Autosomal dominant cerebellar ataxias: new genes and progress towards treatments

Giulia Coarelli, Marie Coutelier, Alexandra Durr

Dominantly inherited spinocerebellar ataxias (SCAs) are associated with phenotypes that range from pure cerebellar to multisystemic. The list of implicated genes has lengthened in the past 5 years with the inclusion of SCA37/*DAB1*, SCA45/*FAT2*, SCA46/*PLD3*, SCA47/*PUM1*, SCA48/*STUB1*, SCA50/*NPTX1*, SCA25/*PNPT1*, SCA49/*SAM9DL*, and SCA27B/*FGF14*. In some patients, co-occurrence of multiple potentially pathogenic variants can explain variable penetrance or more severe phenotypes. Given this extreme clinical and genetic heterogeneity, genome sequencing should become the diagnostic tool of choice but is still not available in many clinical settings. Treatments tested in phase 2 and phase 3 studies, such as riluzole and transcranial direct current stimulation of the cerebellum and spinal cord, have given conflicting results. To enable early intervention, preataxic carriers of pathogenic variants should be assessed with biomarkers, such as neurofilament light chain and brain MRI; these biomarkers could also be used as outcome measures, given that clinical outcomes are not useful in the preataxic phase. The development of bioassays measuring the concentration of the mutant protein (eg, ataxin-3) might facilitate monitoring of target engagement by gene therapies.

Lancet Neurol 2023; 22: 735–49

Sorbonne Université, ICM Institut du Cerveau, Pitié-Salpêtrière University Hospital, Paris, France (G Coarelli MD PhD, M Coutelier MD PhD, Prof A Durr MD PhD)**; Institut National de la Santé Et de la Recherche Médicale, Paris, France** (G Coarelli, M Coutelier, Prof A Durr)**; Centre National de la Recherche Scientifique, Paris, France** (G Coarelli, M Coutelier, Prof A Durr)**; Assistance Publique-Hôpitaux de Paris, Paris, France** (G Coarelli, M Coutelier, Prof A Durr)

Correspondence to:
Prof Alexandra Durr, Sorbonne Université, ICM Institut du Cerveau, Pitié-Salpêtrière University Hospital, 75646 Paris, France
alexandra.durr@icm-institute.org

Introduction

Dominantly inherited cerebellar ataxias are rare neurological diseases with wide clinical and genetic heterogeneity. 39 genes that include 44 autosomal dominant spinocerebellar ataxia (SCA) loci are registered in the Online Mendelian Inheritance of Men database and dominantly inherited variants have also been described in other genes.[1] The prevalence of each subtype is not well defined, since analyses that can detect the different causal variants are difficult to access in many countries. The most frequent SCA subtypes are caused by heterozygous CAG repeat expansions encoding polyglutamine stretches.

In the past decade, next-generation sequencing has remodelled the genotypic landscape of SCAs. In this Review, we discuss the advances in gene identification over the past 5 years, the availability of associated diagnostic tools, and new developments in the epidemiology and the description of the phenotypes of polyglutamine and non-polyglutamine SCAs that are emerging from large cohort studies. We also discuss new therapeutic approaches and the clinical utility of diagnostic and prognostic biomarkers.

Epidemiology

A systematic review reported an average SCA prevalence of 2·7 per 100 000 individuals worldwide, albeit not on the basis of comprehensive screening methods.[2] The most common SCA subtypes are SCA1/*ATXN1* (MIM 164400), SCA2/*ATXN2* (MIM 183090), SCA3/*ATXN3* (MIM 109150), SCA6/*CACNA1A* (MIM 183086), SCA7/*ATXN7* (MIM 164500), SCA17/*TBP* (MIM 607136), and DRPLA/*ATN1* (dentatorubral-pallidoluysian atrophy; MIM 125370). SCA3 is the most prevalent subtype worldwide, with founder expansions described in families of Portuguese–Azorean, Japanese, and German ancestry.[3] Founder effects are reported for SCA2 (the second most prevalent subtype) in the Holguin province of Cuba, the French West Indies, and India.[3] SCA6 is the third most prevalent subtype and is especially common in Japan, Taiwan, Australia, Germany, the UK, and the USA.[3] SCA1 is most prevalent in Poland, Russia, and South Africa. For SCA7, founder effects are reported in Scandinavian countries, South Africa, and Mexico.[3] DRPLA and SCA17 are particularly rare, even though DRPLA accounts for a substantial percentage of Japanese, Spanish, and Portuguese families with SCA. Non-coding repeat expansions or point mutations and rearrangements are responsible for less than 6% of SCAs.[3,4] However, this proportion could be underestimated because the prevalence of the most recently identified non-coding repeat expansion, in SCA27B/*FGF14*, is not yet known. Some subtypes of non-coding repeat SCA are highly represented in specific regions: SCA10 in Central and South America, particularly in Mexico, SCA12 in India, and SCA31 and SCA36 in Japan.[3]

Clinical features of SCAs

Age at onset and genetic modifiers of polyglutamine SCAs

SCAs are characterised by cerebellar ataxia expressed as lack of coordination, gait imbalance, clumsy voluntary limbs movements, dysarthria, dysphagia, and oculomotor abnormalities. Other neurological and extra-neurological signs can occur depending on the subtype. In polyglutamine SCAs, disease onset typically occurs in the third or fourth decade and can be estimated on the basis of CAG repeat length.[5] An interaction in trans between normal and expanded alleles for *ATXN1*, *CACNA1A*, and *ATXN7* can also affect age at onset. In a cohort of 1255 patients, other SCA genes also had polygenic effects, with longer CAG-repeat lengths associated with earlier onset: *ATXN7* in SCA2; *ATXN2*, *ATN1*, and *HTT* in SCA3; *ATXN1* and *ATXN3* in SCA6, and *ATXN3* and *TBP* in SCA7.[6] Anticipation is a hallmark of polyglutamine subtypes of SCA: successive generations show

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

younger ages at onset and more severe phenotypes, owing to the instability of CAG repeat expansions in germline cell division, which also explains the stronger association of paternal inheritance with infantile forms.[7] Infantile and juvenile forms of polyglutamine SCA have been reported for large CAG repeats in *ATXN2* and *ATXN7* (130 to >200 CAG repeats *vs* a pathogenic threshold of 32 in *ATXN2* and 37 in *ATXN7*).[3] In SCA7, congenital phenotypes are paternally transmitted and include cardiac and renal impairment, leading to death at age 0·4–2·3 years, whereas juvenile forms are from maternal descent in up to 40% of patients, do not show extra-neurological involvement, and initially present with isolated visual loss in 80% of patients.[7] Finally, interruptions in CAG repeats also modify the age at onset. CAT interruptions in *ATXN1* CAG expansions delay the disease onset,[8] whereas CAA interruptions in *ATXN2* CAG tracks switch the typical phenotype of cerebellar ataxia to autosomal dominant parkinsonism.[3]

Severity of polyglutamine SCAs

The severity of polyglutamine SCA phenotypes also correlates with the CAG repeat size.[4] Polyglutamine SCAs are better characterised than non-polyglutamine SCAs, as their natural history has been explored by several consortia. In the European integrated project on SCAs (EUROSCA) study, the rate of clinical progression based on the Scale for the Assessment and Rating of Ataxia (SARA) score was fastest for SCA1 (mean 2·11 points per year), followed by SCA3 (1·56 points per year), SCA2 (1·49 points per year), and SCA6 (0·8 points per year).[9] The 10-year survival rate was 57% for SCA1, 74% for SCA2, 73% for SCA3, and 87% for SCA6.[10] Predictors for shorter survival were dysphagia and higher SARA score for SCA1, and CAG repeat length, higher SARA score, and older age at inclusion for SCA2, and CAG repeat length, higher SARA, older age at inclusion, and dystonia for SCA3.[10] Severe bulbar dysfunction due to motor neuron degeneration, in particular in the hypoglossal nucleus, has been reported in a mouse model of SCA1, which aligns with dysphagia as a predictor of poor survival in patients with SCA1.[11] A French cohort[12] and the Clinical Research Consortium for Spinocerebellar Ataxias of North America[13] also confirmed SCA1 as the most severe SCA subtype, with the exception of the infantile and juvenile presentations of SCA2 and SCA7.

See Online for appendix

The EUROSCA study also explored the patients' quality of life. The decline in quality of life was linked to higher scores on the Inventory of Non-Ataxia Signs for SCA3, and higher SARA scores, cognitive impairment, and longer CAG expansions for SCA1. Depression was more frequent in patients with SCA1 who had cognitive impairment compared with people who had SCA1, but no cognitive impairment.[9] We can extrapolate that, in the first few years after the onset of cerebellar ataxia, quality of life is primarily affected not by cerebellar ataxia, but by other neurological signs and mood disorders. In a cohort of patients with mild SCA3, quality of life was more altered by fatigue than by ataxia severity, and depression was associated with disease duration and fatigue rather than motor impairment,[14] outlining the discrepancy between clinicians' and patients' points of view. Depression and fatigue should, therefore, be taken into consideration in clinical trial outcome measures. In the Pan American Hereditary Ataxia Network cohort, a questionnaire for health professionals showed an association between lower socioeconomic status and worse management of the disease, from diagnosis to rehabilitation care.[15]

Preataxic carriers of pathogenic CAG repeats can be studied to investigate early pathological changes. In SCA1, SCA2, SCA3, and SCA6 carriers, the RISCA study showed faster progression of the SARA score and grey-matter loss from the brainstem and cerebellum closer to the onset of ataxia.[16] READISCA, an ongoing National Institutes of Health-funded international clinical trial readiness study for SCA1 and SCA3 carriers, aims to identify reliable biomarkers in both pre-ataxic and ataxic individuals that could be used as outcomes in clinical trials (NCT03487367).

Clinical differences between polyglutamine and non-polyglutamine SCAs

SCAs due to point mutations, rearrangements, and non-coding repeat expansions are not as well described as polyglutamine SCAs, as their rarity prevents the gathering of data from large cohorts (table 1; appendix pp 1–5). In 2020, we launched an international multicentre cross-sectional study to collect clinical and genetic data for non-expansion SCAs. This study showed even more heterogeneous clinical presentations among carriers of mutations in each gene than for polyglutamine SCAs. Although non-polyglutamine SCAs can occur early in childhood, they are less severe and show slower progression than polyglutamine SCAs (Durr A, unpublished). Paediatric forms, which are rare in polyglutamine SCAs, have also been described in non-polyglutamine SCAs, sometimes with the same pathogenic variant as adult SCAs. For example, SCA5/*SPTBN2* and SCA21/*TMEM240* can manifest with congenital onset mimicking cerebral palsy[17,18] or with adult-onset ataxia.[19] Cerebellar ataxia in childhood is often associated with intellectual disability,[4,20] suggesting the co-occurrence of neurodevelopmental dysfunction and neurodegenerative processes in non-polyglutamine SCAs.[4] SCA48/*STUB1* is specifically associated with predominant cognitive impairment[21] in early disease stages, whereas cognitive impairment often occurs later in polyglutamine SCAs (panel 1).

Conventional mutations (point mutations or rearrangements) in *CACNA1A* are frequent among people with autosomal dominant ataxia and associated with diverse phenotypes, including familial hemiplegic

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

	OMIM number	Gene	Gene OMIM number	Mutation type	Key symptoms and signs in addition to cerebellar ataxia	Other phenotypes (transmission mode, OMIM number)
Coding polyglutamine repeat						
SCA1	164400	*ATXN1*	601556	(CAG)n repeat	Bulbar symptoms, ophthalmoplegia, spasticity, or amyotrophy	..
SCA2	183090	*ATXN2*	601517	(CAG)n repeat	Slow saccades, parkinsonism, areflexia, sensory neuropathy, or juvenile forms	Susceptibility to amyotrophic lateral sclerosis (autosomal dominant, 183090) or Parkinson's disease (autosomal dominant, 168600)
SCA3	109150	*ATXN3*	607047	(CAG)n repeat	Diplopia, nystagmus, spasticity, depression, sensory neuropathy, or parkinsonism	..
SCA6	183086	*CACNA1A*	601011	(CAG)n repeat	Down-beat nystagmus	..
SCA7	164500	*ATXN7*	607640	(CAG)n repeat	Visual loss, spasticity, or juvenile forms	..
SCA17	607136	*TBP*	600075	(CAG)n repeat	Dementia, psychiatric disorders, spasticity, or extrapyramidal signs	Susceptibility to Parkinson's disease (autosomal dominant, 168600) or Huntington's disease-like presentation
DRPLA	125370	*ATN1*	607462	(CAG)n repeat	Seizures	..
SCA8	608768	*ATXN8* or *ATXN8OS*	613289, 603680	(CAG)n repeat	Spasticity or psychiatric disorders	Susceptibility to Parkinson's disease (autosomal dominant, 168600)
Non-coding repeat						
SCA10	603516	*ATXN10*	611150	(ATTCT)n repeat	Seizures	..
SCA12	604326	*PPP2R2B*	604325	(CAG)n repeat	Tremor	..
SCA27B	..	*FGF14*	601515	(GAA)n repeat	Episodic onset, down-beat nystagmus, or hyper-reflexia	..
SCA31	117210	*BEAN1*	612051	(TGGAA)n repeat	..	..
SCA36	614153	*NOP56*	614154	(GGCCTG)n repeat	Amyotrophy, fasciculations, hearing loss, or cognitive impairment	..
SCA37	615945	*DAB1*	603448	ATTTC(n) repeat	Abnormal vertical pursuit	..
Conventional mutations						
SCA5	600224	*SPTBN2*	604985	Missense or in-frame deletions	Down-beat nystagmus	SCAR14 (autosomal recessive, 615386)
SCA11	604432	*TTBK2*	611695	Frameshift	Hyper-reflexia	..
SCA13	605259	*KCNC3*	176264	Missense	Intellectual disability	..
SCA14	605361	*PRKCG*	176980	Missense or exon deletions	Myoclonus	..
SCA15, SCA16	606658	*ITPR1*	147265	Exon deletions	..	SCA29 (autosomal dominant, 117360) or Gillepsie syndrome (autosomal dominant or autosomal recessive, 206700)
SCA19, SCA22	607346	*KCND3*	605411	Missense or in-frame deletions	Intellectual disability or myoclonus (SCA19)	Brugada syndrome (autosomal dominant, 616399)
SCA21	607454	*TMEM240*	616101	Missense or nonsense	Intellectual disability or extrapyramidal signs	..
SCA23	610245	*PDYN*	131340	Missense	..	..
SCA25	608703	*PNPT1*	610316	Splice site	Sensory neuropathy	Combined oxidative phosphorylation deficiency 13 (autosomal recessive, 614932) or deafness (autosomal recessive, 614934)
SCA26	609306	*EEF2*	130610	Missense	..	..
SCA27A	193003	*FGF14*	601515	Missense, frameshift, or nonsense	Intellectual disability, psychiatric disorders, or tremor	..
SCA28	610246	*AFG3L2*	604581	Missense or frameshift	Ptosis, ophthalmoplegia, or spasticity	Optic atrophy 12 (autosomal dominant, 618977) or SCAR5 (autosomal recessive, 614487)
SCA29	117360	*ITPR1*	147265	Missense	Intellectual disability or myoclonus	SCA15 (autosomal dominant, 606658) or Gillepsie syndrome (autosomal dominant or autosomal recessive, 206700)
SCA34	133190	*ELOVL4*	605512	Missense	Polyneuropathy or skin disorders	Ichthyosis, spastic quadriplegia, mental retardation (autosomal recessive, 614457), or Stargardt macular dystrophy (autosomal dominant, 600110)
SCA35	613908	*TGM6*	613900	Missense or in-frame deletions	Spasticity or spasmodic torticollis	..
SCA38	615957	*ELOVL5*	611805	Missense	Polyneuropathy	..
SCA40	616053	*CCDC88C*	611204	Missense	Spasticity	Congenital hydrocephalus 1 (autosomal recessive, 236600)
SCA41	616410	*TRPC3*	602345	Missense	..	..

(Table 1 continues on next page)

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

	OMIM number	Gene	Gene OMIM number	Mutation type	Key symptoms and signs in addition to cerebellar ataxia	Other phenotypes (transmission mode, OMIM number)
(Continued from previous page)						
SCA42	616795	*CACNA1G*	604065	Missense	Spasticity or myokymia	Early onset severe SCA42 (autosomal dominant, 618087)
SCA43	617018	*MME*	120520	Missense	Polyneuropathy	Charcot-Marie-Tooth diseases, axonal 2T (autosomal dominant or autosomal recessive, 617017)
SCA44	617691	*GRM1*	604473	Missense or frameshift	Spasticity	SCAR13 (autosomal recessive, 614831)
SCA45	617769	*FAT2*	604269	Missense	..	..
SCA46	617770	*PLD3*	615698	Missense	Sensory neuropathy	..
SCA47	617931	*PUM1*	607204	Missense	Developmental syndrome, seizure, and PADDAS if approximately 50% PUM1 protein reduction	..
SCA48	618093	*STUB1*	607207	Missense or frameshift	Cognitive impairment, spasticity, or extrapyramidal signs	SCAR16 (autosomal recessive, 615768)
SCA49	619806	*SAMD9L*	611170	Missense	Hyperreflexia or nystagmus	Ataxia-pancytopenia syndrome (autosomal dominant, 159550) or monosomy 7 myelodysplasia and leukaemia syndrome 1 (autosomal dominant, 252270)
SCA50	..	*NPTX1*	602367	Missense	Down-beat nystagmus, myoclonus, or cognitive impairment	..
..	..	*CACNA1A*	601011	Missense	Down-beat nystagmus	Episodic ataxia 2 (autosomal dominant, 108500), familial hemiplegic migraine 1 (autosomal dominant, 141500), or developmental and epileptic encephalopathy 42 (autosomal dominant, 617106)
Copy number variation						
SCA20	608687	11q12.2–12.3	..	Duplication	Dysphonia	..
SCA39	..	11q21–11q22.3	..	Duplication	Intellectual disability	..
Locus and mutation not identified						
SCA4	600223	16q22.1	..	..	Sensory neuropathy	..
SCA18	..	7q22–q32	..	..	Weakness or hearing loss	..
SCA30	613371	4q34.3–q35.1	..	..	Hyperreflexia	..
SCA32	613909	7q32–q33	..	..	Azospermia	..

Genes are ordered according to the mutation type, then within those categories according to the number of the spinocerebellar ataxia subtype, as designated by the OMIM database. Conventional mutations encompass point mutations and rearrangements. Double dots indicate not applicable. OMIM=Online Mendelian Inheritance in Man. PADDAS=Pumilio1-Associated Developmental Disability, Ataxia, and Seizure. SCA=spinocerebellar ataxia. SCAR=spinocerebellar ataxia recessive.

Table 1: **Autosomal dominant cerebellar ataxias according to mutation type**

migraine, episodic ataxia type 2, and progressive ataxia.[30] Developmental delay, autism, epilepsy, migraine, and paroxysmal tonic upward gaze are also often reported, and the ataxic signs can be initially episodic and then progressive, or immediately progressive, with either congenital or adult onset.[20]

Genetics

Newly identified SCA genes

Over the past 5 years, advances in diagnostic tools have led to the identification of several SCA-causing genes (figure 1, panel 2). An intronic expansion in *DAB1*, comprising a pathological ATTTC pentanucleotide repeat (range 31–75 repeats) flanked by ATTTT repeats ($[ATTTT]_{60–79}[ATTTC])_{31–75}[ATTTT]_{58–90}$), is responsible for SCA37, which clinically presents as ataxia with predominantly vertical abnormal eye movements. Non-pathogenic and pathogenic alleles have the configurations $ATTTT_{7–400}$ and $ATTTT_{60–797}ATTTC_{31–75}ATTTT_{58–90}$, respectively. A negative correlation appears to exist between the age at onset and the ATTTC repeat size.[37]

SCA47/*PUM1* is caused by lowered PUM1 protein levels, with disease severity depending on dosage deficiency. Patients develop Pumilio1-Associated Developmental Disability, Ataxia, and Seizure (PADDAS) if they have a 50% reduction of wild-type protein levels, or late-onset ataxia with incomplete penetrance if they have a 25% decrease.[38]

STUB1 was previously implicated in the autosomal recessive ataxia SCAR16; in 2018, in six patients from a pedigree with a late-onset ataxia and cerebellar cognitive affective syndrome, exome sequencing identified a heterozygous frameshift *STUB1* variant (Leu275Aspfs*16).[29] The gene has subsequently been confirmed to be responsible for dominant adult ataxia with cognitive impairment, sometimes in families with phenotypes reminiscent of Huntington's disease or frontotemporal dementia.[21,39] Women are more likely to be diagnosed with *STUB1*-associated SCA, suggesting incomplete penetrance in men; this difference could be due to lower *STUB1* expression in the CNS in women, making them more susceptible to the effects of

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

haploinsufficiency.[21] Neuropathological studies found severe depletion of Purkinje cells from the cerebellar vermis, without atrophy of the brainstem, hippocampus, or cerebral cortex.[21] These data corroborate the implication of the cerebellum in cognition (panel 1).

NPTX1 was recently identified as the cause of SCA50, via either dominant–negative or haploinsufficiency mechanisms, leading to endoplasmic reticulum stress.[1] The range of phenotypes associated with *NPTX1* has been extended to infantile cerebellar ataxia with secondary generalised epilepsy,[34] underlining the overlap between adult and childhood onset ataxic diseases.

The SCA25 locus on chromosome 2p was identified in 2004 by a linkage study in 18 individuals from a French family with cerebellar ataxia and sensory neuropathy. The causative variant, resulting in exon skipping in *PNPT1*, has recently been identified. Splice and nonsense variants in *PNPT1* have been identified in another French pedigree and in an Australian pedigree.[40]

SCA49 is caused by heterozygous variants in *SAMD9L*, a gene previously implicated in the dominant syndromes ataxia-pancytopenia and Myelodysplasia, Infection, Restriction of growth, Adrenal hypoplasia, Genital problems, and Enteropathy (MIRAGE). The variants in *SAMD9L* were described in a Spanish family with nine patients presenting cerebellar ataxia, dysarthria, gaze-evoked nystagmus, pyramidal syndrome, and axonal sensory polyneuropathy. Ataxia onset ranged from 30 years to 60 years, but hyper-reflexia, nystagmus, or brain MRI white matter changes occurred earlier.[41] Mutations in this gene are also associated with myeloid malignancies and bone marrow failure that might be treated by haematopoietic cell transplantation;[42] hence, the importance of identifying these pathogenic variants. Given the acquired monosomy in haematopoietic cells, genetic tests should be performed on skin fibroblasts.

The most recently identified SCA subtype, SCA27B, is caused by an intronic GAA repeat expansion in *FGF14* that was revealed by long-read sequencing. The core phenotype is an adult-onset, slow progressive cerebellar ataxia with bilateral vestibulopathy, associated in some patients with hyper-reflexia, autonomic dysfunction, and down-beat nystagmus. This disease can be episodic at onset. Its pathological GAA repeat threshold is greater than 300, with incomplete penetrance for 250–300 GAA repeats.[43]

Phenotypic variation linked to multiplicity of variants

In some patients, the presence of two pathogenic variants in known SCA genes can explain atypical presentations. Digenism (ie, mutations in two genes that are not necessarily causative by themselves) could also explain severe courses, unusual signs, or variable penetrance.

In a French cohort of 50 patients with SCA48/*STUB1*, intermediate SCA17/*TBP* alleles (intermediate repeat lengths are between those consistently associated with disease and those consistently found in unaffected individuals) of 41 or 46 CAG and CAA repeats were detected in two families.[21] This observation was repeated in an Italian cohort: in 31 families with an intermediate $TBP_{41–46}$ allele, 30 also carried a pathogenic *STUB1* variant.[44] The interaction of these two genes might explain the incomplete penetrance of intermediate $TBP_{41–48}$ CAG or CAA repeat alleles, with 50% of patients free from ataxia at age 50.[45] In a German family, the synergetic effect of two *TBP* intermediate alleles led to a more severe phenotype than occurred in individuals with only one pathogenic allele.[46] In half of 34 families with SCA48/*STUB1*, we showed that the presence of an intermediate *TBP* allele of more than 39 CAG repeats was significantly associated with more severe cognitive impairment and reduced survival compared with patients carrying only the *STUB1* variant without an intermediate *TBP* allele.[47]

Intermediate alleles as risk factors for other neurodegenerative diseases

Intermediate, non-pathogenic alleles of SCA genes have recurrently been described as risk factors for other neurodegenerative diseases, and they are found more frequently among patients with these diseases than in people without neurological disorders.

TBP intermediate alleles of 41 CAG or CAA repeats were found in four individuals in a cohort of 28 probands

Panel 1: **Cerebellar cognitive affective syndrome**

The implication of the cerebellum in cognition has been suggested over the past four decades and conceptualised under the dysmetria of thoughts hypothesis.[22] Cerebellar lesions due to vascular, traumatic, infectious, neoplastic, or degenerative processes result in behavioural changes, obsessive ideas, lack of empathy, difficulties in emotional recognition, dysphoria, and depression.[22] Advances in neuropsychological understanding led to the description of cerebellar cognitive affective syndrome, and then to the development and validation of a scale to assess it,[23] which was later translated into several languages. This scale covers the fields affected in the syndrome: executive functions, visuospatial cognition, language, and emotion-affect. The first three effects are linked to the connectivity of the posterior lobe, including the medial and hemispheric regions of lobule VIIA crus I or crus II, lobule HVI, and lobule HVIIB, with the prefrontal, parietal, and frontotemporal cortical areas, respectively. Recent functional MRI studies show that paravermal areas are involved in social and emotion-affect tasks.[24] In a cohort of 20 patients with SCA3, cerebellar cognitive affective syndrome scale detected cognitive impairment at a mild or moderate disease stage.[25] The score correlated with disease duration, SARA score, dominant hand 9 hole-peg test results, and walking speed.[25] Preataxic SCA3 carriers had significantly lower scores compared with controls, which was not the case for patients with SCA6 or Friedreich ataxia.[26] Word fluency was the most appropriate test to distinguish carriers from non-carriers.[26] Language impairment has also been described in SCA36/*NOP56*, with decreased phonological verbal fluency in pre-ataxic carriers, and impaired semantic fluency in symptomatic patients.[27] For 64 patients with SCA2, the cerebellar cognitive affective syndrome score was influenced by the level of education and ataxia severity.[28] The scale could detect mild cognitive impairments that were not detected by the Montreal cognitive assessment test; it also showed higher sensitivity.[28] Cognitive alterations are a hallmark of SCA48/*STUB1*, whereby cognition and emotion are altered, and focal atrophy of the cerebellar vermis, lobule V, and lobule VI are detected in the pre-ataxic phase.[29] These neurobehavioral alterations affect the quality of life of patients and caregivers, and should be considered in clinical management and in future clinical trials.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

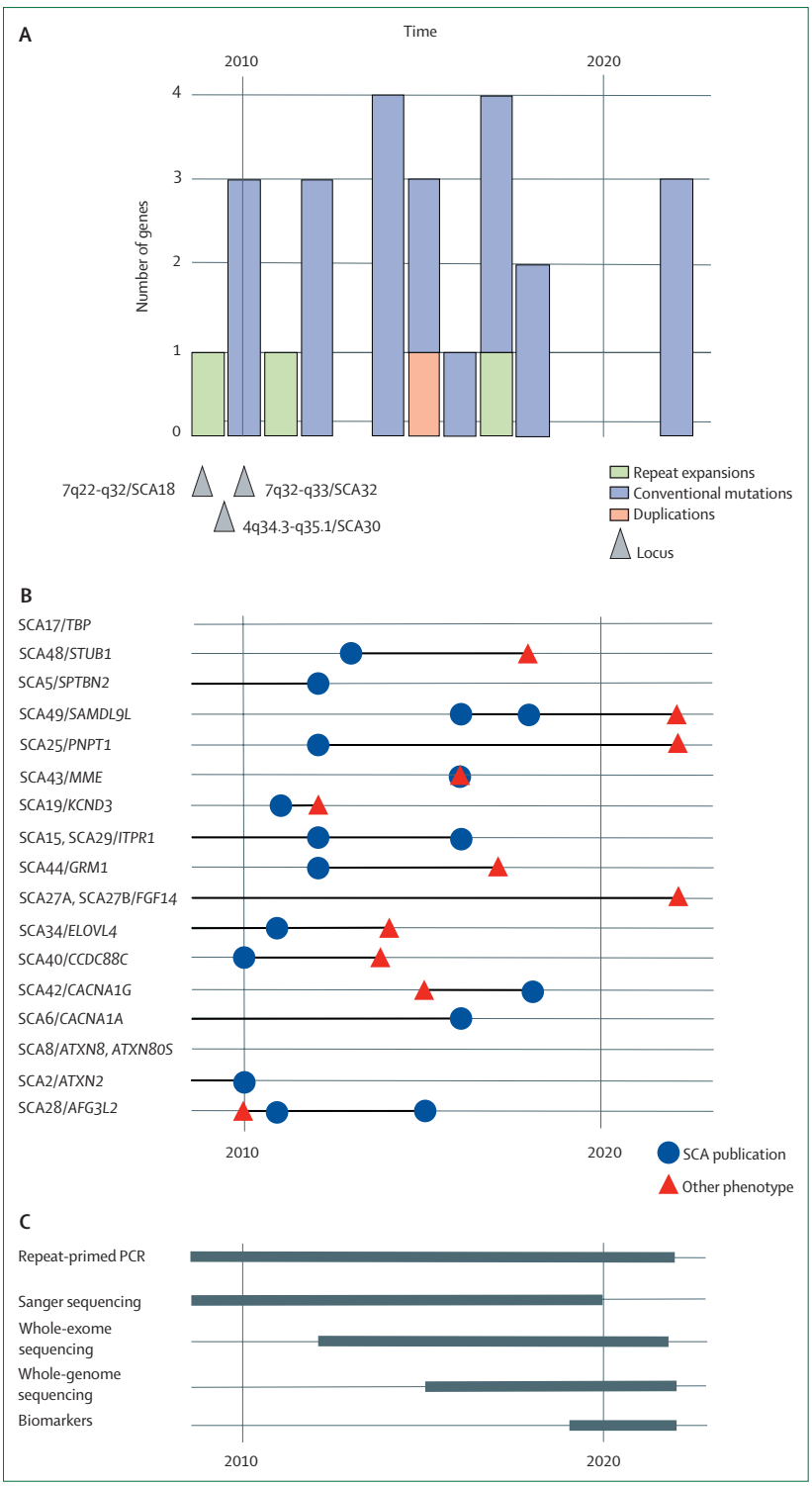


Figure 1: **Progress in the identification of gene variants implicated in spinocerebellar ataxia and their phenotypes, and in diagnostic approaches**
(A) Discovery of gene variants implicated in spinocerebellar ataxias (SCAs). CAG repeats were all reported before 2000, whereas conventional mutations (point mutations and rearrangements) were reported after the advent of exome sequencing. The loci mapped to dominant ataxia for which the causative genetic events could not be identified are represented separately by grey triangles. (B) Phenotypic variability reported for genes implicated in SCAs from the OMIM database. Red triangles indicate when the gene was implicated in the dominant ataxia phenotype, and blue circles indicate when the gene was implicated in phenotypes other than ataxia. (C) The temporal succession of methods available for diagnosis of SCAs. Repeat-primed PCR was a major first step. Sanger sequencing for conventional mutations is now being replaced by next-generation sequencing approaches. Nowadays, whole exome sequencing is the technique of choice in clinics; the usefulness and accuracy of whole exome sequencing is increasing, but its use is still restricted because of its high cost. The development of algorithms to genotype repeats from next-generation sequencing data could make repeat-primed PCR obsolete. A version of this figure that includes gene variants implicated in SCAs before 2010 is given in the appendix (pp 16–17). SCA=spinocerebellar ataxia.

with multiple system atrophy.[48] In a Taiwanese cohort of 325 patients with amyotrophic lateral sclerosis and 1500 healthy controls, two patients carried an intermediate *TBP* allele of 44 or 46 repeats and a pathological expansion in *C9orf72*. These data suggest that *TBP* alleles with more than 44 repeats are risk factors for amyotrophic lateral sclerosis, with an odds ratio of 23·2.[49]

Intermediate $(CAG)_{27–31}$ *ATXN2* (SCA2) alleles could also be risk factors for amyotrophic lateral sclerosis because ATNX2 protein increases the toxicity of TDP43 in *Drosophila melanogaster* and human cells.[50] In a study of 915 patients with sporadic or familial amyotrophic lateral sclerosis, 5% carried an intermediate *ATXN2* allele,[50] a finding validated in other series.[51,52] In an Italian cohort, survival was inversely correlated with the length of the repeat, with shorter survival in patients carrying more than 31 repeats.[52] In a study of more than 9000 individuals with amyotrophic lateral sclerosis, amyotrophic lateral sclerosis with frontotemporal dementia, frontotemporal dementia alone, or Lewy body dementia, and healthy controls, *ATNX2* intermediate alleles were confirmed to be risk factors for amyotrophic lateral sclerosis (odds ratio [OR] 6·3), amyotrophic lateral sclerosis with frontotemporal dementia (OR 27·5), and frontotemporal dementia (OR 3·1).[53] The association between the shorter survival and the presence of an *ATXN2* intermediate allele was not replicated. The role of *ATXN2* in frontotemporal dementia remains unclear. In an Italian frontotemporal dementia cohort, intermediate *ATNX2* alleles were not more frequent in patients than in controls, but were associated with more severe phenotypes, with earlier age at onset, parkinsonism, and psychotic symptoms at onset.[54] In a patient aged 70 years with frontotemporal dementia carrying *ATXN2* alleles with 39 and 27 CAG repeats, post-mortem analysis found TDP43-positive cytoplasmic inclusions in the upper layers of the cortex, whereas the cerebellum examination was unremarkable, without ubiquitin or p62 inclusion.[55] TDP43 inclusions have been described in other polyglutamine diseases such as Huntington's disease, SCA3, and SCA7, suggesting common pathological pathways.[55] In mice overexpressing

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

TDP43, CNS administration of antisense oligonucleotides targeting *ATXN2* mRNA increased survival.[56] A clinical trial (NCT04494256) of an *ATXN2* antisense oligonucleotide is ongoing for patients with amyotrophic lateral sclerosis, with or without a 30–33 CAG repeat *ATXN2* allele.

Other SCA genes containing CAG repeat expansions might also be risk factors for amyotrophic lateral sclerosis. In a cohort of 11700 patients with amyotrophic lateral sclerosis and controls, intermediate *ATXN1* alleles (33–39 CAG or CAT repeats) were significantly associated with amyotrophic lateral sclerosis.[57] As reported for ATXN2, ATXN1 increases the aberrant localisation of TDP43 in *Drosophila melanogaster* by a cytoplasmic gain of function. In addition, polyglutamine expansions in *ATXN1* aggravate the phenotype of *Drosophila melanogaster* that have expansions in *C9orf72*.[57] In another Italian cohort, intermediate *ATXN1* alleles were found in 20% of sporadic and familial patients (10 of 51) who had *C9orf72* repeat expansions.[58]

A study on more than 14000 DNA samples from five European population-based cohorts found a high prevalence of individuals carrying intermediate (10·7%) or small (1·3%) pathological alleles of one SCA gene (*ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, *ATXN7*, or *TBP*). The presence of intermediate alleles of polyglutamine SCA genes should be considered for further research and for genetic counselling, given their possible role as risk factors for other neurodegenerative diseases.[45]

Biomarkers

The correlations and temporal dynamics of the results from different fluid analyses, paraclinical assessments (eg, disease scales and oculomotor, cognitive, and postural assessments), and radiological examinations might, in the future, be used to define a disease trajectory and individually optimise treatments options. Therapeutic advances require reliable biomarkers to monitor treatment, detect patients with more rapid progression, and predict the conversion from pre-ataxic to manifest stages. We provide a comprehensive overview of biomarkers for SCAs, with emphasis on those that have been the most extensively studied (figure 2).

Fluid biomarkers

One of the most studied fluid biomarkers is the neurofilament light chain (NfL), a subunit of the neuronal cytoskeleton; its expression levels increase in blood and CSF after axonal damage, with a strong correlation. In polyglutamine SCAs, NfL expression has predictive, diagnostic, and prognostic value (figure 2). NfL shows continuous variation between controls, pre-ataxic carriers of gene variants associated with SCAs, and patients who are symptomatic, with established cut-off levels, allowing for the prediction of progression before the onset of clinical signs.[59,60] Serum NfL increases 7·5 years before the expected age at symptom onset in carriers of SCA3 and 5 years before the expected age at onset in carriers of SCA1.[60,61] Among polyglutamine SCAs, carriers of SCA3 have the highest NfL levels, followed by carriers of SCA7, SCA1, and SCA2.[59] However, NfL levels were stable after 2 years, possibly because of slow progression of the disease or because they reached a plateau.[59] As a prognostic biomarker, NfL expression levels correlate with disease severity in polyglutamine SCAs;[59] the potential prognostic value of NfL has been explored extensively in individuals with SCA3[59,60] and SCA2.[62] They also predict faster clinical and radiological progression: patients with higher NfL levels at baseline had higher SARA scores and decreased cerebellum volume at the 2-year follow-up.[59] For future clinical trials, these data could help to stratify carriers of SCA who are symptomatic with rapid progression, or who are pre-symptomatic but approaching symptom onset.

Ataxin-specific bioassays are of great interest and identifying these proteins in various biosamples could

***Panel 2:* Diagnostic next-generation sequencing**

The profusion of genes implicated in SCAs, the variety of mutation types, and the absence of clear-cut genotype-phenotype correlations in most instances renders classic sequential testing of candidate genes obsolete (figure 1). To detect repeat expansions that account for the most frequent polyglutamine SCAs, targeted fragment analysis remains the gold-standard in most diagnostic laboratories,[4] but has to be done for each locus independently. Next-generation sequencing typically analyses short-read fragments (two sets of 150 base pairs), which cannot be mapped to the reference human genome when the expansion is too large. Long-read sequencing is under development but remains experimental and expensive. Bioinformatics tools can estimate the expansion size from genome short-read data[31] and were also shown to be effective with exome sequencing, allowing for accurate estimates of the sizes of polyglutamine SCA repeats, with an underestimation of longer alleles.[32] The detection of intronic expansions, such as FGF14 expansion,[33] would require genome sequencing. Conventional mutations are detected by targeted Sanger sequencing or panel-based approaches; however, the accuracy of these tecniques decreases upon description of additional genes or phenotype broadening.[30] Exome sequencing is increasingly accessible and allows post-hoc re-examination of data upon description of novel genes.[34] Causative deep intronic variants have been described in spinocerebellar degeneration, for example, in SPG7.[35] Genome sequencing allows non-coding variants and large structural changes to be identified,[36] but these are difficult to interpret functionally. In a research setting, we advocate the use of whole genome sequencing, given the extensive range of detected variants; in clinical practice, whole exome sequencing constitutes a good compromise between time, cost, and the expected result yield.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

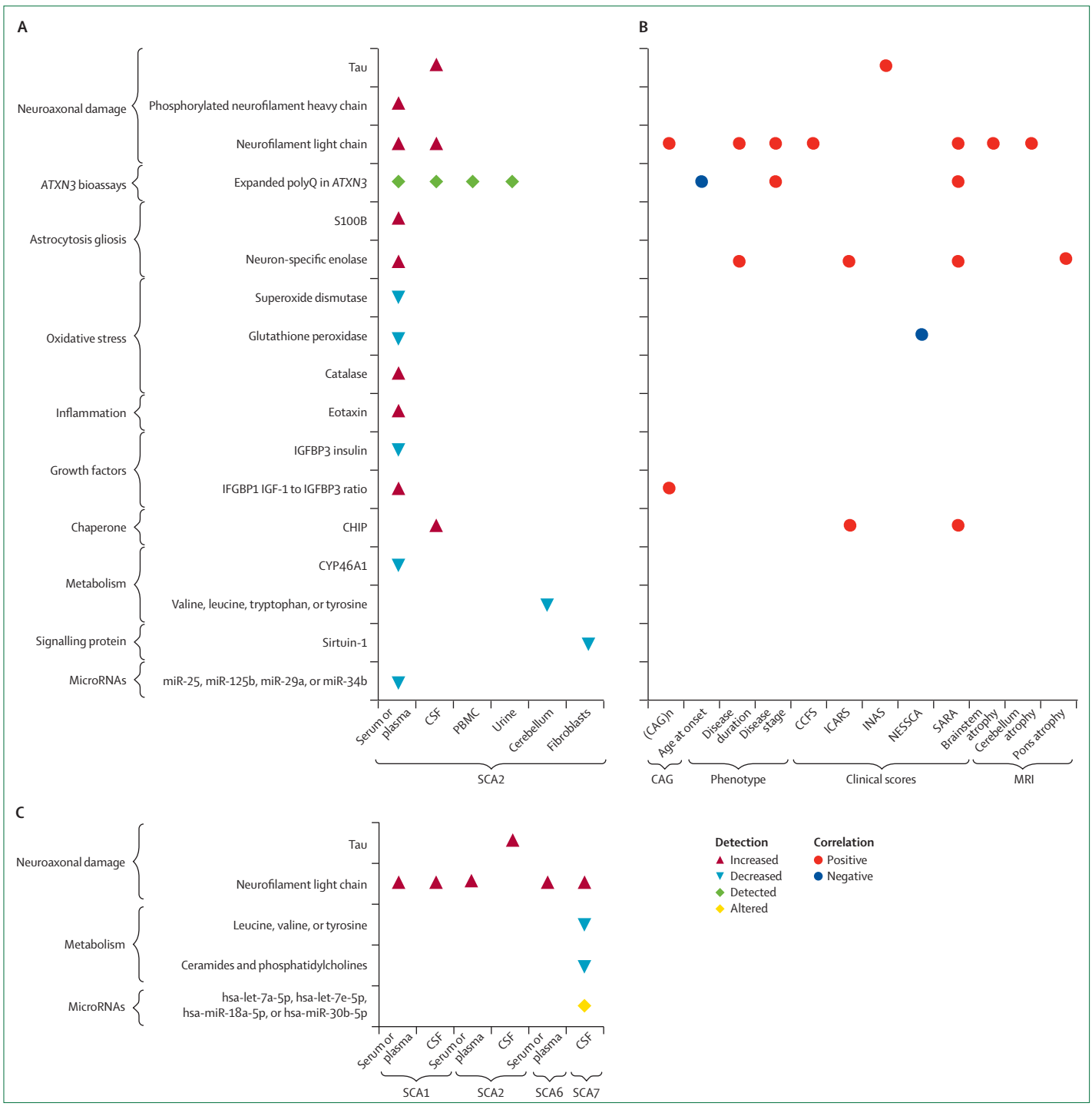


Figure 2: **Fluid biomarkers detected in individuals with spinocerebellar ataxias compared with controls, and their correlation with clinical and radiological features**
The figure focuses on SCA3 as this disease is the focus of most biomarker research. (A) Fluid biomarkers showing dysregulation in SCA3, classified in physiologically relevant groups. For microRNA, "altered" indicates that some were upregulated and others were downregulated. No symbol indicates that data are not available. (B) Correlation of fluid biomarkers detected in SCA3 with the number of CAG repeats, phenotypic traits, clinical scores, and brain MRI features. (C) Fluid biomarkers showing dysregulation in people with SCA1, SCA2, SCA6, and SCA7 compared with people not diagnosed with SCAs, classified in physiologically relevant groups. References are reported in the appendix (pp 13–15). CCFS=composite cerebellar functional severity. ICARS=international cooperative ataxia rating scale. INAS=inventory of non-ataxia signs. NESSCA=neurological examination score for spinocerebellar ataxia. PBMC=peripheral blood mononuclear cells. polyQ=polyglutamine. SARA=scale for the assessment and rating of ataxia. SCA=spinocerebellar ataxia.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

facilitate monitoring of treatment responses (figure 2). To date, only ataxin-3 assays have shown reliable results in the research setting for CSF, plasma, and urine.[63–65] Levels of polyglutamine-expanded ataxin-3 in plasma and CSF correlate with pathological CAG repeat expansion and SARA scores.[63,65] Expanded ataxin-3 was also detected in urine samples from symptomatic and pre-symptomatic carriers, and showed strong correlation with plasma levels and earlier age at onset.[64]

Tau, which is released from damaged neurons, is another potential fluid biomarker. In a pilot study in patients with SCA1, SCA2, or SCA6, the tau concentration in CSF was higher in carriers of SCA2 than in people who did not have SCAs.[66] In a recent study of carriers of SCA3, plasma T-tau levels were increased compared with non-carriers.[67] However, pre-symptomatic carriers had higher CSF concentrations than patients, perhaps indicating the validity of the biomarker in early phases of the disease. We also list other fluid biomarkers in figure 2.

Radiological biomarkers

Radiological biomarkers are more effective than clinical scores to track longitudinal progression in SCAs.[68] The hallmark of SCAs is cerebellum atrophy, although the brainstem is the most affected region in polyglutamine SCAs, with the exception of SCA6.[4] During the pre-ataxic phase, cerebellum and pons atrophy are evident in carriers of SCA2[69] and SCA3.[70] For SCA3, volumes of the medulla oblongata, pallidum, and C2–C3 spinal cord are also reduced in pre-ataxic carriers.[70] In a study including carriers of SCA1, pre-ataxic individuals did not differ from non-carriers.[71] After 1 year of follow-up, however, cerebellum volume was reduced in the carriers, highlighting the potential use as biomarker in pre-ataxic stages. In patients with SCA2 with moderate disease who were followed up for 12 months, only two regions, the pons and the cerebellar lobule crus I, showed atrophy progression.[72] On the basis of previous MRI scans, Coarelli and colleagues[72] speculated that the annual progression of atrophy could be used as a biomarker. In carriers of expansions implicated in SCA1,[73] SCA3,[70] and SCA7,[74] the cervical spinal cord showed atrophy correlating with pathological CAG repeat size and SARA score. In addition to volume analysis, microstructural changes of the white matter were shown by diffusion tensor MRI in polyglutamine SCAs,[74] even in the premanifest phase in carriers of SCA1 and SCA3.[75,76] Magnetic resonance spectroscopy also provided promising biomarkers,[77] with evidence of higher sensitivity than MRI before symptom onset.[76,78]

Paraclinical biomarkers

Postural and gait assessments can detect ataxia-specific anomalies, such as high variability of spatiotemporal gait parameters, wide-base support, reduced gait cycle duration, and stride length due to poor dynamic balance and stability.[79,80] In the largest study exploring wearable sensors in SCA (163 patients with SCA1, SCA2, SCA3, or SCA6, and 42 pre-ataxic carriers of polyglutamine SCAs), gait variability was the most discriminative feature and associated with disease severity.[81] Measures such as toe-out angle, double support time, and elevation of feet allowed discrimination between pre-ataxic carriers and non-carriers, but with less power than for discrimination between ataxic patients and non-carriers.[67] Because day-to-day and within-day fluctuations result in differences in clinical scale scores in patients with ataxia, digital technologies, such as video-based assessments of ataxia, can help to assess movement anomalies comprehensively.[82]

Oculomotor parameters, such as saccade peak velocity, saccade latency, saccade accuracy, and anti-saccadic task, show early abnormalities especially for SCA2 carriers.[83,84] Oculomotor alterations strongly correlate with pathological CAG repeat length and pontine atrophy,[69,84] and worsened in longitudinal follow-up.[84] Electro-oculographical measures of saccades are therefore potential biomarkers of disease progression.

Treatments

Pharmacological treatments

Because of the low prevalence and genetic complexity of SCAs, clinical trials are often conducted on cohorts that include people with different genotypes. This approach might be appropriate for physical or speech therapy, but is questionable for mechanistically targeted approaches. No curative or neuroprotective treatments for SCAs have been approved by the US Food and Drug Administration or by the European Medicines Agency. The widespread neurodegeneration documented by neuropathological studies in patients with polyglutamine SCAs makes it difficult to target a specific brain region. In clinical practice, symptoms are alleviated using levodopa or dopamine agonists, baclofen and botulinum toxin injections for associated spasticity, and treatments for urinary dysfunction and neuropathic pain when needed.[3] Antidepressants, such as selective serotonin reuptake inhibitors, can decrease anxiety without increasing dizziness.

Some molecules have been tested without observable benefits while other clinical trials are ongoing (table 2; appendix pp 6–8). Riluzole, used as disease-modifying therapy in amyotrophic lateral sclerosis, showed controversial results. A 12-month trial including 20 patients with Friedreich ataxia and 40 patients with SCAs (SCA1, SCA2, SCA6, SCA8, or SCA10) found an improvement of one SARA point for the riluzole group.[90] Because of the clinical and genetic heterogeneity in the cohort, we conducted a 12-months study in a homogenous group of 45 individuals with SCA2, which showed no clinical or radiological improvement.[72] A prodrug of riluzole, troriluzole, was administrated to 218 patients with SCA (SCA1, SCA2, SCA3, SCA6, SCA7, SCA8,

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

	Spinocerebellar ataxia	Treatment (number treated with drug or placebo)	Outcome measures and results	Clinical trial registration number
Completed				
Phase 3, randomised[85]	SCA1, SCA2, SCA3, SCA6, SCA7, SCA10	Troriluzole 200 mg/day for 48 weeks (n=218)	m-SARA change at week 48; no improvement	NCT03701399
Phase 3, randomised[72]	SCA2	Riluzole 100 mg/day (n=45)	SARA change at month 12; no clinical or radiological improvement	NCT03347344
Phase 1–2, randomised[86]	SCA2	Erythropoietin 1 mg/6 months nasally (n=34)	SCAFI change at month 6; no serious adverse events; no improvement in ataxia score but a reduction in saccade latency	RPCEC00000187-Sp
Phase 3, randomised, crossover[87]	SCA3	Acetyl-DL-leucine 5g/day for 6 weeks (n=15/108*)	SARA change at week 6; no improvement	EudraCT 2015-000460-34
Phase 3, randomised[88]	SCA6, SCA31	Rovatirelin 1·6 or 2·4 mg/day for 24 weeks; SCA6 (n=165 cohort 1, n=83 cohort 2); SCA31 (n=72 cohort 1, n=57 cohort 2)	SARA change at week 24; no improvement	NCT01970098; NCT02889302
Phase 2B, randomised[89]	SCA38	Docosahexaenoic acid 600 mg/day (n=10)	SARA change at week 16 and 40; SARA stabilisation, but generalisability limited by small sample size	NCT03109626
Ongoing				
Phase 1/2a, open label	SCA1, SCA3	VO659, intrathecal, dose escalation (10, 20, 40, 70, and 100 mg), four injections every 4 weeks, follow-up 43 weeks	Safety and tolerability	NCT05822908
Phase 3, open label	SCA1, SCA2, SCA3, SCA6	BHV-4157 prodrug of riluzole (n=24), no dose information	SARA change at week 12	NCT03408080
Phase 2, randomised	SCA3	Trehalose orally (n=40), no dose information	SARA score at 3 and 6 months	NCT04399265
Phase 2B/3, randomised	SCA3	Trehalose injection, 0·75 g/kg or 0·50 g/kg by intravenous infusion once a week for 52 weeks (n=245)	Change from baseline in m-SARA total score at week 52	NCT05490563
Phase 1, randomised	SCA3	ASOBIIB132, intrathecal, 5 doses, dose escalation every 4 weeks up to day 85 (n=48)	Safety and tolerability	NCT05160558
Phase 2B/3, randomised	SCA7	Riluzole 100 mg/day for 12 months	Visual acuity expressed as the logarithm of the minimum angle of resolution unit and SARA change at month 18	NCT03660917

Completed and ongoing clinical trials with sample sizes of at least 10 patients that have either completed or been active within the past 5 years (a complete list of trials, including older trials, is given in the appendix pp 6–8). ASO=oligonucleotide antisense. SARA=Scale for Assessment and Rating of Ataxia. m-SARA: modified functional SARA. SCAFI=Spinocerebellar Ataxia Functional Index. SNALP=stable nucleic acid lipid particles. *83 patients with hereditary ataxia and 25 patients with non-hereditary ataxia.

Table 2: **Clinical trials of potential treatments for spinocerebellar ataxia**

or SCA10) in a phase 3 trial (NCT03701399); after 48 weeks, no significant change between the two groups was found on the modified functional SARA.[85]

The SCA38 gene, *ELOVL5*, encodes an elongase involved in the synthesis of very long-chain fatty acids that is highly expressed in Purkinje cells. In a randomised, placebo-controlled study, supplementation with 600 mg per day of docosahexaenoic acid (omega-3 polyunsatured fatty acid) for 16 weeks, followed by an open-label study until week 40, proved safe, improved gait and balance with a 2-point decrease in SARA score, and improved cerebellar hypometabolism.[89] These results persisted after a 2-year follow-up.[91]

Non-pharmacological treatments

Physical therapy improves ataxia symptoms. Treatment for 24 weeks improved SARA scores in patients with SCA2 when administered at high intensity (6 h per weekday),[92] and in patients with SCA7 when administered at moderate intensity (2 h, three times per week) or high intensity (2 h, five times per week).[93] Cheaper and more accessible approaches, such as video games and home-based targeted training (eg, body-balance training for vestibular rehabilitation, coordinative training video games, and spatial displacement recorded by a motion sensing input device) proved safe, feasible, and as effective as traditional rehabilitation therapy in both children and adults.[94]

Although speech therapy is strongly recommended for people with ataxia, few studies have systematically assessed its efficacy. Recently, intensive tailored bio-feedback speech treatment for 20 days was associated with improved intelligibility in 16 patients with SCA1, SCA2, SCA3, or SCA6.[95]

Cerebellar transcranial direct current stimulation (tDCS) is a non-invasive treatment aimed at modulating the excitability of cerebellar connections. After 2 weeks of treatment with cerebellar anodal and spinal cathodal tDCS, improvements were recorded in SARA score, International Cooperative Ataxia Rating Scale score, 9-Hole Peg Test, and 8-min walking time in 20 patients with neurodegenerative ataxia compared with controls.[96] In 61 patients (five with SCA1, 12 with SCA2, one with SCA14, one with SCA28, five with SCA38, ten with multiple system atrophy type C, seven with Friedreich's ataxia, 17 with sporadic adult-onset ataxia, and three with cerebellar ataxia with neuropathy and

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

vestibular areflexia syndrome), a randomised, placebo-controlled study showed that two cycles of 2 weeks of cerebellar and spinal tDCS, 12 weeks apart, led to statistically significant improvements in clinical scores, cerebellar cognitive affective syndrome scale, and quality of life that were stable until week 52.[97] Only one study focused on a defined genotype, including 20 patients with SCA3, showing no evidence of SARA score improvement after 2 weeks of treatment and 12 months of follow-up.[98] However, the speech subscore, the PATA rate task score (a quantitative test used to measure the severity of dysarthria), and the Inventory of Non-Ataxia Signs count improved at 6 months, in particular for hyper-reflexia, dystonia, and urinary symptoms.[98] In another study of 20 patients with SCA3, delay eyeblink conditioning showed improvement for conditioned eyeblink response onset and peak latency after ten sessions of cerebellar tDCS compared with sham stimulation.[99]

In a randomised, double-blind, sham-controlled trial of repetitive transcranial magnetic stimulation of the cerebellum for 10 days, SARA score improved in 20 patients with multiple system atrophy-C compared with 25 controls.[100] Cerebellar transcranial magnetic stimulation might therefore improve balance in ataxic patients and should be further investigated.

Pre-ataxic individuals in preventive trials

In dominantly inherited SCAs, the identification of the causal mutation gives the opportunity to identify carriers who could benefit from treatments preventing disease development. Presymptomatic testing allows individuals to know their genetic status before disease manifestation, which is justified in diseases for which it is possible to delay or avoid onset. In the absence of preventive treatments, the justification is made on the basis of individual choice and autonomy.[101] Only a small number of individuals at risk of the disease request testing,[102] but the percentage might increase if a preventive treatment becomes available.

The rationale for early intervention is the presence of neurodegenerative processes in the pre-ataxic phase (figure 3). In a Huntington's disease mouse model, early neonatal treatment with an ampakine enhanced glutamatergic transmission rescued neural circuit abnormalities and preserved cognitive function, sensorimotor function, and brain volume.[103] These results suggest that intervention several years before expected ataxia onset might prevent the occurrence of symptoms. Staging for polyglutamine subtypes of SCA, similar to the staging proposed for Huntington disease,[104] would be required to stratify carriers and define the best therapeutic window.

Therapeutic development with gene therapies

One of the first feasibility tests of CRISPR-Cas9 to correct the expanded CAG allele was performed in SCA3-derived pluripotent stem cells derived from individuals with pathogenic variants in SCA3, replacing the $(CAG)_{74}$ expanded allele with a normal $(CAG)_{17}$ allele.[105] Several cellular abnormalities including polyglutamine aggregates were reduced, demonstrating the potential of this approach. Currently, antisense oligonucleotides targeting the mRNA transcript are the strategy nearest to clinical use. Promising results were obtained in mouse models of SCA1, SCA2, SCA3, and SCA7[106–109] (appendix pp 9–12). The first clinical trial with a non-allele-specific SCA3 antisense oligonucleotide started in early 2022 (NCT05160558), with a great enthusiasm in the ataxia community, since antisense oligonucleotides are approved and remarkably effective in other neurological

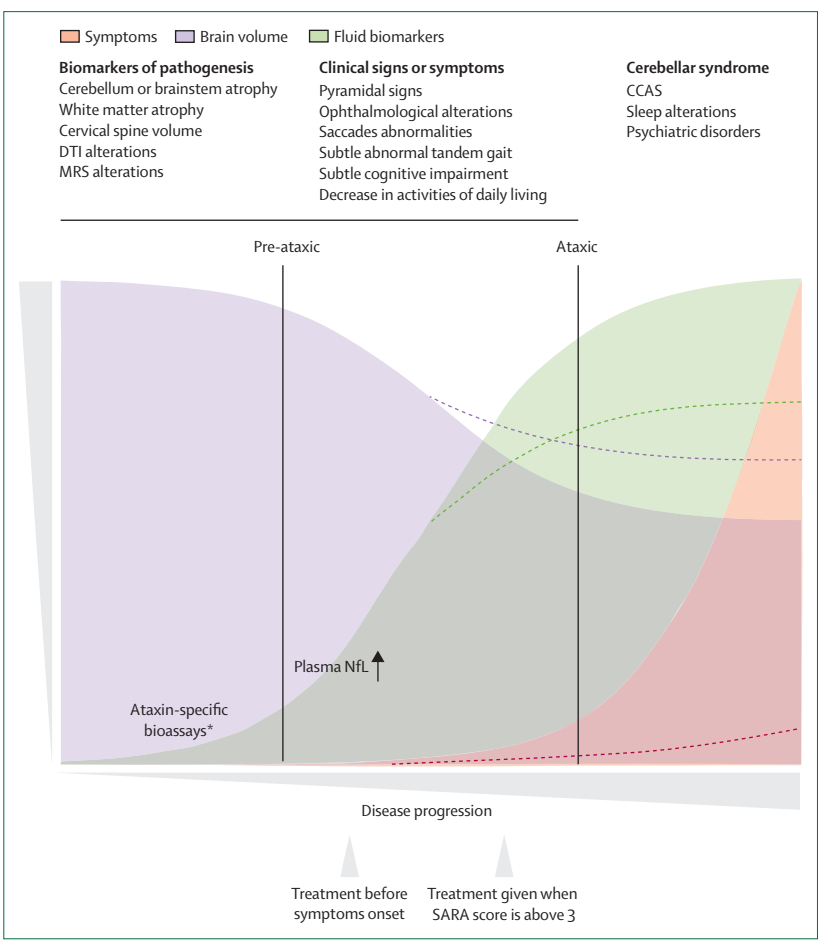


Figure 3: **Theoretical disease stages in polyglutamine spinocerebellar ataxias**
We believe that the natural history of polyglutamine spinocerebellar ataxias can be divided into three main phases: a first pre-ataxic phase, in which only biomarkers of pathogenesis can be detected; a second pre-ataxic stage, in which clinical signs and symptoms unrelated to ataxia appear; and the ataxic phase, with clear cerebellar manifestations (red shaded area). Different biomarkers are altered in the pre-ataxic phases: increases in some biological fluid biomarkers, such as ataxin-3 and NfL, can be detected before the onset of symptoms (green shaded area); and brain imaging can also show early alterations, with a decrease in cerebellum and brainstem volume (purple shaded area). These two elements could be used to determine the best timepoints for a potential treatment (grey triangles). Administration before the onset of symptoms could mitigate or prevent their occurrence and reduce brain volume (dashed lines). CSF tau and $A\beta_{42}$ have been shown in one study to be higher in the ataxic phase of SCA2 and SCA3 than in controls,[66] respectively, but this finding requires replication. CCAS=cerebellar cognitive affective syndrome. DTI=diffusion tensor imaging. MRS=magnetic resonance spectroscopy. NfL=neurofilament light chain. SARA=Scale for Assessment and Rating of Ataxia. *To date, the only assay available in research settings is for ataxin-3 detection in CSF, plasma, and urine.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

diseases, such as spinal muscular atrophy (table 2).[110] However, the phase 3 study of this approach in Huntington's disease (NCT03761849), another polyglutamine disease, was halted after worsening of clinical rating scales and an increase in NfL CSF levels in the group of patients who received higher doses, compared with the low dose and placebo groups.[111] This finding might be linked to a strong decrease of wild-type protein, weak delivery to target neurons, or the inclusion of patients with advanced disease. Allele-specific trials of antisense oligonucleotides (NCT03225833 and NCT03225846) were also stopped in Huntington's disease, because they did not cause the expected mHTT expression decreases. Gene regulation and cellular functions of proteins involved in polyglutamine SCAs are not fully elucidated, and we cannot predict the effects of reducing their expression, especially with non-allele selective antisense oligonucleotides. For example, ataxin-1 protein reduction leads to decreased activity of Capicua (CIC), a tumour suppressor protein, and increased activity of protease β-secretase 1 (BACE1), which has been implicated in the cleavage of amyloid precursor protein.[112] A safety assessment was therefore conducted for a non-selective antisense oligonucleotide in a SCA1 mouse model, and effects on *CIC* and *BACE1* expression were excluded.[113] Furthermore, polyglutamine stretches are present in several proteins and antisense oligonucleotides targeting polyglutamine repeats could trigger off-target mechanisms. Moreover, the reduction in pathogenic protein expression required to conduct a safe trial in a reasonable timeframe (eg, 1 year) is not known.

Conclusions and future directions

In the past 10 years, there has been considerable progress in the understanding of several aspects of SCAs. The formation of large and international cohorts allowed us to better define the natural history of polyglutamine SCAs, and efforts are now underway to tackle non-polyglutamine SCAs. The ever-growing throughput of sequencing technologies has led to the discovery not only of new SCA genes, but also of more complex patterns of interacting variants and risk factors. Biomarkers will be instrumental for the interpretation of genetic results and for finding the optimal treatment window, either during the pre-ataxic stage or at the occurrence of the first symptoms (figure 3). Fluid biomarkers such as NfL in blood, and imaging biomarkers such as cerebellum or brainstem atrophy, will further help in the stratification of carriers of SCA and the identification of the ideal timepoint to initiate treatment and prevent the occurrence of symptoms. Evidently, one difficulty of running a clinical trial in SCAs lies in the low prevalence of these disorders. The Ataxia Global Initiative, initiated in 2021, is a worldwide platform for clinical research in ataxias that gathers academic and industrial researchers, clinicians, and patients' associations. The hope is to facilitate the clinical development of therapies for ataxias and to define trial outcomes, on the basis of harmonised standard operating procedures and taking into account both clinician and patient perspectives.[114] A better understanding of the cellular functions of SCA proteins and the regulation of their expression, brought by studies both of genetics in patients and in models of SCAs, will be crucial in designing new specific therapeutic approaches.

For **Ataxia Global Initiative** see https://ataxia-global-initiative.net/

Search strategy and selection criteria

We searched PubMed for English-language articles published between Jan 1, 2017, and Mar 1, 2023, although well known and seminal older articles were also considered. We used the search terms "spinocerebellar ataxia", "SCA", "polyglutamine diseases", "SCA and biomarkers", "SCA and gene therapy", "SCA and treatment", and all individual SCA genes. The final reference list was generated based on the relevance to the topics covered in this Review. Additionally, we searched ClinicalTrials.gov using "spinocerebellar ataxia" and "SCA".

Contributors

GC performed the literature search and wrote the original draft. MC performed the literature search, wrote the original draft, and prepared figures. AD was responsible for the conceptualisation, supervision, validation, writing, review, and editing of the Review.

Declaration of interests

AD received grants from ANR European Joint Programme on Rare Diseases, National Institutes of Health, Biogen, and Ionis; received consulting fees for Roche, Triplet Therapeutics, and UCB; and participated on data safety monitoring or advisory boards for Roche, UCB, and Wavelife Sciences. GC and MC declare no competing interests.

References

1 Coutelier M, Jacoupy M, Janer A, et al. *NPTX1* mutations trigger endoplasmic reticulum stress and cause autosomal dominant cerebellar ataxia. *Brain* 2022; **145:** 1519–34.
2 Ruano L, Melo C, Silva MC, Coutinho P. The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. *Neuroepidemiology* 2014; **42:** 174–83.
3 Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. *Nat Rev Dis Primers* 2019; **5:** 24.
4 Durr A. Autosomal dominant cerebellar ataxias: polyglutamine expansions and beyond. *Lancet Neurol* 2010; **9:** 885–94.
5 Tezenas du Montcel S, Durr A, Rakowicz M, et al. Prediction of the age at onset in spinocerebellar ataxia type 1, 2, 3 and 6. *J Med Genet* 2014; **51:** 479–86.
6 Tezenas du Montcel S, Durr A, Bauer P, et al. Modulation of the age at onset in spinocerebellar ataxia by CAG tracts in various genes. *Brain* 2014; **137:** 2444–55.
7 Bah MG, Rodriguez D, Cazeneuve C, et al. Deciphering the natural history of SCA7 in children. *Eur J Neurol* 2020; **27:** 2267–76.
8 Kraus-Perrotta C, Lagalwar S. Expansion, mosaicism and interruption: mechanisms of the CAG repeat mutation in spinocerebellar ataxia type 1. *Cerebellum Ataxias* 2016; **3:** 20.
9 Jacobi H, du Montcel ST, Bauer P, et al. Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study. *Lancet Neurol* 2015; **14:** 1101–08.
10 Diallo A, Jacobi H, Cook A, et al. Survival in patients with spinocerebellar ataxia types 1, 2, 3, and 6 (EUROSCA): a longitudinal cohort study. *Lancet Neurol* 2018; **17:** 327–34.
11 Orengo JP, van der Heijden ME, Hao S, Tang J, Orr HT, Zoghbi HY. Motor neuron degeneration correlates with respiratory dysfunction in SCA1. *Dis Model Mech* 2018; **11:** dmm032623.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

12 Monin M, Tezenas du Montcel S, Marelli C, et al. Survival and severity in dominant cerebellar ataxias. *Ann Clin Transl Neurol* 2015; **2:** 202–07.

13 Ashizawa T, Figueroa KP, Perlman SL, et al. Clinical characteristics of patients with spinocerebellar ataxias 1, 2, 3 and 6 in the US; a prospective observational study. *Orphanet J Rare Dis* 2013; **8:** 177.

14 Maas RPPWM, Schutter DJLG, van de Warrenburg BPC. Discordance between patient-reported outcomes and physician-rated motor symptom severity in early-to-middle-stage spinocerebellar ataxia type 3. *Cerebellum* 2021; **20:** 887–95.

15 Jardim LB, Hasan A, Kuo S-H, et al. An exploratory survey on the care for ataxic patients in the American continents and the Caribbean. *Cerebellum* 2022; published online July 7. https://doi.org/10.1007/s12311-022-01442-z.

16 Jacobi H, Reetz K, du Montcel ST, et al. Biological and clinical characteristics of individuals at risk for spinocerebellar ataxia types 1, 2, 3, and 6 in the longitudinal RISCA study: analysis of baseline data. *Lancet Neurol* 2013; **12:** 650–58.

17 van der Put J, Daugeliene D, Bergendal Å, Kvarnung M, Svenningsson P, Paucar M. On spinocerebellar ataxia 21 as a mimicker of cerebral palsy. *Neurol Genet* 2022; **8:** e668.

18 Gouvêa LA, Raslan IR, Rosa ABR, et al. Spinocerebellar atxia type 5 (SCA5) mimicking cerebral palsy: a very early onset autosomal dominant hereditary ataxia. *Cerebellum* 2022; **22:** 316–18.

19 Riso V, Galatolo D, Barghigiani M, et al. A next generation sequencing-based analysis of a large cohort of ataxic patients refines the clinical spectrum associated with spinocerebellar ataxia 21. *Eur J Neurol* 2021; **28:** 2784–88.

20 Hommersom MP, van Prooije TH, Pennings M, et al. The complexities of CACNA1A in clinical neurogenetics. *J Neurol* 2022; **269:** 3094–108.

21 Roux T, Barbier M, Papin M, et al. Clinical, neuropathological, and genetic characterization of STUB1 variants in cerebellar ataxias: a frequent cause of predominant cognitive impairment. *Genet Med* 2020; **22:** 1851–62.

22 Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum - insights from the clinic. *Cerebellum* 2007; **6:** 254–67.

23 Hoche F, Guell X, Vangel MG, Sherman JC, Schmahmann JD. The cerebellar cognitive affective/Schmahmann syndrome scale. *Brain* 2018; **141:** 248–70.

24 Guell X, Gabrieli JDE, Schmahmann JD. Triple representation of language, working memory, social and emotion processing in the cerebellum: convergent evidence from task and seed-based resting-state fMRI analyses in a single large cohort. *Neuroimage* 2018; **172:** 437–49.

25 Maas RPPWM, Killaars S, van de Warrenburg BPC, Schutter DJLG. The cerebellar cognitive affective syndrome scale reveals early neuropsychological deficits in SCA3 patients. *J Neurol* 2021; **268:** 3456–66.

26 Thieme A, Faber J, Sulzer P, et al. The CCAS-scale in hereditary ataxias: helpful on the group level, particularly in SCA3, but limited in individual patients. *J Neurol* 2022; **269:** 4363–74.

27 Martínez-Regueiro R, Arias M, Cruz R, et al. Cerebellar cognitive affective syndrome in Costa da Morte Ataxia (SCA36). *Cerebellum* 2020; **19:** 501–09.

28 Rodríguez-Labrada R, Batista-Izquierdo A, González-Melix Z, et al. Cognitive decline is closely associated with ataxia severity in spinocerebellar ataxia type 2: a validation study of the Schmahmann syndrome scale. *Cerebellum* 2022; **21:** 391–403.

29 Genis D, Ortega-Cubero S, San Nicolás H, et al. Heterozygous STUB1 mutation causes familial ataxia with cognitive affective syndrome (SCA48). *Neurology* 2018; **91:** e1988–e98.

30 Coutelier M, Coarelli G, Monin M-L, et al. A panel study on patients with dominant cerebellar ataxia highlights the frequency of channelopathies. *Brain* 2017; **140:** 1579–94.

31 Ibañez K, Polke J, Hagelstrom RT, et al. Whole genome sequencing for the diagnosis of neurological repeat expansion disorders in the UK: a retrospective diagnostic accuracy and prospective clinical validation study. *Lancet Neurol* 2022; **21:** 234–45.

32 Méreaux J-L, Davoine C-S, Coutelier M, et al. Fast and reliable detection of repeat expansions in spinocerebellar ataxia using exomes. *J Med Genet* 2023; published online Jan 4. https://10.1136/jmg-2022-108924.

33 Rafehi H, Read J, Szmulewicz D, et al. An intronic GAA repeat expansion in FGF14 causes autosomal dominant adult-onset ataxia SCA_{50}/ATX-FGF_{14}. *Am J Hum Genet* 2022; **110:** 105–19.

34 Schöggl J, Siegert S, Boltshauser E, Freilinger M, Schmidt WM. A de novo missense *NPTX1* variant in an individual with infantile-onset cerebellar ataxia. *Mov Disord* 2022; **37:** 1774–76.

35 Verdura E, Schlüter A, Fernández-Eulate G, et al. A deep intronic splice variant advises reexamination of presumably dominant SPG7 cases. *Ann Clin Transl Neurol* 2020; **7:** 105–11.

36 Coutelier M, Holtgrewe M, Jäger M, et al. Combining callers improves the detection of copy number variants from whole-genome sequencing. *Eur J Hum Genet* 2022; **30:** 178–86.

37 Seixas AI, Loureiro JR, Costa C, et al. A pentanucleotide ATTTC repeat insertion in the non-coding region of DAB1, mapping to SCA37, causes spinocerebellar ataxia. *Am J Hum Genet* 2017; **101:** 87–103.

38 Gennarino VA, Palmer EE, McDonell LM, et al. A mild PUM1 mutation is associated with adult-onset ataxia, whereas haploinsufficiency causes developmental delay and seizures. *Cell* 2018; **172:** 924–36.

39 De Michele G, Lieto M, Galatolo D, et al. Spinocerebellar ataxia 48 presenting with ataxia associated with cognitive, psychiatric, and extrapyramidal features: a report of two Italian families. *Parkinsonism Relat Disord* 2019; **65:** 91–96.

40 Barbier M, Bahlo M, Pennisi A, et al. Heterozygous *PNPT1* variants cause spinocerebellar ataxia type 25. *Ann Neurol* 2022; **92:** 122–37.

41 Corral-Juan M, Casquero P, Giraldo-Restrepo N, et al. New spinocerebellar ataxia subtype caused by SAMD9L mutation triggering mitochondrial dysregulation (SCA49). *Brain Commun* 2022; **4:** fcac030.

42 Ahmed IA, Farooqi MS, Vander Lugt MT, et al. Outcomes of hematopoietic cell transplantation in patients with germline *SAMD9*/*SAMD9L* mutations. *Biol Blood Marrow Transplant* 2019; **25:** 2186–96.

43 Pellerin D, Danzi MC, Wilke C, et al. Deep intronic *FGF14* GAA repeat expansion in late-onset cerebellar ataxia. *N Engl J Med* 2022; **388:** 128–41.

44 Magri S, Nanetti L, Gellera C, et al. Digenic inheritance of *STUB1* variants and *TBP* polyglutamine expansions explains the incomplete penetrance of SCA17 and SCA48. *Genet Med* 2022; **24:** 29–40.

45 Gardiner SL, Boogaard MW, Trompet S, et al. Prevalence of carriers of intermediate and pathological polyglutamine disease-associated alleles among large population-based cohorts. *JAMA Neurol* 2019; **76:** 650–56.

46 Reis MC, Patrun J, Ackl N, et al. A severe dementia syndrome caused by intron retention and cryptic splice site activation in *STUB1* and exacerbated by *TBP* repeat expansions. *Front Mol Neurosci* 2022; **15:** 878236.

47 Barbier M, Davoine C-S, Petit E, et al. Intermediate repeat expansions of *TBP* and *STUB1*: genetic modifier or pure digenic inheritance in spinocerebellar ataxias? *Genet Med* 2022; **25:** 100327.

48 Wernick AI, Walton RL, Soto-Beasley AI, et al. Frequency of spinocerebellar ataxia mutations in patients with multiple system atrophy. *Clin Auton Res* 2021; **31:** 117–25.

49 Jih K-Y, Lin K-P, Tsai P-C, Soong B-W, Liao Y-C, Lee Y-C. Investigating TBP CAG/CAA trinucleotide repeat expansions in a Taiwanese cohort with ALS. *Amyotroph Lateral Scler Frontotemporal Degener* 2021; **22:** 442–47.

50 Elden AC, Kim H-J, Hart MP, et al. Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS. *Nature* 2010; **466:** 1069–75.

51 Chiò A, Calvo A, Moglia C, et al. *ATXN2* polyQ intermediate repeats are a modifier of ALS survival. *Neurology* 2015; **84:** 251–58.

52 Borghero G, Pugliatti M, Marrosu F, et al. ATXN2 is a modifier of phenotype in ALS patients of Sardinian ancestry. *Neurobiol Aging* 2015; **36:** 2906.e1–5.

53 Glass JD, Dewan R, Ding J, et al. *ATXN2* intermediate expansions in amyotrophic lateral sclerosis. *Brain* 2022; **145:** 2671–76.

54 Rubino E, Mancini C, Boschi S, et al. ATXN2 intermediate repeat expansions influence the clinical phenotype in frontotemporal dementia. *Neurobiol Aging* 2019; **73:** 231.e7–231.e9.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

55 Fournier C, Anquetil V, Camuzat A, et al. Interrupted CAG expansions in *ATXN2* gene expand the genetic spectrum of frontotemporal dementias. *Acta Neuropathol Commun* 2018; **6:** 41.

56 Scoles DR, Dansithong W, Pflieger LT, et al. ALS-associated genes in SCA2 mouse spinal cord transcriptomes. *Hum Mol Genet* 2020; **29:** 1658–72.

57 Tazelaar GHP, Boeynaems S, De Decker M, et al. *ATXN1* repeat expansions confer risk for amyotrophic lateral sclerosis and contribute to TDP_{-43} mislocalization. *Brain Commun* 2020; **2:** fcaa064.

58 Ungaro C, Sprovieri T, Morello G, et al. Genetic investigation of amyotrophic lateral sclerosis patients in south Italy: a two-decade analysis. *Neurobiol Aging* 2021; **99:** 99.e7–99.e14.

59 Coarelli G, Darios F, Petit E, et al. Plasma neurofilament light chain predicts cerebellar atrophy and clinical progression in spinocerebellar ataxia. *Neurobiol Dis* 2021; **153:** 105311.

60 Wilke C, Haas E, Reetz K, et al. Neurofilaments in spinocerebellar ataxia type 3: blood biomarkers at the preataxic and ataxic stage in humans and mice. *EMBO Mol Med* 2020; **12:** e11803.

61 Wilke C, Mengel D, Schöls L, et al. Levels of neurofilament light at the preataxic and ataxic stages of spinocerebellar ataxia type 1. *Neurology* 2022; **98:** e1985–96.

62 Yang L, Shao Y-R, Li X-Y, Ma Y, Dong Y, Wu Z-Y. Association of the level of neurofilament light with disease severity in patients with spinocerebellar ataxia type 2. *Neurology* 2021; **97:** e2404–13.

63 Prudencio M, Garcia-Moreno H, Jansen-West KR, et al. Toward allele-specific targeting therapy and pharmacodynamic marker for spinocerebellar ataxia type 3. *Sci Transl Med* 2020; **12:** eabb7086.

64 Koike Y, Jansen-West KR, Hanna Al-Shaikh R, et al. Urine levels of the polyglutamine ataxin-3 protein are elevated in patients with spinocerebellar ataxia type 3. *Parkinsonism Relat Disord* 2021; **89:** 151–54.

65 Hübener-Schmid J, Kuhlbrodt K, Peladan J, et al. Polyglutamine-expanded ataxin-3: a target engagement marker for spinocerebellar ataxia type 3 in peripheral blood. *Mov Disord* 2021; **36:** 2675–81.

66 Brouillette AM, Öz G, Gomez CM. Cerebrospinal fluid biomarkers in spinocerebellar ataxia: a pilot study. *Dis Markers* 2015; **2015:** 413098.

67 Garcia-Moreno H, Prudencio M, Thomas-Black G, et al. Tau and neurofilament light-chain as fluid biomarkers in spinocerebellar ataxia type 3. *Eur J Neurol* 2022; **29:** 2439–52.

68 Adanyeguh IM, Perlbarg V, Henry P-G, et al. Autosomal dominant cerebellar ataxias: imaging biomarkers with high effect sizes. *Neuroimage Clin* 2018; **19:** 858–67.

69 Reetz K, Rodríguez-Labrada R, Dogan I, et al. Brain atrophy measures in preclinical and manifest spinocerebellar ataxia type 2. *Ann Clin Transl Neurol* 2018; **5:** 128–37.

70 Faber J, Schaprian T, Berkan K, et al. Regional brain and spinal cord volume loss in spinocerebellar ataxia type 3. *Mov Disord* 2021; **36:** 2273–81.

71 Nigri A, Sarro L, Mongelli A, et al. Spinocerebellar ataxia type 1: one-year longitudinal study to identify clinical and MRI measures of disease progression in patients and presymptomatic carriers. *Cerebellum* 2022; **21:** 133–44.

72 Coarelli G, Heinzmann A, Ewenczyk C, et al. Safety and efficacy of riluzole in spinocerebellar ataxia type 2 in France (ATRIL): a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2022; **21:** 225–33.

73 Martins Junior CR, Martinez ARM, Vasconcelos IF, et al. Structural signature in SCA1: clinical correlates, determinants and natural history. *J Neurol* 2018; **265:** 2949–59.

74 Hernandez-Castillo CR, Diaz R, Rezende TJR, et al. Cervical spinal cord degeneration in spinocerebellar ataxia type 7. *Am J Neuroradiol* 2021; **42:** 1735–39.

75 Li M, Chen X, Xu H-L, et al. Brain structural abnormalities in the preclinical stage of Machado-Joseph disease/spinocerebellar ataxia type 3 (MJD/SCA3): evaluation by MRI morphometry, diffusion tensor imaging and neurite orientation dispersion and density imaging. *J Neurol* 2022; **269:** 2989–98.

76 Chandrasekaran J, Petit E, Park YW, et al. Clinically meaningful magnetic resonance endpoints sensitive to preataxic spinocerebellar ataxia types 1 and 3. *Ann Neurol* 2023; **93:** 686 –701.

77 Miranda CO, Nobre RJ, Paiva VH, et al. Cerebellar morphometric and spectroscopic biomarkers for Machado-Joseph Disease. *Acta Neuropathol Commun* 2022; **10:** 37.

78 Deelchand DK, Joers JM, Ravishankar A, et al. Sensitivity of volumetric magnetic resonance imaging and magnetic resonance spectroscopy to progression of spinocerebellar ataxia type 1. *Mov Disord Clin Pract* 2019; **6:** 549–58.

79 Ilg W, Seemann J, Giese M, et al. Real-life gait assessment in degenerative cerebellar ataxia: Toward ecologically valid biomarkers. *Neurology* 2020; **95:** e1199–210.

80 Buckley E, Mazzà C, McNeill A. A systematic review of the gait characteristics associated with cerebellar ataxia. *Gait Posture* 2018; **60:** 154–63.

81 Shah VV, Rodriguez-Labrada R, Horak FB, et al. Gait variability in spinocerebellar ataxia assessed using wearable inertial sensors. *Mov Disord* 2021; **36:** 2922–31.

82 Grobe-Einsler M, Taheri Amin A, Faber J, et al. Development of $SARA^{home}$, a new video-based tool for the assessment of ataxia at home. *Mov Disord* 2021; **36:** 1242–46.

83 Stephen CD, Schmahmann JD. Eye movement abnormalities are ubiquitous in the spinocerebellar ataxias. *Cerebellum* 2019; **18:** 1130–36.

84 Rodríguez-Labrada R, Velázquez-Pérez L, Auburger G, et al. Spinocerebellar ataxia type 2: measures of saccade changes improve power for clinical trials. *Mov Disord* 2016; **31:** 570–78.

85 Biohaven Pharmaceutical Holding Company Ltd. Biohaven provides update on phase 3 clinical trial evaluating troriluzole for spinocerebellar ataxia (SCA). May 23, 2022. https://www.prnewswire.com/news-releases/biohaven-provides-update-on-phase-3-clinical-trial-evaluating-troriluzole-for-spinocerebellar-ataxia-sca-301552633.html (accessed Nov 17, 2022).

86 Rodriguez-Labrada R, Ortega-Sanchez R, Hernández Casaña P, et al. Erythropoietin in spinocerebellar ataxia type 2: feasibility and proof-of-principle issues from a randomized controlled study. *Mov Disord* 2022; **37:** 1516–25.

87 Feil K, Adrion C, Boesch S, et al. Safety and efficacy of acetyl-DL-leucine in certain types of cerebellar ataxia: the ALCAT randomized clinical crossover trial. *JAMA Netw Open* 2021; **4:** e2135841.

88 Nishizawa M, Onodera O, Hirakawa A, Shimizu Y, Yamada M, Rovatirelin Study Group. Effect of rovatirelin in patients with cerebellar ataxia: two randomised double-blind placebo-controlled phase 3 trials. *J Neurol Neurosurg Psychiatry* 2020; **91:** 254–62.

89 Manes M, Alberici A, Di Gregorio E, et al. Docosahexaenoic acid is a beneficial replacement treatment for spinocerebellar ataxia 38. *Ann Neurol* 2017; **82:** 615–21.

90 Romano S, Coarelli G, Marcotulli C, et al. Riluzole in patients with hereditary cerebellar ataxia: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2015; **14:** 985–91.

91 Gazulla J, Benavente I, García-González E, Berciano J. Two-year follow-up of docosahexaenoic acid supplementation in spinocerebellar ataxia type 38 (SCA38). *J Neurol* 2022; **269:** 5643–46.

92 Rodríguez-Díaz JC, Velázquez-Pérez L, Rodríguez Labrada R, et al. Neurorehabilitation therapy in spinocerebellar ataxia type 2: a 24-week, rater-blinded, randomized, controlled trial. *Mov Disord* 2018; **33:** 1481–87.

93 Tercero-Pérez K, Cortés H, Torres-Ramos Y, et al. Effects of physical rehabilitation in patients with spinocerebellar ataxia type 7. *Cerebellum* 2019; **18:** 397–405.

94 Lacorte E, Bellomo G, Nuovo S, Corbo M, Vanacore N, Piscopo P. The use of new mobile and gaming technologies for the assessment and rehabilitation of people with ataxia: a systematic review and meta-analysis. *Cerebellum* 2021; **20:** 361–73.

95 Vogel AP, Graf LH, Magee M, Schöls L, Rommel N, Synofzik M. Home-based biofeedback speech treatment improves dysarthria in repeat-expansion SCAs. *Ann Clin Transl Neurol* 2022; **9:** 1310–15.

96 Benussi A, Dell'Era V, Cantoni V, et al. Cerebello-spinal tDCS in ataxia: a randomized, double-blind, sham-controlled, crossover trial. *Neurology* 2018; **91:** e1090–101.

97 Benussi A, Cantoni V, Manes M, et al. Motor and cognitive outcomes of cerebello-spinal stimulation in neurodegenerative ataxia. *Brain* 2021; **144:** 2310–21.

98 Maas RPPWM, Teerenstra S, Toni I, Klockgether T, Schutter DJLG, van de Warrenburg BPC. Cerebellar transcranial direct current stimulation in spinocerebellar ataxia type 3: a randomized, double-blind, sham-controlled trial. *Neurotherapeutics* 2022; **19:** 1259–72.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.

99 Maas RPPWM, Schutter DJLG, Toni I, Timmann D, van de Warrenburg BPC. Cerebellar transcranial direct current stimulation modulates timing but not acquisition of conditioned eyeblink responses in SCA3 patients. *Brain Stimul* 2022; **15:** 806–13.

100 Song P, Li S, Wang S, Wei H, Lin H, Wang Y. Repetitive transcranial magnetic stimulation of the cerebellum improves ataxia and cerebello-fronto plasticity in multiple system atrophy: a randomized, double-blind, sham-controlled and TMS-EEG study. *Aging* 2020; **12:** 20611–22.

101 Goizet C, Lesca G, Dürr A, French Group for Presymptomatic Testing in Neurogenetic Disorders. Presymptomatic testing in Huntington's disease and autosomal dominant cerebellar ataxias. *Neurology* 2002; **59:** 1330–36.

102 Pierron L, Tezenas du Montcel S, Heinzmann A, et al. Reproductive choices and intrafamilial communication in neurogenetic diseases with different self-estimated severities. *J Med Genet* 2022; **60:** 346–51.

103 Braz BY, Wennagel D, Ratié L, et al. Treating early postnatal circuit defect delays Huntington's disease onset and pathology in mice. *Science* 2022; **377:** eabq5011.

104 Tabrizi SJ, Schobel S, Gantman EC, et al. A biological classification of Huntington's disease: the Integrated Staging System. *Lancet Neurol* 2022; **21:** 632–44.

105 He L, Wang S, Peng L, et al. CRISPR/Cas9 mediated gene correction ameliorates abnormal phenotypes in spinocerebellar ataxia type 3 patient-derived induced pluripotent stem cells. *Transl Psychiatry* 2021; **11:** 479.

106 Friedrich J, Kordasiewicz HB, O'Callaghan B, et al. Antisense oligonucleotide-mediated ataxin-1 reduction prolongs survival in SCA1 mice and reveals disease-associated transcriptome profiles. *JCI Insight* 2018; **3:** e123193.

107 Scoles DR, Meera P, Schneider MD, et al. Antisense oligonucleotide therapy for spinocerebellar ataxia type 2. *Nature* 2017; **544:** 362–66.

108 McLoughlin HS, Moore LR, Chopra R, et al. Oligonucleotide therapy mitigates disease in spinocerebellar ataxia type 3 mice. *Ann Neurol* 2018; **84:** 64–77.

109 Niu C, Prakash TP, Kim A, et al. Antisense oligonucleotides targeting mutant Ataxin-7 restore visual function in a mouse model of spinocerebellar ataxia type 7. *Sci Transl Med* 2018; **10:** eaap8677.

110 Hoy SM. Nusinersen: first global approval. *Drugs* 2017; **77:** 473–79.

111 Tabrizi SJ, Estevez-Fraga C, van Roon-Mom WMC, et al. Potential disease-modifying therapies for Huntington's disease: lessons learned and future opportunities. *Lancet Neurol* 2022; **21:** 645–58.

112 Suh J, Romano DM, Nitschke L, et al. Loss of ataxin-1 potentiates Alzheimer's pathogenesis by elevating cerebral BACE1 transcription. *Cell* 2019; **178:** 1159–75.e17.

113 O'Callaghan B, Hofstra B, Handler HP, et al. Antisense oligonucleotide therapeutic approach for suppression of ataxin-1 expression: a safety assessment. *Mol Ther Nucleic Acids* 2020; **21:** 1006–16.

114 Klockgether T, Ashizawa T, Brais B, et al. Paving the way toward meaningful trials in ataxias: an ataxia global initiative perspective. *Mov Disord* 2022; **37:** 1125–30.

Copyright © 2023 Elsevier Ltd. All rights reserved.

Descargado para Anonymous User (n/a) en National Library of Health and Social Security de ClinicalKey.es por Elsevier en agosto 01, 2023. Para uso personal exclusivamente. No se permiten otros usos sin autorización. Copyright ©2023. Elsevier Inc. Todos los derechos reservados.