutation; mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes caused by the 3243A>G mutation; maternally inherited Leigh syndrome caused by point mutations in the mtDNA genes *ATP*6, *ND1* and *tRNA* ^{Lys} ; NARP caused by *ATP6* mutations at nt 8993; and Kearns–Sayre syndrome associated with large-scale rearrangements of mtDNA [279, 280]. In these cases, the impaired function of the mitochondria is that which traditionally characterises these organelles as the “powerhouses of the cell”: production of ATP via the concerted action of the tricarboxylic acid cycle and the respiratory chain/oxidative phosphorylation system. Another example of cerebellar ataxia caused by energy production defect is that associated with deficiency of coenzyme Q_{10} (CoQ_{10}) [281]. CoQ_{10}, also known as ubiquinone, is a small lipid-soluble carrier with important antioxidant properties which is required to transfer electrons in the respiratory chain from complexes I and II to complex III [282]. In addition to its electron transfer properties, as a well-known antioxidant, CoQ_{10} protects cells from reactive oxygen species (ROS) damage by scavenging free radicals [283]. In the autosomal recessive form SCAR9, mutations in the gene encoding the mitochondrial kinase ADCK3 [284, 285] block the biosynthesis of CoQ_{10}, ultimately resulting in reduced activity of respiratory chain. Recently, cerebellar phenotypes recapitulating the human disease have been generated by blocking CoQ_{10} biosynthesis in two conditional knockout mice [286]. An impairment in energy production also underlies the pathomechanisms leading to cerebellar

ataxia in some recessively inherited defects of nuclear DNA genes (*POLG* and *C10orf2*) encoding mitochondrial proteins involved in mtDNA replication and maintenance [287, 288]. Several ataxic phenotypes are associated with mutations of the *POLG* gene, encoding the catalytic subunit A of mitochondrial DNA polymerase g [289]. *POLG*-related ataxias have an overlapping clinical spectrum of disorders (ataxia neuropathy spectrum or ANS) organized around ataxia and neuropathy in the absence of significant muscle weakness or myopathy [280, 288, 290]. ANS embraces the phenotypes also referred to as mitochondrial recessive ataxia syndrome [291] and sensory ataxia neuropathy dysarthria and ophthalmoplegia [292] and may partly overlap with spinocerebellar ataxia with epilepsy/myoclonic epilepsy myopathy sensory ataxia phenotype [290]. As a consequence of mitochondrial DNA polymerase mutations, these disorders are characterised by qualitative (multiple deletions) or quantitative (depletion) alterations of mtDNA, which ultimately result in impairment of energy production. Depletion of mtDNA and energy defect is also the mechanism that underlies infantile-onset spinocerebellar ataxia, a recessively inherited disorder caused by mutation in the *C10orf2* gene (previously *PEO1*/*TWINKLE*) which encodes twinkle, a specific mitochondrial helicase involved in DNA replication, and one of its smaller isoform, twinky, whose function is currently unknown [293]. More recently, a pathogenic mechanism involving defective mtDNA maintenance and mitochondrial dysfunction has been proposed also for ataxia with oculomotor apraxia type 1 and spinocerebellar ataxia with axonal neuropathy (SCAN1) by demonstrating mitochondrial localization and function of the proteins defective in these disorders, aprataxin [294] and tyrosyl-DNA phosphodiesterase [295], respectively. The pathogenesis of Friedreich ataxia, a paradigm for mitochondria-related neurodegeneration, is more complex and controversial [296-298]. The main pathophysiological consequences of frataxin deficiency are a severe impairment of iron–sulfur cluster (ISC) biosynthesis that affects ISC-containing enzymes localised in various cellular compartments including the mitochondria (complexes I, II and III of the respiratory chain and aconitase of the tricarboxylic acid cycle), cytosol and nucleus [299]; mitochondrial iron overload [300, 301]; and an increased sensitivity to oxidative stress [300, 302].

The above discussion emphasizes the sensitivity of the spinocerebellar system to bioenergetics perturbations. However, a large number of studies in late-onset neurodegenerative disorders including spinocerebellar ataxias have clearly shown that other mitochondrial functions are greatly important for the disease process, including organelle shaping and trafficking, mitochondrial quality control and apoptosis [303, 304].

Apoptosis via the intrinsic mitochondrial pathway is, in fact, the most common mechanism of cell death in neurodegenerative diseases [303, 305], and direct activation of apoptotic pathways has been demonstrated in several polyglutamine expansion diseases including spinocerebellar ataxias [306-309]. In the intrinsic pathway, several intracellular signals, including DNA damage, endoplasmic reticulum stress, or mitochondrial dysfunction itself, induce mitochondrial membrane permeabilization, which causes the release of pro-apoptotic proteins (cytochrome *c*, Smac/DIABLO and Omi/HtrA2) from the intermembrane space into the cytosol, a process regulated by pro-apoptotic (Bax, Bak) and anti-apoptotic (Bcl-x_L) members of the Bcl-2 family. Cell death occurs by the final activation of effector caspases via maturation of caspase-9 (mediated by cytochrome *c*) or blockage of IAP (inhibitor of apoptosis) proteins (mediated by Smac/DIABLO and Omi/HtrA2) [305]. This mechanism is exemplified by cellular models of SCA3 and SCA7, in which both polyglutamine-expanded proteins, mutant ataxin-3^{Q79} and ataxin-7^{Q75}, induce neuronal death by the activation of the intrinsic mitochondrial apoptotic pathway via upregulation of the mitochondrial pro-apoptotic factor Bax and downregulation of the anti-apoptotic factor Bcl-x_L [308, 309]. More recently, however, expanded ataxin-3 (Q84 and Q104) has been shown to be associated with reduced activity of mitochondrial respiratory chain complex II with no

evidence of activation of the apoptotic cascade [310], as previously reported for another polyglutamine disease [311].

Closely related to mitochondria-mediated apoptosis [312] and crucial for neuronal survival is the dynamic regulation of mitochondrial morphology and assembly of the mitochondria into a continuous network by the concerted action of opposing fission and fusion events [313, 314]. The importance of a proper mitochondrial fission/fusion balance in neurons is illustrated by two neurodegenerative disorders caused by mutations in the mitochondrial fusion GTPases MFN2 and OPA1 [315] and by a mouse model of cerebellar neurodegeneration generated by selectively removing Mfn2 from the cerebellum [316]. Unique among spinocerebellar ataxias, SCA12 has been proposed to be caused by a brain-specific regulatory subunit (Bß2) of the protein phosphatase PP2A that upon cell stress is rapidly targeted to the outer mitochondrial membrane, where it promotes apoptosis by inducing Drp1- and Fis1-dependent mitochondrial fission [317]. The SCA12 mutation is a CAG repeat expansion in the *PPP2R2B* 5′ untranslated region, which functions as a *cis* promoter element that upregulates *PPP2R2B* expression [318]. Therefore, the disease process would originate from an abnormally increased activity of a pro-apoptotic protein, resulting in severe fragmentation of the mitochondrial network. Interestingly, the opposite phenotype (mitochondrial hyperfusion) has been observed in autosomal recessive spastic ataxia of Charlevoix–Saguenay caused by loss-of-function mutations in a protein (sacsin) that co-localises with the mitochondria [319]. In a *Drosophila* model of SCA12, overexpression of *ppp2r2b* induced fission of the mitochondria accompanied by increases in cytosolic ROS, cytochrome *c* and caspase-3 activity [320]. Overexpression of Mn^{2+} SOD2 and antioxidant treatment reduced ROS and caspase-3 activity and extended the life span of SCA12 transgenic flies. Thus, SCA12 well illustrates the tight link that exists between mitochondrial apoptotic pathways, organelle dynamics and oxidative stress in the pathogenesis of mitochondria-mediated spinocerebellar degeneration.

Maintenance of an efficient mitochondrial network by balanced fusion and fission events is intimately connected to mitochondrial quality control. The cell has surveillance mechanisms to eliminate misfolded or unwanted proteins via autophagic and ubiquitin–proteasome systems located in the cytosol. In contrast, the mitochondria do not contain proteasomes and rely on a remarkable number of chaperones and proteases which promote folding of newly imported proteins, protect mitochondrial proteins against heat or oxidative stress and eliminate irreversibly damaged polypeptides [321]. Mutations in mitochondrial quality control genes could hamper the efficient degradation of potentially deleterious proteins, thus leading to neuronal dysfunction and, ultimately, to cell death. SCA28, caused by mutations in the *AFG3L2* gene, provides an example of such perturbation of mitochondrial homeostasis [322]. Notably, it is the only autosomal dominant spinocerebellar ataxia caused by mutations affecting a mitochondrial-resident protein. AFG3L2 is a ubiquitous component of the *m*-AAA metalloprotease complex located in the internal mitochondrial membrane. Interestingly, the homologous protein paraplegin is also a component of the same mitochondrial complex and causes recessive spastic paraplegia type 7, a neurodegenerative disease closely related to spinocerebellar ataxia [323]. AFG3L2 can form both homo-oligomeric (AFG3L2/AFG3L2) and hetero-oligomeric (AFG3L2/paraplegin) complexes. The *m*-AAA complex is part of the mitochondrial inner membrane protein quality control system and participates in the maturation of precursor proteins, the degradation of incorrectly folded polypeptides and the assembly of components of the inner membrane, including complexes of the respiratory chain [324].

So far, only missense mutations have been described, the vast majority of which occur in the highly conserved proteolytic domain [322, 325]. In one consanguineous family, a homozygous mutation has been identified in two siblings with a distinct phenotype

characterised clinically by lower extremity spasticity, peripheral neuropathy, apoptosis, oculomotor apraxia, dystonia, cerebellar atrophy and progressive myoclonic epilepsy [326]. In a cellular model, the mutations impair AFG3L2 proteolytic activity, respiratory chain complex IV activity and, eventually, cell respiration [322]. Although AFG3L2 is ubiquitously expressed, muscle histopathology in patients is normal with no ragged-red fibres, no mtDNA deletions and normal respiratory chain activity [327], which indicates a selective vulnerability of the cerebellum consistent with the high levels of AFG3L2 protein detected in human Purkinje cells [322].

In a conditional mouse model, restricted deletion of the *Afg3l2* gene in Purkinje cells demonstrates that mitochondrial fragmentation is an early event in the disease process and is caused by defective protein synthesis associated with impaired mitochondrial assembly [328]. In a distinct mouse model of the disease, cells lacking Afg3l2 exhibit respiratory dysfunction and fragmentation of the mitochondrial network, which causes the decrease of mitochondrial Ca^{2+} uptake by impairing mitochondrial–ER communication [329]. Altogether, these data provide further evidence that mitochondria-mediated neurodegeneration is a complex multifaceted process in which bioenergetics impairment, albeit important, is only one of the key players [304].

Because the interrelated multilevel pathways that regulate mitochondrial homeostasis are still unclear, the quest for effective treatments that improve mitochondrial function is still an unresolved issue. This knowledge will likely provide clinicians with novel and highly effective therapeutics to, in the very least, delay ataxia neurodegeneration.

Therapeutic Targets in Inherited Ataxias (Massimo Pandolfo)

Hereditary ataxias are characterised by quite diverse genetic, clinical, pathophysiological, pathogenic and neuropathological features; hence, potential therapeutic targets for disease modification depend on the specific condition being considered. So far, even though clinical trials are quite advanced in some cases, like Friedreich's ataxia [330], no molecules have been reported to show efficacy in slowing the progression or the amelioration of neurological symptoms. Furthermore, there is currently no effective symptomatic treatment for ataxia. Physical therapy will not be addressed here, but it should be noticed here that intensive coordinative training may improve functional performance in various cerebellar and afferent ataxias [331, 332] and remains, along with other rehabilitative approaches, the main therapeutic option that we can currently offer these patients.

Potential disease-modifying therapeutics for inherited ataxias can be divided into two main categories: (1) those that modulate gene expression and (2) those that target specific pathogenic mechanisms triggered by the genetic defect.

Modulating the Expression of the Mutated Gene

Therapies that modulate gene expression may target the pathogenic process in inherited ataxias at its roots. Several inherited ataxias are due to altered levels of expression of the causative gene without changes in the encoded protein sequence (FRDA and fragile × tremor–ataxia syndrome) or to expression of a mutated allele encoding a toxic protein (polyQ diseases). Increasing gene expression in FRDA, decreasing gene expression in FXTAS, or preventing the expression of the mutated allele in polyQ diseases represents potentially valuable therapeutic approaches for these disorders. Furthermore, induction of exon skipping may reestablish the reading frame after frameshift mutations in some recessive ataxias or prevent the incorporation of the exon containing the pathogenic mutation, as in SCA6. Ataxias due to loss-of-function mutations may in principle benefit from gene or protein replacement therapies.

In FRDA, the GAA repeat expansions in the *FXN* gene induce a closed chromatin conformation, characterised by increased DNA methylation and by specific posttranslational modifications in the core histones, in particular loss of acetylation at various lysines and increased trimethylation at histone H3 lysine 9 (H3K9) [333]. Pharmacological inhibitors of HDACs may counteract these chromatin changes and reactivate *FXN* expression. Experiments in peripheral blood mononuclear cells from FRDA patients and in knock-in animal models carrying expanded GAA repeats indicated that a specific family of benzamide HDAC inhibitors can increase frataxin levels, whilst most other HDAC inhibitors are ineffective [334-336]. Benzamide HDAC inhibitors specifically target HDAC1 and HDAC3 and have a slow-on/slow-off kinetic, and both characteristics are essential for frataxin upregulation [337]. Importantly, frataxin upregulation is obtained at doses that cause minimal overall gene expression changes, suggesting that toxicity due to gene expression dysregulation is unlikely [334]. A phase I study with one of these molecules is ongoing.

The current model of FXTAS pathogenesis is that of RNA toxicity [338] (discussed earlier in this manuscript). Pre-mutation fragile × (FRAXA) alleles containing 50–200 CGG triplets in the 5′ untranslated region (UTR) of the *FMR1* gene are transcribed at higher levels than normal alleles. *FMR1* RNA containing such FRAXA pre-mutation repeats accumulates in nuclear foci, probably as a consequence of the tendency of the repeats to form hairpin structures, and sequesters specific RNA binding proteins, whose normal function is then compromised. FXTAS patient-derived lymphoblasts and fibroblasts show increased histone acetylation at the FMR1 locus, which correlates with increased gene expression. Furthermore, experiments in *Drosophila* showed that the simultaneous overexpression of HDACs 3, 6, or 11 suppresses the neurodegeneration induced by a CGG-containing transgene [339]. Histone acetyltransferase (HAT) inhibitors have been shown to repress *FMR1* mRNA expression in pre-mutation carrier cell lines and extend life span in CGG repeat-expressing *Drosophila* [339], providing a proof of principle that HAT inhibitors or HDAC activators might be used to selectively repress transcription at the *FMR1* locus in individuals affected with FXTAS.

In polyQ diseases, altered normal functionality and the acquisition of novel toxic properties by the polyQ proteins are thought to contribute to pathogenesis [17]. Therefore, suppressing the expression of the mutated protein is an appealing therapeutic approach. In a transgenic mouse model of SCA1, recombinant AAV expressing short hairpin RNAs directed against different portions of the ataxin-1 mRNA improved motor coordination and restored cerebellar morphology, clearing the characteristic ataxin-1 containing nuclear inclusions in Purkinje cells [340]. Ataxins 3 and 7 have been similarly targeted [341]. However, this approach does not differentiate between the mutated and the normal allele of the target gene. The resulting downregulation of both mutated and normal protein may lead to functional consequences due to loss of normal function. This is more than a potential concern, as indicated by the appearance of pathological phenotypes in knockout animals for genes involved in polyQ diseases and particularly by the fact that partial loss of function is likely to contribute to the pathogenesis of several polyQ diseases. Thus, specific suppression of the mutated allele has been attempted by using RNAi molecules whose target sequences include single nucleotide polymorphisms (SNPs) that are in linkage disequilibrium with the mutated allele [342]. Whilst results in animal and cell culture models indicate that this approach may be effective, the need for a SNP that differentiates the alleles limits its application to a portion of patients with specific polyQ diseases. The possibility to target the CAG repeat is also being studied, but the abundance of CAG repeat-containing human transcripts (estimated at ~200) makes off-target effects likely. It has been suggested that modified siRNAs functioning like some naturally occurring miRNAs that inhibit translation rather than inducing mRNA cleavage may be used to achieve downregulation of a specific polyQ

protein [341]. The key to success is therefore the identification of the best reagent to obtain specific allele suppression, in terms of type of RNAi and of choice of target sequence. A gene replacement strategy that combines non-allele-selective gene silencing with the expression of an exogenous normal allele is also being considered.

The use of antisense oligonucleotides (ASOs) has also been explored as a way of suppressing polyQ protein expression through translational blockade or RNaseH activation. A variety of chemical modifications that favour one or the other mechanism, stability and cell penetration, have been considered, particularly in models of Huntington's disease [343]. A clinical trial in HD with intraventricularly administered ASOs is underway.

SCA6 is caused by an expanded CAG repeat in the gene encoding the Ca(V)2.1 voltage-gated calcium channel alpha subunit (*CACNA1A*). The corresponding polyQ tract is located in an intracytoplasmic portion of the protein near its carboxy-terminus, which does not participate in channel function and is encoded by an alternatively spliced exon, so only a fraction of Ca(V)2.1 molecules contains it. Interestingly, inclusion of this exon in the mature mRNA is enhanced by the presence of an expanded CAG repeat. Thus, suppressing the polyQ-encoding Ca(V)2.1 splice variant with a splice isoform-specific RNAi strategy may represent a potential therapy for SCA6. This was achieved in a variety of cell-based models including a human neuronal cell line using a human miR124-based RNAi construct [344].

Delivery to the CNS, which is protected by the blood–brain barrier, and across cell membranes remains a major problem that needs to be resolved to make RNAi and ASO approaches a viable option to treat polyQ diseases and other conditions that may benefit from specific suppression or modulation of gene expression. Chemical modifications and non-viral and viral vectors are all being considered for this purpose, but progress beyond animal models has so far been limited [345].

Targeting the Pathogenic Mechanisms Triggered by the Genetic Defects

Antioxidants have been proposed for the treatment of many neurodegenerative diseases, including inherited ataxias, but clinical results have been so far mostly disappointing. A reason for the limited success of antioxidant treatments is probably the lack of specificity of what has been attempted. Better understanding of the sources and mechanisms of oxidative damage in different conditions, including the role that oxidative stress has in each case and the specific pathways that are activated, is necessary to design more effective, targeted treatments [346].

Lipid-soluble antioxidants have been used to treat FRDA. In this disease, defective iron–sulphur (Fe–S) cluster biogenesis in the mitochondria causes iron accumulation in these organelles and impaired electron transport in the respiratory chain. Both processes lead to increased formation of toxic free radicals, hence the rationale for antioxidant use. Randomised, placebo-controlled trials (RCTs) have been conducted so far with the short-chain coenzyme Q analogue idebenone and with A0001 (alpha-tocopherylquinone), which is a lipid-soluble antioxidant and a respiratory chain stimulator molecule related to both coenzyme Q and vitamin E [330]. Despite some promising results in a phase 2 study, no efficacy of idebenone in improving ataxia or cardiomyopathy could be demonstrated in two phase 3 studies. A phase 2A trial with A0001 showed signs of efficacy on ataxia [347], but the short duration of the study (4 weeks) imposes caution, so further trials are necessary before a conclusion about efficacy can be reached. Deferiprone, an orally administered, membrane-permeable iron chelator, also functions as an antioxidant by removing excess redox-active iron from the mitochondria. A 6-month phase 2 RCT in FRDA, however, was inconclusive (unpublished data).

A role of oxidative stress is postulated in other ataxias as well. Oxidative stress is the primary cause of DNA damage in neurons and has a key role in the pathogenesis of ataxias due to defective DNA repair, providing a rationale for antioxidant treatment. No RCT has been performed to date, but encouraging results have been obtained in cellular and animal models. The observation of the amelioration of ataxia in AT patients treated with steroids, originally for lymphoma, prompted further consideration of glucocorticoids for this condition [348]. The neurological benefit is probably due to the fact that these molecules penetrate into the CNS, where they act as anti-inflammatory and antioxidant drugs. However, the side effects of glucocorticoids, particularly when life-long exposure starting in childhood is envisioned, including a possibly increased risk of infection in the already immunocompromised AT patients, impose caution before this treatment can be recommended.

In dominant SCAs, mitochondrial dysfunction and oxidative damage are also thought to play a role, supporting the use of antioxidants as potential therapeutics, but there is currently little clinical evidence of efficacy. Other proposed general therapeutic targets include the formation of toxic aggregates of polyQ proteins or protein fragments, transcriptional dysregulation by polyQ nuclear aggregates, Purkinje cell dysfunction due to altered Ca^{2+} signalling and homeostasis, and altered physiological properties of cerebellar neurons due to changes in ion channel expression at the cell membrane. Additional specific approaches depend on the function of the mutated gene.

Conformational therapeutics to counteract polyQ protein aggregation (discussed in earlier section) has mostly been attempted for HD. Utilised molecules include the polyphenol epigallocatechingallate and the sulfobenzoic acid derivative C2-8. Results in HD animal models were mildly encouraging [349], but further studies are necessary to refine this approach and determine its applicability to SCAs.

Transcriptional dysregulation is considered a likely pathogenic mechanism in polyQ diseases, possibly due to sequestration of transcription factors by toxic protein aggregates in the nucleus [17] (discussed in earlier sections). In particular, sequestration of the histone acetyl transferase CBP leads to diffuse histone hypoacetylation and transcriptional repression, suggesting that HDAC inhibitors may be beneficial [350]. Most supporting data come from HD animal models, but a beneficial effect of the HDAC inhibitor sodium butyrate was also shown in an SCA3 model [351].

Altered Ca^{2+} signalling in Purkinje cells is thought to be a general pathogenic mechanism in SCAs [352] (discussed in earlier sections). Inositol 1,4,5-trisphosphate receptor type 1, ITPR1, a ligand-gated ion channel that releases Ca^{2+} from the ER, is a key regulator of Purkinje cell activity, whose function may be disrupted by interaction with polyQ proteins or, in SCA15 and 29, directly by gene mutations. Proposed interventions include inhibition of Ca^{2+} release from the ER with dantrolene or similar drugs (in SCA2 and SCA3) [353], inhibition of the calcium-activated proteases calpains (in SCA2) [21] and modulation of calcium-activated potassium channels (in SCA2) [22].

Changes in potassium currents have been detected in Purkinje cells in an SCA1 mouse model. In this model, increased K^+ conductance correlates with decreased Purkinje cell firing rate and motor impairment. Treatment with the K^+ channel inhibitors 3-aminopyridine and 3,4-diaminopyridine corrected the electrophysiological abnormality, restored motor function and, if started early in the disease course, partially prevented cell loss [229]. No human trials have so far been conducted.

Modulators of Phenotype and Neurodegeneration in Spinocerebellar Ataxias (Giovanni Stevanin and Alexis Brice)

Spinocerebellar ataxias are clinically and neuropathologically extremely heterogeneous. For example, onset is generally observed during the third or fourth decade, but can also occur in childhood or old age. In addition, neuropathologically, prominent atrophy of the cerebellum and brain stem is usually observed, but other structures may also be affected, sometimes with only very slight lesions in the vermis. This leads to a considerable range of phenotypes. This clinical and pathological heterogeneity has been partially explained by various, mostly genetic, factors. Since SCAs are rare and those caused by polyglutamine/CAG expansions are by far the most frequent forms, potential modulators have been described so far mainly in these subtypes of SCAs.

The Nature of the Mutation

The major contributor to the phenotypical heterogeneity is the pathological mutation. Its nature affects disease progression. Indeed, disease progression is usually slower in patients with conventional mutations in SCA genes, in whom brain atrophy is often restricted to the vermis or hemispheres of the cerebellum, whilst the disease progresses faster and is multifocal in patients with CAG/polyQ expansions [24], therefore affecting neuropathology profiles. In addition, among SCAs caused by CAG repeat expansions, a prospective study of 526 patients showed that progression was faster in SCA1 patients compared to SCA2, SCA3 and SCA6 [2].

The Size of the Pathological Expansion

Among the frequent SCAs caused by CAG/polyglutamine expansions, age at onset varies as a negative function of the size of the expansion [354]. The number of CAG repeats on the expanded allele accounts for 59 % (SCA6) to 88 % (SCA7) of the variability of the age at onset, which is broad enough in any given SCA to preclude precise age at onset prediction on the basis of repeat size.

CAG repeat size also affects disease severity and frequency of several clinical signs, and therefore also partly accounts for phenotypic variability among patients [24, 355]. This is illustrated in DRPLA, in which longer repeats are associated with an earlier age at onset and a phenotype characterised by progressive myoclonus, epilepsy and dementia, whereas smaller repeats result in a high frequency of choreoathetosis and psychiatric manifestations in adults [356, 357]. Furthermore, SCA2 patients with small expansions may present with a parkinsonism or motor neuron disease, sometimes without ataxia [358, 359]. In SCA3/MJD patients, the frequency of pyramidal signs increases with the size of the expanded repeat, whereas the frequency of altered vibration sense decreases [360, 361]. In SCA7 patients, the frequency of decreased visual acuity, ophthalmoplegia and Babinski signs increases with the number of CAG repeats [362].

Disease duration until death is also negatively correlated with the number of CAG repeats on the expanded allele at the SCA7 locus and is limited to a few months or years in very early-onset patients [362].

Finally, somatic mosaicism of the mutation (i.e. its size varying among tissues) has been hypothesized to play a role in the specificity of the lesions, but this question remains unsolved.

Other Genetic Factors

The correlation factor between age at onset and CAG repeat size in polyglutamine SCAs ranges from 0.5 to 0.7 in most studies, suggesting that other genetic factors contribute to the variability. The involvement of other “familial”, and therefore likely genetic, factors that cluster within families has been suggested very early [363] and confirmed more recently [364]. Indeed, in SCA1, SCA3 and SCA6, the length of the non-expanded repeat *in trans* has a modest but significant influence on the age at onset [361, 364], and repeats in the *RAI1* or *CACNA1A*/*SCA6* genes affect the age at onset in SCA2 patients [188, 365, 366]. Age at onset in SCA3 patients is also dependent on *SCA2* normal allele sizes [367]. However, most of these studies have not yet been replicated and the proportion of age at onset variance explained by these potential modifiers is usually very small. This calls for large collaborative worldwide efforts.

Besides the genes already described to impact on SCA pathology, microarray experiments and yeast two-hybrid screens have revealed a number of interesting genes that might modulate the ataxia phenotype, although this remains to be proven at the cellular level. The ataxia interactome that connects most of the known ataxia genes demonstrated that many ataxia-causing proteins share interacting partners, particularly among the transcription regulation, nuclear import, RNA splicing and ubiquitinylation processes [40]. These pathways have also been evidenced in genetic screens in SCA *Drosophila* models [178, 368-370]. The role of microRNA as potent phenotypic modulators has also been shown in fly models [92] and has been discussed in previous sections.

Non-genetic Factors

The clinical phenotype is influenced by disease duration in all forms of SCAs. The frequency of ophthalmoplegia, amyotrophy, sphincter disturbances and dysphagia increases with disease duration in the autosomal dominant cerebellar ataxias (ADCA) type I. In SCA6 patients, whilst the phenotype may remain pure during the first 10 years of disease duration, additional signs can occur later. Gender has also been shown to modulate SCA3 and SCA6 disease progression [2].

The cell context may also affect the toxicity of the proteins and then neurodegeneration. First, neurons are post-mitotic cells and are therefore thought to be more sensitive to this toxicity. Cell-specific properties may also affect the polyglutamine toxicity level. Somatic mosaicism, differences in DNA repair and protein degradation pathways have been proposed to explain the sensitivity of certain subcellular populations of neurons. Although spatiotemporal accumulation of the pathological protein occurs in polyglutamine SCAs, it seems that there is a disconnection between the presence of the inclusions and neurodegeneration. Indeed, the density of the neuronal intranuclear inclusions in a given structure does not seem to correlate with the degree of neurodegeneration. This is particularly striking in SCA17 in which the density in inclusions never reach 3 % of the neurons in affected or in unaffected brain regions. In SCA17, except for the cerebral cortex, there is an inverse correlation between the presence of NIIs and the severity of lesions in a given structure [371, 372], i.e. no NIIs are detected in the Purkinje [373] and granule cell layers or in the locus coeruleus, all of which degenerate, but they are detected in the putamen, dentate nucleus and pontine nuclei, which are unaffected or only mildly affected [371]. It is also becoming more and more evident that posttranslational modifications of the proteins (cleavage, phosphorylations, etc.) that may differ according to the structures are critical steps for protein toxicity. This is particularly evident for the ATXN1 protein, the phosphorylation of which is involved in its stabilization, interactions, and toxicity [49, 374] and opens the way to therapeutic assays [375]. Sumoylation of ATXN7 has also been

connected to the pathological process in SCA7 [376]. Another point of interest is the abnormal conformation of the protein that benefits from the use of chaperones to improve the phenotype of fly, mouse and cell SCA models [51, 377-382].

Although these pathologies are inherited, the environment is also hypothesized to play a role in the modulation of polyglutamine toxicity. A study had shown that environmental enrichment of R6/1 mice, models of Huntington's disease, delays the onset of motor symptoms [383]. Along the same line, mild exercise in the SCA1 mouse model improved survival and motor functions by compensation of the hyper-repression effect on transcription of the polyglutamine expansion [57]. We are just now learning the complex genetic interactions among the different factors involved including the environment taken place in the modulation of the disease phenotype.

Conclusions

Clearly, one of the seminal discoveries in the research of spinocerebellar ataxias is the identification of the causative gene defect as the initial step to further investigate the underlying molecular mechanisms in each specific ataxia subtype, with the ultimate goal of finding treatments. Identifying the mutation enables characterising the biological functions of the gene products, uncovering the molecular pathways implicated and understanding the effects of the mutation in the affected neuronal systems. A comprehensive understanding of the mechanisms that are fundamental for dysfunction and degeneration of the affected neural systems in spinocerebellar ataxias is essential for developing effective therapeutic approaches. The identification of earlier molecular dysfunction in SCAs helps to direct the study of mechanisms of neurotoxicity to earlier stages of the disease. Applying effective treatments to SCAs in the window of reversibility of early neuronal damage is now the major challenge, and the key barrier to effective therapy is that SCAs present clinically when neuronal loss is well advanced and thus irreversible. Current treatments are almost all directed at modifying symptoms; few address underlying pathogenic mechanisms and are inevitably delivered too late to rescue dying neurons. In this consensus manuscript, we have attempted to offer an overview and discuss the most relevant pathways and topics relevant in the neurodegeneration process in spinocerebellar ataxias, including transcription, aggregation, autophagy, ion channels, mitochondria, RNA toxicity, and their components and modulators of the disease phenotype, with the aim of discussing the current strategies being translated into treatments. Despite the many novel findings we have discussed in the preceding sections, a common view is shared that further basic research is needed, particularly that aimed at understanding and identifying the players and their interactions triggering the early neuronal dysfunction by each of the mutated genes, when neurodegenerative rescue is still possible. This would help direct the therapeutic strategies at earlier stages of the disease with the hope of not only halting the disease progression but also of the possibility of motor recovery in ataxia disorders.

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Abbreviations

AFG3L2	ATPase family member 3-like 2
ATN1	Human atrophin-1 protein
Atxn	Mouse ataxin
ATXN	Human ataxin
BDNF	Brain-derived neurotrophic factor
CAG	Codon that codes for glutamine
Ced	*C. elegans* cell death gene
DCD	Dark cell degeneration
DRPLA	Dentatorubral–pallidoluysian atrophy
EAAT1	Excitatory amino acid transporter 1
FDA	US Food and Drug Administration
FRDA	Friedreich's ataxia
FXTAS	Fragile X-associated tremor/ataxia syndrome
GABA	γ-Aminobutyric acid
HAT	Histone acetyltransferase
HD	Huntington's disease
HDAC	Histone deacetylase
hnRNP K	Heterogeneous nuclear ribonucleoprotein K
IP3R1	Inositol 1,4,5-triphosphate receptor type 1
miRNA	MicroRNA
mTOR	Mammalian target of rapamycin
NIIs	Neuronal intranuclear inclusions (bodies)
PC	Purkinje cells
PolyQ	Polyglutamine
PPP2R2B	Human protein phosphatase 2, regulatory subunit B, beta
RBP	RNA-binding protein
RCT	Randomised, placebo-controlled trial
ROS	Reactive oxygen species
SCAs	Spinocerebellar ataxias
TBP	TATA-binding protein
UPS	Ubiquitin–proteasome system
VGICs	Voltage-gated ion channels

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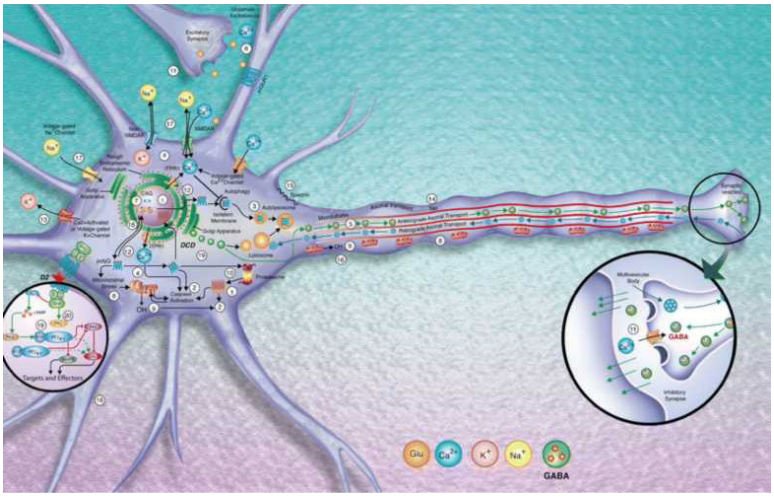

Fig. 1.

Most common molecular pathways identified triggering neurodegeneration in the SCAs. *DCD* dark cell degeneration (SCA2, SCA3, SCA7, SCA28). *1* Aggregation (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA17, SCA35, DRPLA). *2* Caspase activation (SCA1, SCA2, SCA3. SCA6, SCA7, SCA8, SCA12, SCA17, DRPLA). *3* Autophagy (SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, DRPLA). *4* Ca^{2+} homeostasis/signaling alterations (SCA1, SCA2, SCA6, SCA14, SCA15, SCA16). *5* Disruption of axonal transport and vesicle trafficking (SCA5, SCA11, SCA27). *6* Glutamate excitotoxicity (SCA1, SCA2, SCA3, SCA6, SCA12). *7* Interference with transcription (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA12, SCA17, DRPLA). *8* Mitochondrial impairment (SCA1, SCA2, SCA3, SCA6, SCA17, SCA8, SCA17, SCA28, DRPLA). *9* Oxidative stress (SCA2, SCA3, SCA7, SCA12). *10* Alterations of proteasome degradation (SCA1, SCA3, SCA5, SCA7, SCA14). *11* Early synaptic neurotransmission deficits (SCA1, SCA2, SCA3, SCA5, SCA6, SCA7, SCA8, SCA14, SCA17, SCA31, DRPLA). *12* Unfolded protein response (UPR) (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA17, DRPLA). *13* Potassium channel dysfunction (SCA13, SCA19/22). *14* Tau phosphorylation dysregulation (SCA11). *15* Neuronal membrane skeleton defects (SCA5). *16* Neurite alterations (SCA1, SCA10, SCA14). *17* Voltage-gated Na^{+} channel dysregulation (SCA27). *18* Proteostatic disruption (SCA26). *19* Protein phosphatase 2A (PP2A) activity dysregulation (SCA1, SCA2, SCA12). *20* Protein kinase C (PKC) activity deficits (SCA1, SCA14).

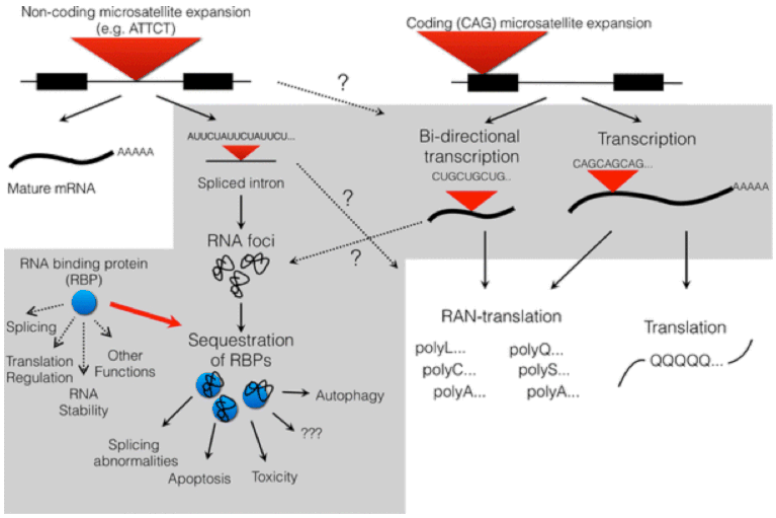

Fig. 2.

Toxic RNA species and their effects. Non-coding microsatellite expansions, such as the ATTCT expansion in SCA10, are transcribed, but not translated. The RNA form foci which bind and sequester RNA binding proteins (RBPs). Sequestration of the RBP is hypothesized to alter the normal function of RBP and have deleterious downstream effects on RNA splicing, translational regulation, apoptosis and autophagy, in addition to other uncharacterized and unknown effects. Coding microsatellite expansions have long been recognised as a protein gain of function producing polyglutamine-containing proteins. However, their gene loci can also serve as a substrate for bidirectional transcription. The natural sense and antisense transcripts may then be used in RAN translation.

Table 1

Genetic heterogeneity and molecular pathways underlying spinocerebellar ataxias

SCA subtype	Genomic location	Gene	Protein	Function	DNA mutation	References
SCA1	6p22.3	ATXN1	Ataxin-1	Transcription regulation	$(CAG)_n$	[1, 34]
SCA2	12q24.12	ATXN2	Ataxin-2	RNA metabolism	$(CAG)_n$	[384–386]
SCA3/MJD	14q32.12	ATXN3	Ataxin-3	De-ubiquitination, transcription regulation	$(CAG)_n$	[387]
SCA4	16q24-ter	SCA4	U	U	U	[388]
SCA5	11q13.2	SPTBN2	β-spectrin, non-erythrocytic 2	Neuronal membrane skeleton	ID, MM	[389]
SCA6	19p13.2	CACNA1A	CACNA1A	Ca2+ signalling/homeostasis	$(CAG)_n$	[187]
SCA7	3p14.1	ATXN7	Ataxin-7	Transcription regulation	$(CAG)_n$	[390]
SCA8	13q21	ATXN8OS/ATXN8	Ataxin-8	U	(CUG/CAG)n	[266, 271]
SCA9	Reserved	U	U	U	U	[391]
SCA10	22q13.31	ATXN10	Ataxin-10	Neuritogenesis	Intronic (ATTCT)n	[232]
SCA11	15q15.2	TTBK2	Tau tubulin kinase 2	Implicated in tau phosphorylation	FM, MM	[112]
SCA12	5q32	PPP2R2B	PPP2R2B	Regulation of PP2 activity, transcription regulation	5'-UTR $(CAG)_n$	[392]
SCA13	19q13.33	KCNC3	KCNC3	K^+ signalling	MM	[203, 393]
SCA14	19q13.42	PRKCG	PRKCG	Phosphorylation	ID, MM	[394]
SCA15[a]	3p26.1	ITPR1	Inositol 1,4,5-triphosphate receptor	Inositol 1,4,5-triphosphate calcium signalling	D,MM	[217, 219]
SCA16	8q23-q24.1	ITPR1	Inositol 1,4,5-triphosphate receptor	Inositol 1,4,5-triphosphate calcium signalling	D,MM	[218]
SCA17/HDL4	6q27	TBP	TBP	General transcription (TFIID complex)	$(CAG)_n$	[77]
SCA18	7q22-q32b	U	U	U	U	[395, 396]
SCA19	1p21-q21[b]	KCND3	Potassium Voltage-Gated Channel, Shal-Related Subfamily, Member 3	K^+ signalling	D, MM	[216]
SCA20	11q12.2-11q12.3	U	U	Chromosomal duplication	U	[397]
SCA21	7p21.3-p15.1[b]	U	U	U	U	[398, 399]
SCA22	1p21-q23[b]	KCND3	Potassium voltage-gated channel, Shal-related subfamily, member	K^+ signalling	D, MM	[215]

SCA subtype	Genomic location	Gene	Protein	Function	DNA mutation	References
			3			
SCA23	20p13	PDYN	Prodynorphin	Synaptic transmission	MM	[400]
SCA24	U	U	U	U	U	_ [c]
SCA25	2p21-p15[b]	U	U	U	U	[393]
SCA26	19p13.3[b]	EEF2	Eukaryotic translation elongation factor 2	RNA metabolism translation elongation proteostatic disruption	MM	[401]
SCA27	13q33.1	FGF14	FGF14	Signal transduction, regulation Na_V channels	FM, MM	[402]
SCA28	18p11.21	AFG3L2	ATPase family gene 3-like 2	ATP-dependent protease activity	MM	[13, 403]
SCA29a	3p26	U	U	U	U	[404]
SCA30	4q34.3-q35.1[b]	U	U	U	U	[405]
SCA31	16q21-q22	BEAN	BEAN	U	Intronic $(TGGAA)_n$	[233]
SCA32	7q32-q33	U	U	U	U	[406]
SCA33	U	U	U	U	U	-
SCA34	6p12.3-q16.2	U	U	U	U	[407]
SCA35	20p13	TGM6	Transglutaminase 6	Cross-linking of proteins and the conjugation of polyamines to proteins	MM	[408, 409]
SCA36	20p13	NOP56	NOP56 ribonucleoprotein	Involved in the early to middle stages of 60S ribosomal subunit biogenesis	Intronic (GGCCTG)	[83]
SCA37	1p32	U	U	U	U	[410]
DRPLA	12p13.31	ATN1	Atrophin-1	Transcription repression (nuclear receptor co-repressor)	$(CAG)_n$	[411–413]
16q-ADCA	16q22.1	PLEKHG4	Puratrophin-1	Intracellular signalling, cytoskeleton dynamics	5'-UTR SNP	[414, 415]

Genes noted in genomic location according to Ensembl

[a] SCA29 maps to the same genomic location than SCA15

[b] Genes noted according to HGNC

[c] Previously noted as autosomal recessive spinocerebellar ataxia with saccadic intrusions mapping to 1p36 [416]

Table 2

Channel genes of the ataxia channelopathies

Gene	Ataxia	Mutation	Channel type
CACNA1A	SCA6	CAG repeat	VG
	EA−2	Frameshift, splice site, missense	
KCNC3 (*Kv3.3*)	SCA13	Missense	VG
KCNN3 (*hSKCa3*)	Sporadic Ataxia	CAG repeat	VG
KCNA1	EA-1	Missense	VG
KCND3	SCA19/22	Missense, 3 nt in-frame deletion	VG
ITPR1	SCA15/16	Heterozygous gene deletion	LG
SLC1A3	EA	Missense	LG/AT
ATP1A3	EA	Missense	AT
ATP2B3	XLCCA	Missense	AT

SCA, spinocerebellar ataxia; *EA*, episodic ataxia; *XLCCA*, X-linked congenitalcerebellar ataxia. *VG* voltage gated; *LG*, ligand gated; *AT*, active transporter.