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Spinocerebellar ataxias: prospects and challenges for therapy development

Tetsuo Ashizawa^{1,*}, Gülin Öz², and Henry L. Paulson³

¹Stanley H. Appel Department of Neurology, Houston Methodist Research Institute, Houston, TX, USA

²Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, MN, USA

³Department of Neurology, University of Michigan, Ann Arbor, MI, USA

Abstract

The spinocerebellar ataxias (SCAs) comprise more than 40 autosomal dominant neurodegenerative disorders that present principally with progressive ataxia. Within the past few years, studies of pathogenic mechanisms in the SCAs have led to the development of promising therapeutic strategies, especially for SCAs caused by polyglutamine-coding CAG repeats. Nucleotide-based gene-silencing approaches that target the first steps in the pathogenic cascade are one promising approach not only for polyglutamine SCAs but also for the many other SCAs caused by toxic mutant proteins or RNA. For these and other emerging therapeutic strategies, well-coordinated preparation is needed for fruitful clinical trials. To accomplish this goal, investigators from the United States and Europe are now collaborating to share data from their respective SCA cohorts. Increased knowledge of the natural history of SCAs, including of the premanifest and early symptomatic stages of disease, will improve the prospects for success in clinical trials of disease-modifying drugs. In addition, investigators are seeking validated clinical outcome measures that demonstrate responsiveness to changes in SCA populations. Findings suggest that MRI and magnetic resonance spectroscopy biomarkers will provide objective biological readouts of disease activity and progression, but more work is needed to establish disease-specific biomarkers that track target engagement in therapeutic trials. Together, these efforts suggest that the development of successful therapies for one or more SCAs is not far away.

The spinocerebellar ataxias (SCAs) are a group of autosomal dominant disorders characterized by progressive ataxia due to degeneration of the cerebellum and its afferent and efferent pathways¹. The prefix ‘SCA’ with an associated number (which reflects the order of genetic discovery) is assigned to dominantly inherited ataxias when their genetic loci are defined. Although the term SCA describes a broad category of disorders in which

*tashizawa@houstonmethodist.org.

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spinocerebellar degeneration occurs — including phenotypically similar recessive disorders (sometimes called recessive SCAs), mitochondrial disorders and sporadic disorders — here we focus on the autosomal dominant SCAs. Currently, SCAs numbered from 1 to 46 are registered in the Online Mendelian Inheritance of Men (OMIM) database at the National Center for Biotechnology Information (NCBI), although some are vacant (such as SCA9) and others overlap (for example, SCA15 and SCA16 are both designated to the same disorder). In general, SCAs fall into two major categories on the basis of their genetic mutations: SCAs caused by microsatellite repeat expansions (FIG. 1; TABLE 1) and SCAs caused by point mutations (TABLE 2). When considering disease-causative mechanisms, SCAs resulting from repeat expansions can be further divided into those caused by polyglutamine (polyQ)-coding CAG repeat expansions and those caused by non-protein-coding repeats (TABLE 1). The pathogenic mechanisms of SCAs are complex and differ substantially among these diverse classes of the mutation². The clinical features, management and pathogenic mechanisms of the SCAs or specific subsets of SCAs have been reviewed extensively elsewhere^{2–6}. Here, we focus primarily on challenges in therapeutic development for the SCAs. We review the scientific premise and rigour of preclinical and molecular data relevant to such challenges and assess current gaps that need to be filled before promising drugs for SCAs can be tested in clinical trials.

Diagnosis

Key observations that support a diagnosis of an SCA in patients with progressive cerebellar ataxia include a family history of similar disease and a high index of suspicion of a genetically based disease. However, a lack of family history does not necessarily exclude SCA⁵, as incomplete family history, uninformed adoption and other causes of nonaternity, early death of a transmitting parent, low penetrance and de novo mutations can be present. When apparent sporadic ataxia is evaluated, treatable causes must be excluded carefully before hereditary causes of ataxia are considered⁶ (FIG. 2). In early stages of SCA, the phenotype can present as purely cerebellar, but subsequent, non-ataxic manifestations usually emerge. Owing to phenotypic overlap, a specific diagnosis of SCA is usually difficult without DNA testing, although certain findings can help to predict the genotype (see notable characteristic clinical signs in TABLES 1,2).

The most common SCAs are repeat-expansion diseases. A first step in establishing a diagnosis of a specific SCA is to screen for these repeat expansions, particularly for the most common subtypes — SCA1, SCA2, SCA3, SCA6 and SCA7. An important consideration is that sporadic-onset ataxia in an adult can be Friedreich ataxia, the most common recessive ataxia, which also results from a repeat expansion that can be easily tested for. Detection and sizing of repeat-expansion mutations are currently accomplished by conventional PCR, repeat-primed PCR or Southern blot analyses, depending on the size of the repeat. Internal repeat sequence irregularities are found in some SCAs, which can alter the characteristics of repeat length stability^{7–10}. The expansion size and, in some SCAs, repeat-interrupting motifs can substantially alter disease penetrance, age at onset or even clinical manifestations. In SCA1, for example, CAT interruptions are an important determinant for the difference between normal alleles and disease alleles; a CAT interruption in the SCA1 CAG expansion reduces penetrance of the mutation^{7,11}. Interruptions in the repeat expansions are also

associated with a parkinsonian phenotype in SCA2 (REFS^{8,12,13}), SCA10 (REF.¹⁴), SCA17 (REFS^{15,16}) and possibly SCA8 (REF.¹⁶) and might increase the risk of amyotrophic lateral sclerosis in SCA2 (REFS^{17–19}) and epilepsy in SCA10 (REF.²⁰) (TABLE 1).

For SCAs caused by point mutations, whole-genome sequencing (WGS) and whole-exome sequencing (WES) are useful for the detection of mutations in known SCA genes and in the identification of new genetic causes of SCA²¹. However, detection of variants of unknown importance by WES or WGS could necessitate an extensive family study for co-segregation of the variant with the disease as well as assessment of the biological consequences of the variant in silico and in experimental models to determine the potential pathogenic importance of the variant. Repeat expansions are difficult to detect with WGS and WES because short sequence reads obtained in next-generation sequencing (NGS) cannot be assembled effectively in repeat regions, but new NGS technologies that enable long sequence reads are emerging, including CRISPR–Cas9-targeted direct genomic single-molecule real-time sequencing (SMRT)¹⁴, nanopore²² sequencing and analytical advances such as the RepeatHMM alignment²³.

Treatment

With a few exceptions (for example, SCA6), SCAs are relentlessly progressive, fatal diseases. No drugs for SCAs have been approved by the FDA or European Medicines Agency (EMA). However, multiple studies support the efficacy of coordinative physical therapy^{24–30} with the caveat that all previous studies were unblinded or evaluator-blinded trials with a small number of participants (allied health care in ataxia has been reviewed systematically elsewhere³¹). A double-blind sham-controlled trial of transcranial magnetic stimulation involving 74 patients with spinocerebellar degeneration suggested that this treatment can alleviate ataxia for a week^{32,33}. Many agents for SCAs have been tested in clinical trials, including randomized, double-blind, placebo-controlled studies (Supplementary Table 1), and more therapies are being tested in ongoing clinical trials (Supplementary Table 2). Development of efficacious drugs for SCAs, both symptomatic and disease-modifying, is urgently needed.

Disease-modifying drugs

For dominantly inherited diseases such as the SCAs, the most compelling therapeutic targets lie upstream in the pathogenic cascade, regardless of the type of mutation and pathogenic mechanism (FIG. 3). Directing treatment to the root cause (in the case of SCAs, the mutation) or targets close to the root cause generally makes sense, although this concept has not yet been clinically tested in the treatment of SCAs. A special consideration for SCAs that result from a repeat expansion is that the expansion size generally determines the disease severity, progression rate and age of onset. Different degrees of expansion could change the pathogenic process, both quantitatively and qualitatively, which could confound the selection of targets for molecular interventions. The time of intervention is also likely to be a crucial issue for disease-modifying treatments. Data from SCA animal models suggest that prevention or delay of disease onset is easier than slowing, halting or reversing the disease process in symptomatic patients, especially in advanced stages of disease^{34–37}.

PolyQ SCAs.

At least seven degenerative ataxias are caused by expanded CAG repeats encoding polyQ tracts: SCAs 1, 2, 3, 6, 7, 17 and dentatorubral-pallidoluysian atrophy, the last of which shares features with the SCAs and another polyQ disease, Huntington disease (HD) (TABLE 1). In these disorders, a gain of toxic function by the mutant protein plays a key part in the pathogenic mechanism², although the precise basis of this toxicity remains unresolved. Although the normal functions of SCA polyQ disease proteins differ greatly, several of them might interact with one another directly or indirectly in the protein interactome of vulnerable cells in the nervous system^{38,39}. The native physiological *functions* of the protein can also be compromised by the expansion and lead to partial loss of function in some SCAs^{2,38,40,41} as in HD^{42,43}. Although research points to aberrant properties of the mutant polyQ disease protein as key drivers of disease, RNA transcripts containing the expanded CAG repeat also might be toxic, as demonstrated in experimental models of HD and of several polyQ SCAs^{44–48}.

A further complication of our understanding of disease mechanisms is the fact that the disease gene can also produce an antisense transcript from the opposite DNA strand, which contains a complementary expanded RNA repeat, as shown in SCAs 8, 2 and 7 (REFS^{49–52}). Furthermore, some expanded repeats form hairpin structures that can trigger noncanonical (non-ATG initiated) translation of protein across the repeat in all three reading frames⁵³. This repeat-associated non-ATG (RAN) translation, which was first described in SCA8 (REF.⁵³), has since been demonstrated in cellular and animal models of several SCAs and other repeat-expansion disorders. However, the extent of the pathogenic contribution of RAN translation to SCAs and other ataxias remains uncertain^{53–57}. Nevertheless, these observations highlight that multiple toxic molecules can be generated from the expanded repeat in polyQ and other SCAs resulting from repeat expansions (FIG. 3).

Expanded microsatellite repeats generally exhibit repeat length instability in the germ line and soma, and polyQ-coding CAG repeats are no exception. With respect to intergenerational instability, the pattern of instability (for example, predilection towards further expansion and the extent of repeat size change) varies depending on the disease gene and the sex of the transmitting parent. Such differences are mostly attributable to germline instability patterns, which differ between men and women, whereas somatic instability differs between tissues⁵⁸. Repeat-expansion size has profound effects not only on the age at disease onset but also on disease phenotype, which further complicates the application of therapeutic strategies that are based on downstream protein interactions in some of the SCAs.

The dominant nature of the SCAs indicates several points of potential therapeutic intervention, illustrated in FIG. 3. As for many genetic disorders, the ideal treatment would be correction of the mutation. Although genome editing is technically feasible, therapeutic applications of zinc-finger nucleases, transcription activator-like effector nucleases (TALENs) and CRISPR–Cas nucleases in SCAs currently face numerous challenges, including delivery, off-target effects, indel formation at the double-strand break by nonhomologous end joining and other toxicity or safety concerns^{59–62}. Furthermore, the

discovery of anti-CRISPR proteins that inhibit the CRISPR–Cas system could complicate this promising technology⁶³.

Targeting of the mutant mRNA transcript might be the next best option after genome editing for engaging the root cause of disease^{2,64} (FIG. 3). Experimental results with antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), short hairpin RNAs (shRNAs) and artificial microRNAs (miRNAs) in cellular and animal models of polyQ diseases have shown promising preclinical efficacy^{65,66} (TABLE 3). Most of these strategies have not yet advanced to human clinical trials, with the exception of ASOs. For example, a phase I/IIa trial of an ASO targeting *HTT* mRNA in participants with HD achieved a dose-dependent reduction in the levels of mutant huntingtin protein measured in cerebrospinal fluid (CSF)⁶⁷.

Specific therapeutic targets might also be identifiable when the downstream pathogenic pathways triggered by a given mutant polyQ protein are well characterized (FIG. 3). An example in SCA1 is inhibitors of nuclear mitogen and stress-activated protein kinase 1 (MSK1; also known as RPS6KA5) in the RAS–mitogen-activated protein kinase (MAPK)–MSK1 signalling pathway. MSK1 regulates phosphorylation at a critical amino acid in mutant ataxin 1 (REF.⁶⁸). Genetic reduction of the levels of MSK1 was beneficial in SCA1 mouse models and resulted in decreased levels of mutant ataxin 1 and, correspondingly, reduced neurodegeneration and an improved disease phenotype⁶⁹.

For some SCAs, unbiased screening of small molecules has identified compounds that might have therapeutic benefits even when the mechanism of action remains unknown. For example, compound screening in a nematode model of SCA3 identified citalopram, a widely used antidepressant, as a promising candidate drug. Citalopram was shown to decrease the levels of ataxin 3 and improve motor behavioural phenotype in an SCA3 mouse model⁷⁰. Similar screening efforts in cell-based platforms identified aripiprazole, an atypical antipsychotic, as a compound that might reduce levels of mutant ataxin 3 (REF.⁷¹).

The accumulation of aggregated protein in polyQ SCAs suggests that efforts to enhance protein quality-control pathways in the brain offer a route to disease-modifying therapy (reviewed elsewhere^{2,72}). Increasing the expression of specific molecular chaperones or quality-control ubiquitin ligases can suppress disease features in a variety of cellular and animal models of disease^{73–77}. Conversely, quality-control pathways are impaired in several polyQ diseases^{78–81}, which further supports the utility of boosting pathways that maintain protein homeostasis. Despite the attraction of co-opting protein quality control for therapy, compounds that act in this manner have not yet progressed to clinical trials in SCAs.

SCAs caused by toxic RNA.

Some rare SCAs are caused by an expanded microsatellite repeat in an intron (including SCAs 10, 31, 36 and 37) or 3' untranslated region (such as SCA8) (FIG. 1; TABLE 1). In these disorders, expanded repeats consist of trinucleotide, pentanucleotide or hexanucleotide units and bind to RNA binding proteins (RBPs). This binding can result in a loss of function of the RBP or the formation of stress granules, which leads to cellular toxicity. Viable strategies that intervene in the upstream portion of the pathogenic pathway might include reduction of the level of toxic RNA by ASO or other RNA interference (RNAi) technology,

disruption of the interaction between the toxic RNA and the RBP by decoys or competitors, overexpression of the RBP and modulation of stress granule formation. These approaches also would eliminate expression of toxic polypeptides produced through RAN translation of non-coding RNA repeats^{53–57}. Other approaches such as unbiased screening and interventions that target pathways downstream of the toxic RNA effects might also yield therapeutic strategies, but will require further characterization of the pathogenic pathway of each disease.

SCAs caused by point mutation.

The use of NGS has led to the discovery of an increasing number of SCAs caused by point mutations. These mutations are mostly missense but a few involve deletion or duplication of a DNA segment consisting of a small number of nucleotides (TABLE 2). The majority of these disorders are rare, with some affecting only a single family. Most of the mutations identified are predicted to lead to a novel toxic function or a dominant negative effect by the mutant protein. Therapeutic strategies for such SCAs might involve gene silencing, skipping of the mutated exon by RNAi or ASO technologies or intervention in specific downstream pathways. Several SCAs of this class are caused by mutations in ion channels or in proteins involved in signal transduction pathways linked to cell surface receptors^{82,83} (TABLE 2). Thus, pharmacological modifications of the dysfunctional molecules in these SCAs might lead to sustainable symptomatic improvements.

Symptomatic treatments

No efficacious symptomatic treatments currently exist for SCAs. The FDA has approved 4-aminopyridine (4-AP) for improvement of gait disturbance in multiple sclerosis (MS) but not in the SCAs^{84,85}. Nevertheless, 4-AP has been shown to normalize cerebellar Purkinje cell firing and alleviate motor coordination deficits in mouse models of SCA1 and SCA6 (REFS^{86,87}). The Ministry of Health in Japan has approved the thyrotropin-releasing hormone mimetic agent taltirelin hydrate for spinocerebellar degeneration but it has not been approved in other countries^{88,89}. Although many FDA-approved drugs have been tested in randomized, double-blind, placebo-controlled trials in individuals with SCA (Supplementary Table 1), none has resulted in approval for treatment of SCAs by the FDA or the EMA. The failure of such trials stems in part from inconsistent outcomes, underpowered trial designs or suboptimal data analyses. Most of these clinical trials were based on a limited scientific premise, and many lacked rigorous preclinical data (Supplementary Table 1). Although serendipity should not be ignored and can lead to valuable discoveries of new drugs, solid scientific premise and rigorous preclinical data will be essential for future symptomatic drug treatments and have been highlighted by the NIH as crucial elements for translational and clinical research aiming to successfully develop new therapeutics⁹⁰.

An attractive route to symptomatic therapy is modulation of the ion channels that underlie cerebellar circuitry (reviewed previously⁹¹). Several lines of evidence indicate the involvement of impaired cerebellar electro-physiology in ataxia. Mutations in genes that encode potassium and calcium channels or relevant signalling receptors underlie various forms of ataxia in mice and humans, including SCAs and episodic ataxias. In addition, changes in the intrinsic excitability of cerebellar Purkinje cells and synaptic signalling

pathways precede robust neurodegeneration in numerous mouse models of polyQ SCAs (reviewed previously²). Furthermore, restoration of normal cerebellar electrophysiology, genetically or pharmacologically, has proved beneficial in mouse models of SCA^{86,87,91,92}. Potassium channels, which play a key part in regulation of the excitability and dendritic plasticity of cerebellar Purkinje cells, are a particularly attractive therapeutic target^{93–99}. Thus, a building scientific premise exists for the use of activators of small-conductance, calcium-activated potassium channels, such as chlorzoxazone¹⁰⁰ and NS13001 (REF.⁹²), as well as compounds with complex actions on ion channels such as riluzole. Riluzole elicited a substantial improvement in the Scale for the Assessment and Rating of Ataxia (SARA) total score in heterogeneous groups of patients with ataxia, including those with SCAs^{101,102}. As noted earlier in the article, 4-AP also might be worth studying, particularly given its clinical usefulness in treating gait disturbance in MS (TABLE 4).

Preparation for sound clinical trials

Future clinical trials of therapeutic compounds must be carefully justified with a strong scientific premise and rigorous preclinical evidence of efficacy. These considerations are particularly important for trials of disease-modifying therapies, partly because of the scarcity of patients with SCA. The collective prevalence of all known types of SCAs has been estimated as 1.0–5.6 per 100,000 individuals^{3,4,103–106}; as such, the number of individuals with any one of the SCAs is far less than 200,000 in the United States and satisfies the FDA and NIH criteria for rare diseases¹⁰⁷. The limited number of patients available for clinical trials restricts the number of applicable clinical trial designs and the number of drugs that can be tested. Investigators will need to establish which cohort of participants will be studied, the natural history of the specific SCA being investigated, the clinical outcome measures that will be used, which biomarkers can be used to objectively track the disease-related biological changes and the expected effect size and the potential adverse events of the agents to be tested. With the availability of such information, statistically valid clinical trial designs must be carefully chosen with the strictest control of variables achievable given the inherently small sample size of these rare diseases.

Assessment measures

Natural history

Under NIH funding, the Clinical Research Consortium for Studies of Cerebellar Ataxias (CRC-SCA) obtained natural history data on the most common types of polyQ SCAs (namely, SCAs 1, 2, 3 and 6) with SARA¹⁰⁸ as the primary outcome measure¹⁰⁹. The study included 60 individuals with SCA1, 75 with SCA2, 138 with SCA3 and 72 with SCA6, all of who were enrolled from 2009 to 2012 at 12 US sites. The European Ataxia Study Group (EASG), which includes the EUROSCA team and the Spastic Paraplegia and Ataxia network (SPATAX) team, enrolled 107 patients with SCA1, 146 with SCA2, 122 with SCA3 and 87 with SCA6 in their natural history study at 17 European ataxia referral centres¹¹⁰. For SCA3, the European SCA3/Machado Joseph Disease Initiative (ESMI) has compiled data on 570 participants with SCA3 from 7 multinational investigators, including those in EASG^{111,112}. Collectively, these studies have shown that disease progression data obtained

with the SARA are best fitted with a linear model for all genotypes, that SCA1 is the fastest progressing SCA, that SCA3 is the most prevalent SCA and that patients with SCA6 have substantially later onset and slower progression than those with SCAs 1, 2 and 3.

The responsiveness of the SARA score to clinical change is calculated as the standardized response mean (SRM), which is the mean annual change in SARA score divided by the s.d. of the annual change. The mean \pm s.d. of the annual change of the SARA total score can be obtained from the CRC-SCA and EUROSCA natural history studies. Using the EUROSCA data, the minimal sample size required to achieve 80% power with an effect size of 50% was estimated to be 142 individuals (71 per group) for SCA1, the fastest progressing SCA¹¹⁰ (FIG. 4). For SCA2, SCA3 and SCA6, the minimal sample size is comparable to or larger than that for SCA1. Data obtained in the CRC-SCA cohort indicate that the sample size would need to be even larger. As such, we will face the challenge of insufficient sample sizes unless we identify drugs with a very large effect size. The rate of progression of each SCA varies in different populations (Supplementary Table 3), and further investigations are needed to determine whether the differences are due to biological disparity or artefacts caused by procedural variation. The required sample size can also be estimated from the difference between the mean progression in SARA score of the placebo group and of the intervention group (estimated on the basis of the hypothetical effects of the intervention)¹¹³. This estimation of sample size from placebo groups facilitates the design of double-blind, randomized, placebo-controlled clinical trials.

The effect size of potential therapeutic compounds in humans will be difficult to predict even when data from well-performed preclinical studies are available. Thus, identification of a sufficiently large cohort of study participants available for clinical trials is crucially important. The European and US investigators continue to increase the size of respective cohorts and extend the longitudinal data collection. The collaborative approach adopted by the ESMI for SCA3 has now been extended to SCA1 by a new US–European joint leadership initiative that involves multiple large international SCA consortia (FIG. 5). These studies focus on individuals in whom SCA is premanifest or who are at an early stage of the disease¹¹⁴ because convincing data suggest that early-stage neurodegeneration has reversibility that is lost as the disease progresses and cellular dysfunction and cell death increase in the brain¹¹⁵. Investigators in other parts of the world, particularly East Asia and South America, have also shown interest in such a collaborative approach.

Clinical outcome

The primary clinical outcome assessment measure used in most natural history studies of SCAs has been the SARA¹⁰⁸, a semi-quantitative scale. Other validated semi-quantitative ataxia scales include the International Cooperative Ataxia Rating Scale (ICARS)¹¹⁶, Modified ICARS (MICARS)¹¹⁷, Brief Ataxia Rating Scale (BARS)¹¹⁸ and Neurological Examination Score for Spinocerebellar Ataxia (NESSCA)¹¹⁹. The SARA has been the scale of choice in clinical studies of SCA within the past few years because it is simple, can be completed in 10 minutes and has been extensively validated and correlated with measures of the quality of life in patients with SCAs^{120,121}. Although composite ataxia measures, such as Composite Cerebellar Functional Severity (CCFS)¹²², SCA Functional Index (SCAFI)¹²³

and spatiotemporal movement capture of intralimb variability¹²⁴, provide quantitative data, the responsiveness of these measures has not consistently demonstrated superiority over SARA. A study of 171 patients (including 43 with SCA1, 61 with SCA2, 37 with SCA3 and 30 with SCA6) in the EUROSCA natural history cohort compared the responsiveness of different clinical assessment tools in participants after a 1-year follow-up period. Standardized response means were 0.50 for SARA and -0.48 for SCAFI, and sample size was estimated to be 250 per group for SARA and 275 per group for SCAFI for a two-arm interventional trial aiming at 50% reduction of progression and 80% power¹²⁵. A similar 1-year follow-up study, conducted in France, of 25 individuals with SCA1, 35 with SCA2 and 58 with SCA3 showed sample size estimates of 175 for SARA and 260 for CCFS¹²⁶. In 49 patients with SCA2 evaluated with SARA, NESSCA, INAS, SCAFI and CCFS, the only instrument that presented good responsiveness to change in 1 year was SARA¹²¹.

Wearable devices to measure ataxia and ataxia-related activities would enable data to be recorded in the daily living environment^{127,128}. Such measures, which result from remarkable advances in data capture and analysis, would provide better information about participants' performance in variable conditions than the typical 'snap shot' obtained during clinic visits and might be more clinically meaningful.

Genetic and environmental modifiers

Several genetic variants have been reported as predictors of the age at onset in patients with SCA3. These variants include the size of the polyQ-coding CAG repeat in the normal allele in eight genes (*ATXN1-3*, *ATXN7*, *ATXN17*, *CACNA1A*, *ATN1* and *HTT*)^{129,130}, two single-nucleotide polymorphisms (rs709930 and rs910369) in the 3' untranslated region of the *ATXN3* gene¹³¹, the *APOE* ϵ 2 allele¹³², the *C9orf72* GGGGCC repeat size¹³³, promoter sequence variation and expression levels of inflammatory genes such as *IL1A*, *IL1B*, *IL6* and *TNF*¹³⁴ and the presence of parkinsonism and/or dystonia¹³⁵. However, the findings from most of these genetic association studies remain to be confirmed. For example, the association of *APOE* ϵ 2 with decreased age at onset¹³² was not confirmed in one study¹³⁶, and different associations between disease onset and genes that contain polyQ-coding CAG repeats were obtained in populations from Europe¹²⁹, China¹³⁰ and Brazil¹³⁷. Living environment might also affect symptoms and signs of SCAs, as has been suggested in other genetic neurodegenerative disorders. Identification of genetic and environmental predictors will enable the definition of patient subgroups with homogeneous disease evolution and the capture of patients at a high risk of disease, both of which will be crucial to stratification of participants in trials.

Biomarkers

Although the field of translational medicine has broadened the definition of a biomarker, the core definition is a biological characteristic that can be measured and evaluated objectively as an indicator of normal biological processes, pathogenic processes or pharmacological responses to therapeutic intervention¹³⁸. Biomarkers are crucial for new drug discovery and development and are often used to stratify patient populations to reduce variability of the

clinical outcome (FIG. 6). Although reliable molecular biomarkers in body fluids are yet to be discovered for the SCAs, MRI-based biomarkers have shown promising results.

Imaging biomarkers

As in other neurodegenerative conditions, clinical outcome assessment measures are the primary outcome measures in clinical trials of SCAs and are likely to remain so for the foreseeable future. However, use of clinical outcome assessment measures to assess whether therapies slow disease progression in the SCAs is challenging because of their slow progression and phenotypic variability and because they require long clinical trials with large sample sizes (FIG. 4). Clinical outcome assessment measures also lack sensitivity in the earliest stages of disease, including premanifest stages when neuroprotective agents are likely to be most effective, and usually have poor test–retest reliability¹³⁹. Consequently, although such measures are an essential component of any SCA treatment trial, they should be supplemented with non-invasive neuroimaging to directly assess treatment effects on the brain. Validated imaging biomarkers of CNS pathology can contribute to patient stratification, in combination with genotypic, demographic and clinical outcome assessment data, to enable the individuals most likely to benefit from prospective therapies to be selected (FIG. 6). Validated imaging biomarkers also enable enrolment of mutation carriers at the premanifest stage of SCA by providing evidence of early pathological changes in the brain. Finally, they could enable a reduction in sample sizes if they are approved as primary outcome measures by the FDA or EMA. As detailed earlier in the article, estimated sample sizes range from 71 to 301 patients in each group for a two-arm interventional trial that aims to reduce disease progression by 50% in 1 year in the common SCAs when SARA is used as the outcome measure^{110,125}. On the other hand, 37 patients would be needed per arm of the trial to detect a comparable change by the most sensitive volumetric MRI measure (SRM of -1.3) reported across SCAs¹⁴⁰ in 1 year with the same power. This number is in contrast with 78 patients per arm of the trial for SARA (SRM of 0.9) reported in the same cohort¹⁴⁰.

Several studies have demonstrated regional metabolic abnormalities and dopaminergic dysfunction in SCAs via PET, including at the premanifest stage¹¹⁴. MRI-based modalities have the advantage of a wider availability than PET and avoid concerns about the repeated radiation exposure associated with PET. Hence, MRI-based modalities have been used in multisite settings and have been more widely validated in SCAs than has PET. In addition, conventional structural MRI has been the standard of care to monitor the characteristic cerebellar and brainstem atrophy in patients with SCAs.

Among the many MRI modalities, morphometric MRI, diffusion MRI and magnetic resonance spectroscopy (MRS) have been evaluated as biomarkers in SCAs by a number of groups worldwide¹⁴¹. In addition, the utility of task-based and resting-state functional MRI^{142,143} is gathering increased interest for monitoring of functional abnormalities.

Regarding macrostructural MRI measures, the EASG group conducted single-site and multisite investigations to establish the sensitivity of volumetric MRI to morphometric alterations in the most common SCAs^{112,144,145}. Morphometric T1-weighted MRI data analysed with a 3D volumetric method and voxel-based morphometry reveal prominent reductions in grey matter and white matter in the cerebellum and brainstem in individuals

with SCAs¹⁴⁵. Although these macrostructural changes correlate with SARA¹⁴⁵, the volumetric measures were shown to be more sensitive to change than SARA in a longitudinal multisite study¹⁴⁰, which provides a strong rationale to supplement clinical outcome assessments with these objective, non-invasive MRI markers in trials (FIG. 6).

Regarding microstructural MRI measures, many groups have demonstrated regional damage to white matter in common SCAs via diffusion tensor imaging (DTI)^{146–151}. In cross-sectional investigations, differences in DTI metrics between patients with SCAs and healthy controls were reported in multiple brain regions, including cerebellar peduncles, cerebellum, brainstem and cerebral white matter. Most of these studies also showed correlations between DTI metrics and clinical severity in SCAs. The sensitivity of DTI metrics to progressive changes in SCAs is largely unexplored, except for one report in SCA2 that showed progressive microstructural damage to white matter tracts¹⁵². In addition, the standard DTI model could miss subtle alterations in white matter and does not resolve crossing fibres. These limitations can be overcome by more sophisticated diffusion models, such as high angular resolution diffusion imaging^{153,154}, which need to be validated in large patient cohorts in multisite longitudinal settings.

Complementary to these morphometric MRI measures, proton MRS enables non-invasive and regional quantification of endogenous neurochemicals, thereby providing biochemical and metabolic information¹⁵⁵. The sensitivity of MRS to neurochemical abnormalities in SCAs has been demonstrated consistently by different groups on the basis of a few metabolites accessible at low magnetic fields^{156,157}. Within the past few years, increased field strength has enabled quantification of neurochemical profiles of up to 15 metabolites. This capability enabled the detection of robust neurochemical alterations, including molecules reflecting neuronal loss or dysfunction (such as *N*-acetylaspartate and glutamate) and gliosis (such as myo-inositol), among differences in other metabolites, in the cerebella and brainstems of patients with SCAs^{158–161}. Similar to morphometric measures, the neurochemical alterations measured by MRS correlated with SARA^{158,159,161} but were more sensitive to change than SARA in a longitudinal 3T MRI study¹⁶². MRS biomarkers were further validated in animal models of SCA and were shown to be sensitive to the progression¹⁶³ and reversal^{164,165} of SCA1 pathology. Neurochemical abnormalities were detected in the animals at the pre-symptomatic stage¹⁶³ and before the appearance of gross histopathological changes¹⁶⁶. Importantly, MRS detected treatment effects in a conditional transgenic SCA1 mouse model with the same sensitivity and specificity as invasive outcome measures and had higher sensitivity and specificity than standard motor behavioural assessment¹⁶⁵. Finally, MRS measures were demonstrated to be reproducible within site¹⁶⁷ and between sites^{168,169}, which is crucial for utility in future multisite trials.

In light of mounting evidence that argues for administration of therapies in the earliest stages of neurodegeneration¹¹⁵, the sensitivity of MRI measures to premanifest abnormalities has been investigated in patients with SCAs. Although conventional MRI has limited sensitivity at the premanifest stage^{170,171}, sophisticated analyses of MRI structural data that use volumetry and voxel-based morphometry confer sensitivity to early changes. A large multisite EASG study (RISCA) of individuals at risk of SCA (with SARA < 3) showed substantial grey matter loss in the brainstem and cerebellum in individuals with an *ATXN1*

or *ATXN2* mutation and showed a loss of brainstem volume in individuals carrying an *ATXN2* mutation¹¹¹. In addition, the feasibility of detecting premanifest abnormalities with MRS and diffusion MRI has been demonstrated^{151,158,170,172}. Notably, neurochemical abnormalities were detectable by MRS in a small cohort of premanifest carriers of common SCA-causative mutations whose estimated disease onset was within 10 years, showing that such changes may be detected up to 10 years before onset of ataxia¹⁵⁸.

In summary, numerous studies have demonstrated the sensitivity of biomarkers on MRI and MRS to cerebral changes in patients with SCAs, as well as their correlations with disease severity^{112,140,144–149,158–161,173}. Furthermore, morphological MRI and MRS have shown abnormalities in premanifest carriers of SCA-causative mutations^{111,158}. However, further studies must validate the capability of these modalities to predict disease onset in premanifest individuals, to facilitate participant selection for trials and to enable disease progression to be monitored in early-stage patients in multicentre longitudinal settings.

Biofluids and other biomarkers

Biofluid biomarkers are attractive because they are generally less expensive and are potentially easier to access than imaging biomarkers. Although the genetic mutation is the definitive diagnostic biomarker in SCAs, useful body fluid biomarkers for disease activities and disease progression are yet to be developed. CSF levels of tau¹⁷⁴, indices of oxidative stress in serum¹⁷⁵, serum cytokines¹⁷⁶, serum level of glutathione *S*-transferase¹⁷⁷ and circulating plasma DNA level¹⁷⁸ are altered in some SCAs. However, these measures have not proved to be useful in clinical trials owing to insufficient specificity or sensitivity for, or limited correlations with, target disease measures. In the past few years, SCA consortia have initiated the search for body fluid biomarkers via transcriptomics, proteomics and investigations of molecules of particular interest in CSF, plasma, serum, exosomes and peripheral cells. Among these markers, the CSF level of ataxin 1 (*ATXN1*), *ATXN2*, *ATXN3*, *ATXN7* and other SCA disease proteins that possess toxic gain-of-function properties is considered to be a promising biomarker for monitoring the response to nucleotide-based gene-silencing therapeutic approaches such as ASOs or RNAi (FIG. 6). Other preliminary biomarker studies in SCAs include the frequency of micronuclei in buccal cells¹⁷⁹, retinal nerve layer thinning on optical coherence tomography^{180,181}, various measures of CNS function (including cognition¹⁸², eye motility^{183–188}, rapid eye movement (REM) sleep and other sleep-related functions^{189–191}), peripheral nerve electrophysiological measures¹⁹² and quantitative measures of gait and other motor activities^{184,193,194}. However, further studies are needed to determine the utility of these potential biomarkers.

The importance of stringent adherence to sample and data acquisition and processing protocols when using biomarkers cannot be overemphasized. Standard operating procedures for sample collections are essential and should be based on careful consideration of the stability of biomarker molecules, the nature of assays to be used, the condition of the patient at the time of sample or data acquisition and the circumstances in which the sample is collected.

Conclusions

SCAs are autosomal dominant degenerative disorders that primarily affect the cerebellum and its efferent and afferent pathways. Although clinical characteristics can help to guide physicians towards the correct diagnosis, the diagnosis of SCAs ultimately depends on genetic testing. DNA testing technologies have rapidly improved with NGS technologies although challenges remain, especially in repeat-expansion disorders. Although currently no symptomatic or disease-modifying drugs for SCAs have been approved by the FDA or the EMA, promising candidate drugs are being developed that are based on a strong scientific premise and rigorous preclinical studies. However, SCAs are rare diseases, and clinical trials for these drugs face challenges. Strategies to ensure the feasibility of scientifically sound clinical trials for SCAs include the identification or development of drugs with a large effect size, establishment of sufficiently large cohorts of individuals with SCAs, characterization of cohorts for natural history of the disease, development of responsive clinical outcome assessment measures, identification of disease modifiers to enable refinement of study participant stratification, identification and characterization of biomarkers of disease-related biological changes and adoption of valid clinical designs for small sample sizes. Employment of these strategies should enable decisive clinical trials of new drugs. Given the success of large-scale clinical research efforts in the SCAs in the past few years and continued coordination among ataxia investigators worldwide, we are cautiously optimistic that drugs will be found that are beneficial for those with SCAs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing interests

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Key points

- Spinocerebellar ataxias (ScAs) are a group of dominantly inherited degenerative disorders that principally involve the cerebellum and its connections.
- Insights into the pathogenic mechanisms of many ScAs have suggested promising routes to symptomatic and disease-modifying therapy.
- clinical research consortia for ScAs have started international collaborations to share and analyse natural history data.
- the Scale for Assessment and rating of Ataxia is the best validated clinical outcome assessment measure, but additional measures should be developed with improved responsiveness to changes that are directly relevant to patients' lives.
- mrI and magnetic resonance spectroscopy have emerged as potentially powerful biomarkers for disease activities and progression, but target engagement biomarkers, especially molecular biomarkers in biofluids, are yet to be developed.
- collective efforts in ScA clinical research within the past few years have improved the prospects for eventual successful therapeutic development for the ScAs.

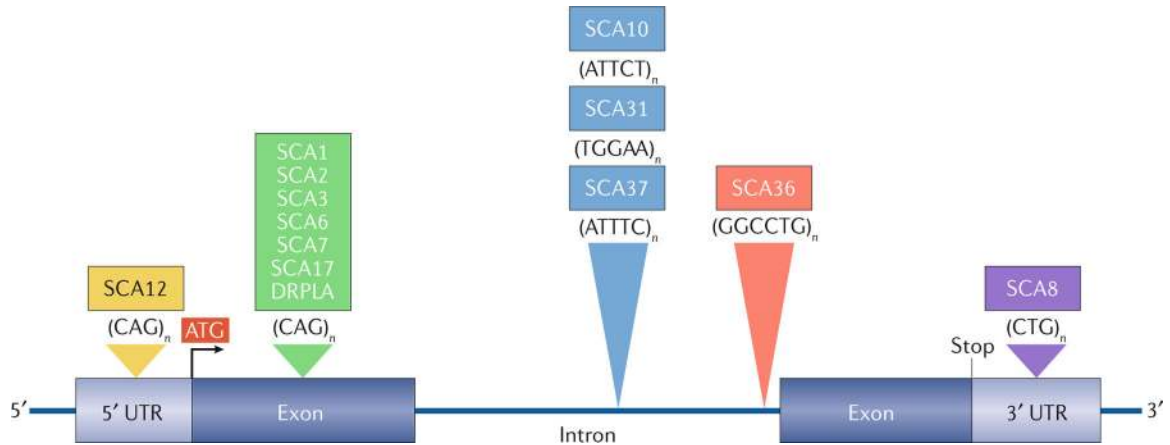


Fig. 1 | Hereditary degenerative ataxias caused by expanded microsatellite repeats.

A CAG repeat expansion within the open reading frame of the respective genes associated with the spinocerebellar ataxias (SCAs) 1, 2, 3, 6, 7 and 17 and dentatorubral-pallidoluyisian atrophy (DRPLA; green) encodes an elongated polyglutamine (polyQ) tract in the protein product. The CAG repeat in SCA12 (yellow), present in *PPP2R2B*, is shown in the 5' untranslated region (UTR) in this figure but can be intronic depending on the transcription start site. In SCA8 (purple), a CTG repeat is located in the 3' UTR of *ATXN8OS*. However, the complementary CAG repeat on the opposite strand encodes polyQ in *ATXN8*. Four large intronic microsatellite repeats include three pentanucleotide repeats (blue) in SCAs 10, 31 and 37 and one hexanucleotide repeat (red) in SCA36. In SCA31, a TGGAA repeat is located in *BEANI*, and a TTCCA repeat is found in *TK2* on the opposite strand, although only the UGGAA-containing transcripts are shown to be pathogenic. Likewise, the large ATTTC repeat, but not the ATTTT repeat, is pathogenic in SCA37. In SCA10, the risk of epilepsy increases sixfold when the ATTCT repeat is interrupted by a stretch of ATCCT repeat. In SCA36, an expanded GGCCTG repeat (with high sequence homology with the GGGGCC repeat in *C9orf72*) is present in *NOP56*.

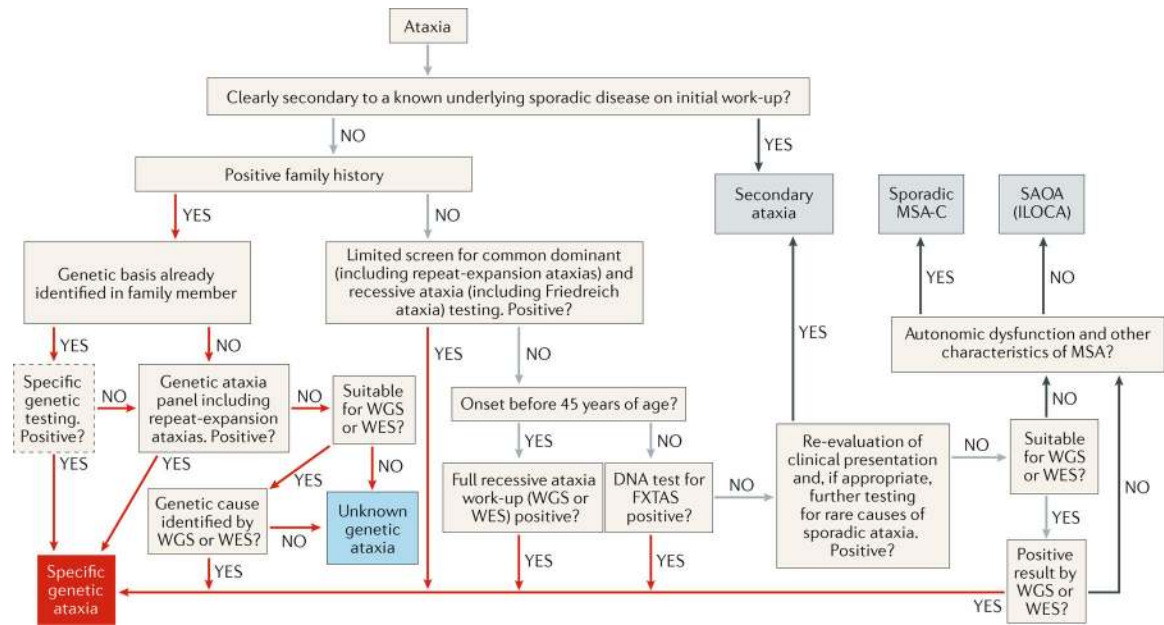


Fig. 2 |. Diagnostic algorithm for progressive ataxias.

Red arrows show steps to the diagnosis of inherited ataxias. Grey arrows indicate processes in which a genetic ataxia is still included in the differential diagnosis. Black arrows are routes to diagnoses of non-genetic ataxias. Obvious secondary ataxia should be excluded before a diagnosis of a spinocerebellar ataxia (SCA) can be made. The next step is to determine whether ataxia is inherited. If genetic diagnosis is already known in the family, optional confirmatory genetic testing is advised. If genetic diagnosis is unknown, panel testing or selective genotyping for dominant and/or recessive ataxias is recommended. If results are negative, whole-exome sequencing (WES), and potentially whole-genome sequencing (WGS), can lead to the specific genetic diagnosis. When no family history is present of a similar ataxic disorder, treatable causes of progressive ataxias should be explored on the basis of the differential diagnosis (for example, immune-mediated ataxias). Once treatable causes are excluded, genetic testing can be considered in patients with apparently sporadic ataxia. After exclusion of secondary ataxias and genetic ataxias, the diagnosis of either probable multiple system atrophy of cerebellar type (MSA-C) or sporadic adult-onset ataxia (SAOA; also known as idiopathic late-onset cerebellar ataxia (ILOCA)) can be established on the basis of the diagnostic criteria. FXTAS, fragile X-associated tremor/ataxia syndrome.

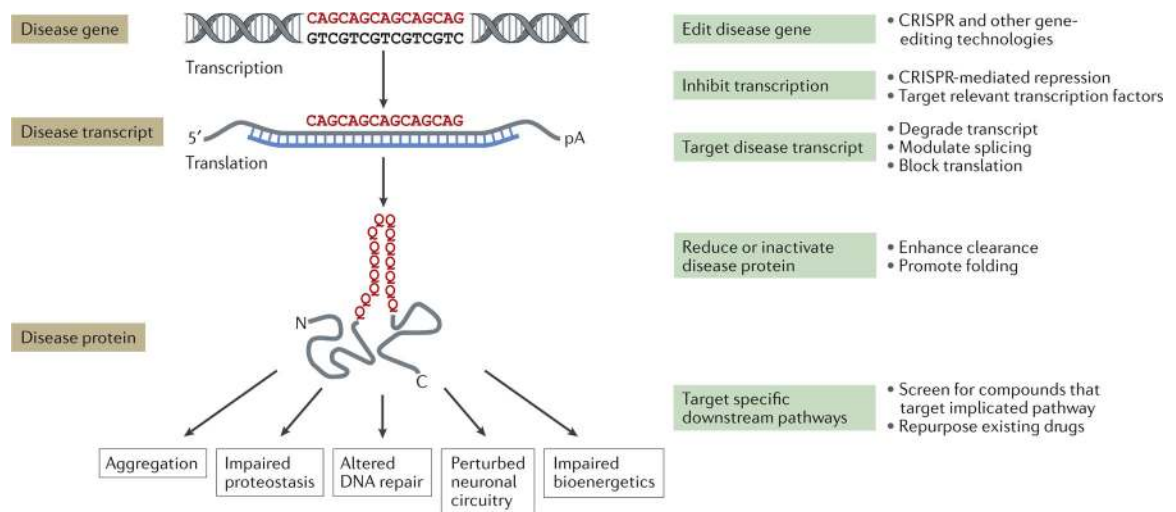


Fig. 3 |. Therapeutic strategies for the SCAs.

A generic CAG repeat polyglutamine disease gene is used to illustrate positions along the pathogenic cascade for which disease-modifying therapeutic approaches are being developed. Examples of specific strategies at each point are shown on the right. Five representative downstream consequences of the spinocerebellar ataxia (SCA) disease protein are shown that represent potentially targetable pathways shared across multiple SCAs; this list is not intended to be comprehensive. C, carboxyl terminus; N, amino terminus; pA, polyadenosine tail.

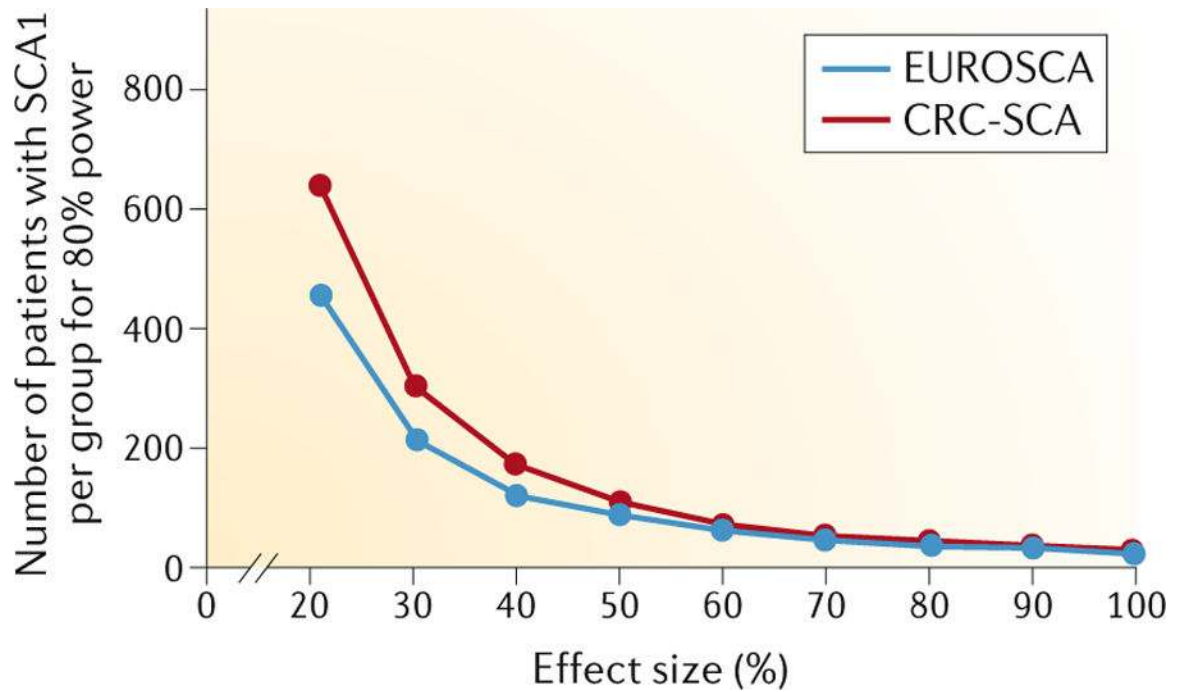


Fig. 4 |. Sample size estimation for evaluation of drug efficacy in SCA1.

FIGure shows the estimated sample size required for the efficacy of a drug to be tested in a clinical trial of patients with spinocerebellar ataxia 1 (SCA1). Among individuals with common SCAs, patients with SCA1 have shown the fastest progression rate with an annual increase of the Scale for Assessment and Rating of Ataxia (SARA) total score of 1.61 ± 0.41 (mean \pm s.e.) in the 2-year Clinical Research Consortium for Studies of Cerebellar Ataxias (CRC-SCA) study and of 2.11 ± 0.12 in the 5-year EUROSCA study. On the basis of the progression data, the sample size needed for two-group interventional trials of 1-year duration was calculated to be $P < 0.05$ for various effect sizes of the intervention. The estimated sample size per group to achieve 80% power with effect sizes ranging from 20% to 100% is shown. The estimates were calculated separately from the CRC-SCA data (red) and the EUROSCA data (blue).

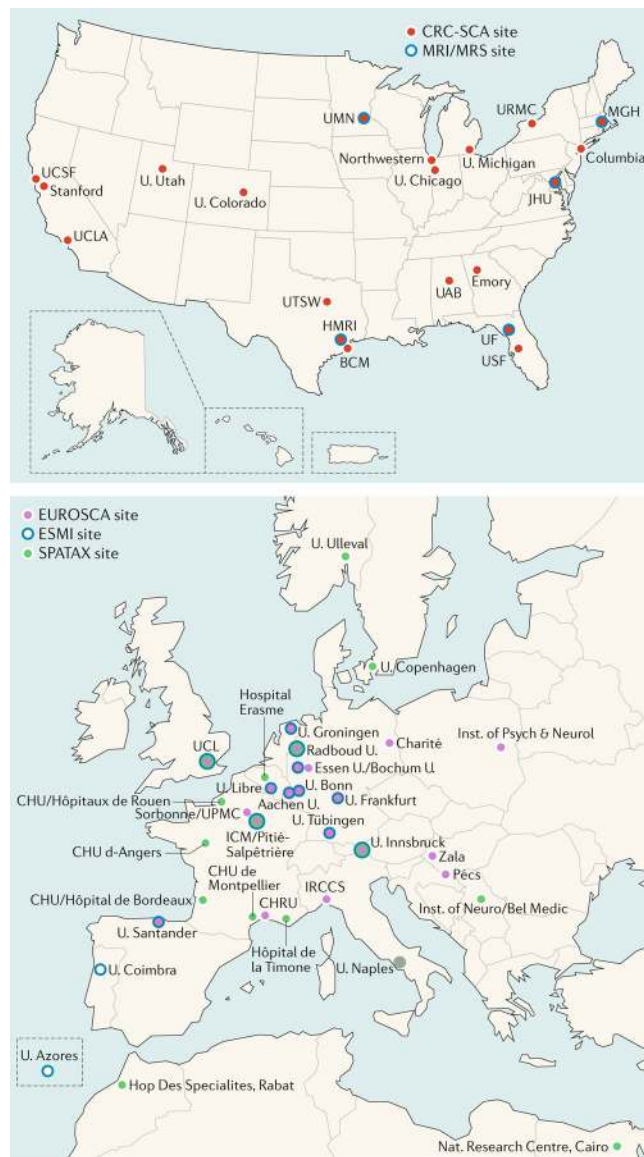


FIG. 5 | Transatlantic SCA consortia.

Twenty US institutions (top panel) are participating in the Clinical Research Consortium for Studies of Cerebellar Ataxias (CRC-SCA). The European consortia (bottom panel) operate in multiple organizations including the German Centre for Neurodegenerative Diseases (DZNE), the European Ataxia Study Group (EASG), the Spastic Paraplegia and Ataxia network (SPATAX) and the European SCA3/Machado Joseph Disease Initiative (ESMI). The US CRC-SCA and these European counterparts are now collaborating in translational and clinical research of spinocerebellar ataxias (SCAs). BCM, Baylor College of Medicine; BRP, Bioengineering Research Partnerships; Charité, Charité Universitätsmedizin Berlin; CHRU, Regional Hospital University Centre; CHU, Hospital University Centre; HMRI, Houston Methodist Research Institute; Hop Des, Hopital Des; ICM, Brain & Spine Institute; Inst., Institute; IRCCS, Istituto Di Ricovero e Cura a Carattere Scientifico; JHU, Johns Hopkins University; MGH, Massachusetts General Hospital; MRS, magnetic resonance

spectroscopy; Nat., National; Pécs, University of Pécs; Psych & Neurol, Psychiatry and Neurology; U., University or University of; UAB, University of Alabama–Birmingham; UCL, University College London; UCLA, University of California–Los Angeles; UCSF, University of California–San Francisco; UF, University of Florida; UMN, University of Minnesota; UPMC, Université Pierre et Marie Curie; USF, University of South Florida; UTSW, University of Texas Southwestern. The complete list of institutions involved is available in supplementary materials.

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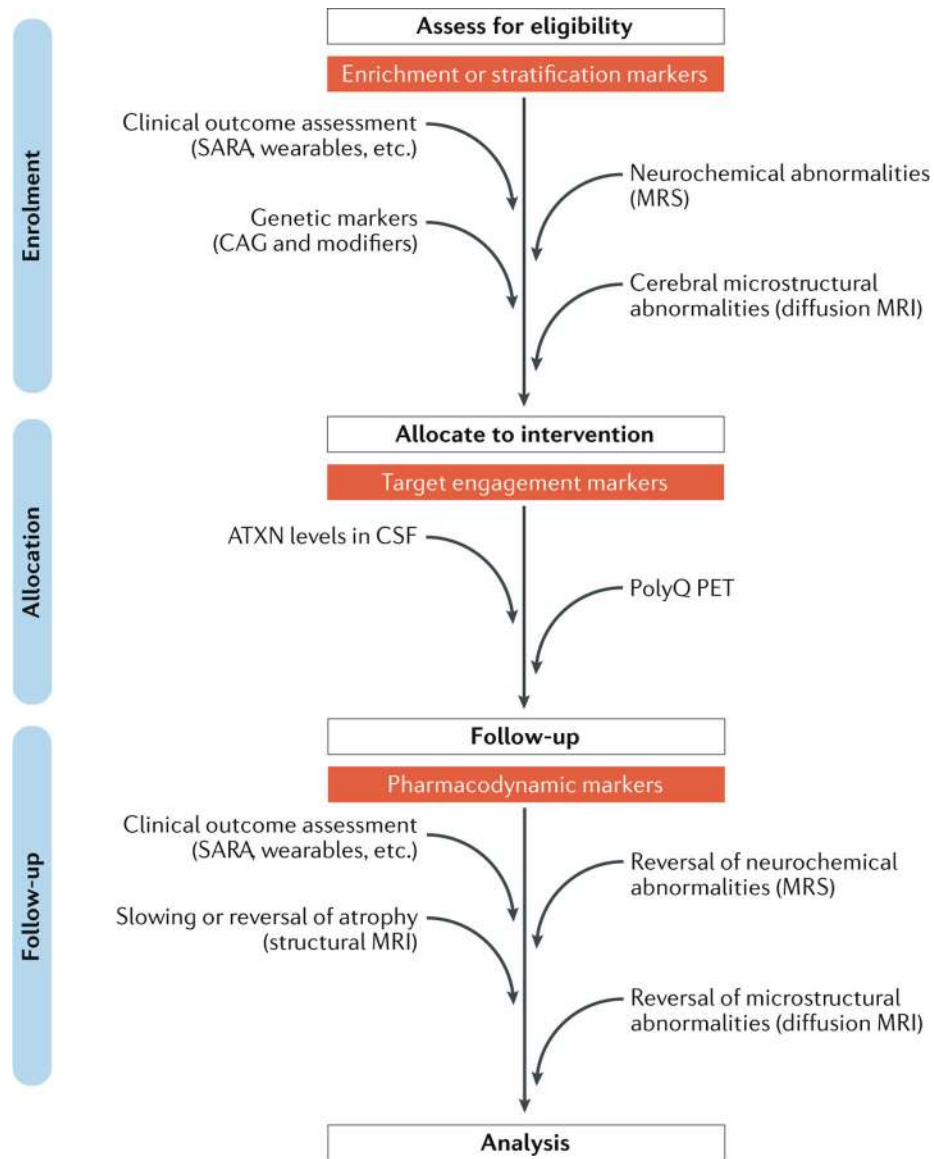


Fig. 6 |. Biomarkers for SCAs.

Diagram shows the stages at which clinical outcome assessment measures and biomarkers are expected to have utility in a hypothetical gene-silencing trial of a polyglutamine (polyQ) spinocerebellar ataxia (SCA) in which a patient cohort with early and premanifest disease is targeted. Clinical outcome assessment, genetic markers (for example, size of CAG triplet repeat and other modifiers of age of onset) and MRI or magnetic resonance spectroscopy (MRS) markers might facilitate the selection of patients with minimal cerebral involvement and enable premanifest enrolment of patients who already show cerebral changes. Measures of the disease protein in cerebrospinal fluid (CSF) are being developed to monitor target engagement in those who have been allocated to a gene-silencing intervention. Use of a PET tracer that specifically binds to polyQ repeats could provide direct evidence of clearance of the mutant protein or aggregates from the brain¹⁹⁵. Finally, MRI and MRS markers are expected to aid treatment monitoring as secondary outcome measures that supplement the

primary clinical outcome assessment measures. Furthermore, MRI and MRS markers might also serve as safety markers to ensure that the treatment does not exacerbate the cerebral pathology. The biomarkers shown are not intended to be comprehensive and need further development and/or validation, particularly in the premanifest and early disease stages, for the proposed uses in trials. ATXN, ataxin; SARA, Scale for Assessment and Rating of Ataxia.

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SCAs caused by microsatellite repeat expansions

Table 1 |

Disease	Gene (repeat location)	Repeats, principal repeat unit			Notable characteristic clinical signs	Anticipation
		Normal	Intermediate	Disease		
<i>SCAs caused by polyglutamine-coding CAG repeat expansions</i>						
SCA1	<i>ATXN1</i>	6–39 ^a	40	41–83	Hypermetric saccades and pyramidal signs	+
SCA2	<i>ATXN2</i>	<31	31–33	34–200	Slow saccades and areflexia	^b
SCA3	<i>ATXN3</i>	12–44	45–55	56–86	Bulged eyes and motor neuron signs	+
SCA6	<i>CACNA1A</i>	<18	19	20–33	Downbeat nystagmus	–
SCA7	<i>ATXN7</i>	4–19	28–33	34 to >460	Visual loss	+
SCA17	<i>TBP</i>	25–40	–	41–66	Huntington disease-like	^b
DRPLA	<i>ATN1</i>	6–35	36–48	49–88	Huntington disease-like	+
<i>SCAs caused by non-coding microsatellite repeat expansions</i>						
SCA8 ^c	<i>OSATXN8</i> (3' UTR)	15–34, CTG or CAG	34–89, CTG or CAG	89–250, CTG or CAG	Reduced penetrance	–
SCA10 ^d	<i>ATXN10</i> (intron)	8–32, ATTCT	33–799, ATTCT	800–4,500, ATTCT, ATTCC, ATCCT or ATCCC	Some families with epilepsy	+
SCA12	<i>PPP2R2B</i> (5' UTR)	7–28, CAG	29–66, CAG	67–78, CAG	Tremor	–
SCA31 ^e	<i>BEAN</i> (intron)	<400, ATTTT	Unknown	500–760 TGGAA	Pure cerebellar ataxia	+
SCA36	<i>NOF56</i> (intron)	3–14, GGCCGTG	Unknown	650–2,500	Motor neuron disease	–
SCA37 ^f	<i>DABI</i> (5' UTR; intron)	<400, ATTTT	Unknown	31–75, ATTTC repeats within ATTTT repeats	Pure cerebellar ataxia	–

DRPLA, dentatorubral-pallidoluysian atrophy; SCA, spinocerebellar ataxia; UTR, untranslated region.

^aIn SCA1, CAT interruption(s) are present in many normal alleles¹¹.

^bCAA interruptions affect repeat stability in SCA2 and SCA17 and affect toxicity and, potentially, phenotype in SCA2.

^cExpanded SCA8 repeats can contain one or more CCG, CTA, CTC, CCA or CTT interruptions, which affect the stability of the repeat and, potentially, the penetrance.

^dIn SCA10, the presence of ATCCT repeats, which often accompanies an ATCCC repeat tract, is associated with epilepsy and alters the pattern of repeat instability and anticipation.

^eIn SCA31, the presence of TGGAA repeats is essential for pathogenicity.

^fIn SCA37, the presence of ATTTTC repeats is pathogenic. Data were extracted from Online Mendelian Inheritance of Men (OMIM) and GeneReviews of corresponding SCAs.

Table 2 |

SCAs caused by point mutations

Disease	Gene	Mutation	Notable characteristic clinical signs
SCA5	<i>SPTBN2</i>	Missense	Downbeat nystagmus and some patients with spasticity, anticipation
SCA11	<i>TTBK2</i>	Missense	Some patients with pyramidal signs
SCA13	<i>KCNC3</i>	Missense	Variable between families
SCA14	<i>PRKCG</i>	Missense	Tremor or myoclonus, facial myokymia
SCA15 and 16	<i>ITPR1</i>	Deletion	Pure cerebellar ataxia with tremor
SCA18	<i>IFRD1</i>	Missense	Sensorimotor neuropathy
SCA19 and 22	<i>KCND3</i>	Missense, in-frame 3bp deletion	Extracerebellar features variable between families
SCA20	Multiple (<i>DAGLA</i>) ^a	260kb duplication	Pure cerebellar ataxia with spasmodic dysphonia, palatal tremor
SCA21	<i>TMEM240</i>	Missense	Cognitive impairment, extrapyramidal signs
SCA23	<i>PDYN</i>	Missense	Extracerebellar features variable between families
SCA26	<i>EEF2</i>	Missense	Pure cerebellar ataxia
SCA27	<i>FGF14</i>	Missense	Mental retardation, tremor
SCA28	<i>AFC3L2</i>	Missense	Spastic ataxia
SCA29	<i>ITPR1</i>	Missense	Pure cerebellar ataxia, congenital non-progressive
SCA34	<i>ELOVL4</i>	Missense	Hyperkeratosis, MSA-C-like
SCA35	<i>TGM6</i>	Missense	Hyperreflexia and variable other extracerebellar features
SCA38	<i>ELOVL5</i>	Missense	Pure cerebellar ataxia, some patients have sensory neuropathy
SCA40	<i>CCDC88C</i>	Missense	Spastic ataxia
SCA41	<i>TRPC3</i>	Missense	Pure cerebellar ataxia
SCA42	<i>CACNA1G</i>	Missense	Dementia
SCA43	<i>MME</i>	Missense	Peripheral neuropathy
SCA44	<i>GRM1</i>	Missense, +1bp frameshift	Spasticity
SCA45	<i>FAT2</i>	Missense	Pure cerebellar ataxia (single family)
SCA46	<i>PLD3</i>	Missense	Sensory neuropathy

MSA-C, multiple system atrophy of cerebellar type. Data were extracted from Online Mendelian Inheritance of Men (OMIM) and GeneReviews of corresponding SCAs.

^aThe duplicated region in direct orientation contains 12 or more genes, including *DAGLA*.

Table 3 |

Candidate disease-modifying drugs for treatment of SCAs

SCA type	Candidate drug	Scientific premise	Preclinical study	Comments
SCA1	MSK1 inhibitor	Inhibitors of the RAS-MAPK-MSK1 pathway decrease levels of ATXN1 and alleviate neurodegeneration in cellular and animal models of SCA1 (REFS ^{68,69})	Further screening and optimization is ongoing	Strong scientific premise. Rigorous preclinical studies are planned. No relevant human clinical observations
SCA1	Stereotactic AAV-mediated delivery of miRNA-like RNAi	RNAi suppresses polyglutamine-induced neurodegeneration in an SCA1 mouse model ¹⁹⁶ . Therapeutic benefits after RNAi expression vector delivery to deep cerebellar nuclei ¹⁹⁷	RNAi prevents and reverses phenotypes induced by mutant human ATXN1 (REF ¹⁹⁸)	Preclinical study is ongoing in B. Davidson's laboratory under the NIH CREATE BIO ¹⁹⁹ grant support, which mandates rigorous preclinical study designs and go/no-go milestones ²⁰⁰
SCA2	Dantrolene	Inhibits intracellular Ca ²⁺ release and protects Purkinje cells from cell death in the SCA2-58Q mouse model ²⁰¹	Feeding SCA2-58Q mice with dantrolene alleviated age-dependent motor deficits (beam-walk and rotarod assays) ²⁰¹	Modest scientific premise. Needs rigorous preclinical studies. No relevant human clinical observations
SCA3	Dantrolene	Inhibits intracellular Ca ²⁺ release and protects neuronal cells in pontine nuclei and substantia nigra regions from cell death in SCA3-YAC-84Q transgenic mice ²⁰²	Feeding SCA3-YAC-84Q transgenic mice with dantrolene improved their motor performance ²⁰²	Modest scientific premise. Needs rigorous preclinical studies. No relevant human clinical observations
SCA3	Citalopram	Identified in an unbiased screening for inhibition of mutant ATXN3 aggregation and reduction of ATXN3 neurotoxicity through neuronal serotonin pathways in cell and animal models ⁷⁰	Efficacy of citalopram was verified in multiple SCA3 transgenic animal models, with chronic treatment leading to decreased neuronal ATXN3 aggregates, astrogliosis, weight loss and motor dysfunction ⁷⁰	Strong scientific premise. Good preclinical studies in two independent laboratories. No relevant human clinical observations
SCA3	Aripiprazole	Identified in an unbiased screen of FDA-approved drugs for reduction of the level of mutant ATXN3 in a cell-based assay ⁷¹	Not yet done	Unknown mechanism(s) of the effect on the mutant ATXN3. Needs rigorous preclinical studies in SCA3 animal model(s). No relevant human clinical trials or observations
SCA3	Lentiviral delivery of allele-specific ²⁰³ and allele-nonspecific ^{204,205} siRNA against <i>Atxn3</i> in a rat model	Silencing of <i>Atxn3</i> mitigates degeneration in rat. Suppression of wild-type <i>Atxn3</i> has no adverse effects and allele-nonspecific silencing might be beneficial in rat ²⁰³⁻²⁰⁵	Further preclinical studies are needed	Strong scientific premise for targeting the mRNA of the mutant ATXN3. Therapeutic efficacy shown in the rat model needs to be replicated in mouse models. Needs rigorous preclinical studies in SCA3 animal models. No relevant human clinical trials or observations
SCA3	Stereotactic AAV delivery of miRNA	RNAi suppresses ATXN3 levels and alleviates molecular phenotype in SCA3 mouse models ^{206,207}	RNAi has induced no behavioural changes	Strong scientific premise for targeting the mRNA of the mutant ATXN3. Needs rigorous preclinical studies in SCA3 animal models. No relevant human clinical trials or observations
SCA1, SCA2 and SCA3	ASO against <i>ATXN1</i> , <i>ATXN2</i> or <i>ATXN3</i>	In these SCAs, toxic gain-of-function mechanisms are well established. Targeting the mRNA containing toxic polyglutamine expansion is supported by a strong rationale ²	Reduction of mutant ATXN2 (REF ²⁰⁸) and ATXN3 (REF ²⁰⁹) mRNA by ASO treatment, and skipping of CAG-repeat-containing exon 10 of ATXN3 (REF ²¹⁰), are promising therapeutic approaches	Strong scientific premise for targeting the mRNA of the mutant ATXNs. Needs rigorous preclinical studies in animal models of SCA. No relevant human clinical trials or observations

SCA type	Candidate drug	Scientific premise	Preclinical study	Comments
SCA6	miR-3191-5p	In SCA6, the CAG expansion is found in the second cistron (α IACT) of <i>CACNA1A</i> . miR-3139 attenuates IRES-driven translation of toxic α IACT ⁶⁶	AAV9-miR-3191-5p protected α IACT-Q33 mice from ataxia, motor deficits and Purkinje cell degeneration ⁶⁶	Toxic mutant mRNA is the target. Needs rigorous preclinical studies in SCA6 animal models. No relevant human clinical trials or observations
SCA7	Direct delivery of AAV or miRNA to retina in an SCA7 mouse model ²¹¹	In SCA7, toxic gain-of-function mechanisms are well established ^{2,3} . Targeting of the mRNA containing a toxic polyglutamine expansion is supported by a strong rationale. Eyes are severely affected in SCA7 and are readily accessible for delivery of miRNA ²¹¹	Non-allele-specific suppression of ATXN7 levels was accompanied by preservation of retinal function in SCA7 mice	Both wild-type and mutant <i>ATXN7</i> mRNA are targeted. Needs rigorous preclinical studies in SCA7 animal models. No relevant human clinical trials or observations
SCA7	Direct delivery of AAV or miRNA to cerebellum of a mouse model of SCA7 (REF ²¹²)	In SCA7, toxic gain-of-function mechanisms are well established. Targeting of the mRNA containing a toxic polyglutamine expansion is supported by a strong rationale	Non-allele-specific suppression of ATXN7 levels was accompanied by improvement of ataxic phenotype in SCA7 mice	Both wild-type and mutant <i>ATXN7</i> mRNA are targeted. Needs rigorous preclinical studies in SCA7 animal models. No relevant human clinical trials or observations

α IACT, α I A carboxyl terminus; AAV, adeno-associated virus; ASO, antisense oligonucleotide; ATXN, ataxin; CREATE BIO, Cooperative Research to Enable and Advance Translational Enterprises for Biotechnology Products and Biologics; IRES, internal ribosome entry site; MAPK, mitogen-activated protein kinase; miRNA, microRNA; MSK1, nuclear mitogen and stress-activated protein kinase 1; RNAi, RNA interference; SCA, spinocerebellar ataxia; siRNA, small interfering RNA.

Table 4 |

Candidate symptomatic drugs for treatment of SCAs

SCA type	Candidate drug	Scientific premise	Preclinical study	Comments
SCA6 and other SCAs	4-Aminopyridine	Restoration of pacemaker activities of Purkinje cells by blocking the voltage-dependent family of potassium channels ⁸⁷	Alleviated motor coordination deficits and restored Purkinje cell firing precision in SCA6 mice homozygous for 84 polyQ repeats ⁸⁷	Approved by the FDA for symptomatic improvement of walking in multiple sclerosis. A randomized, double-blind, placebo-controlled study showed a decreased number of attacks in patients with episodic ataxia 2 (ref: ²¹³). A phase I study ²¹⁴ and a small open-label study ²¹⁵ have been done in patients with SCAs
SCA2 and other SCAs	Chlorzoxazone	KCNN1 channel activator: Normalization of the Purkinje cell spontaneous firing rate in SCA2 transgenic mice with 58 polyQ repeats ¹⁰⁰ and in Cacna1a- mutant mice ⁹³	Not yet done	Chlorzoxazone is approved by the FDA and has been used extensively as a muscle relaxant
SCA44	Nitazoxanide	Negative allosteric modulator of metabotropic glutamate receptor 1 and 5 with potent inhibition of mutant forms of these receptors in transfected cells ²¹⁴	Not done in SCA44 models, but similar modulators alleviated ataxia in an SCA1 mouse model ^{216,217}	Nitazoxanide is approved by the FDA and is used for various helminthic, protozoal and viral infections ²¹⁸

KCNN1, small-conductance calcium-activated potassium channel protein 1; polyQ, polyglutamine; SCA, spinocerebellar ataxia.