SPINOCEREBELLAR ATAXIA TYPE 1: EPIDEMIOLOGY, GENETICS, AND FUTURE THERAPEUTIC PROSPECTS

SPINOCEREBELÁRNA ATAXIA TYPU 1: EPIDEMIOLÓGIA, GENETIKA A PERSPEKTÍVY BUDÚCEJ TERAPIE

DEREKA Tetiana[1,2], SHEIKO Vitalii[3]

[1] *Faculty of Healthcare, Alexander Dubcek University of Trencin, Trencin, Slovak republic*
[2] *Educational and Scientific Institute of Health, Rehabilitation and Physical Education National University of Ukraine of Physical Education and Sport, Kiev, Ukraine*
[3] *Faculty of Chemistry and Biology, Ternopil Volodymyr Hnatiuk National Pedagogical University, Ternopil, Ukraine*

ABSTRACT

Background: Spinocerebellar ataxia type 1 (SCA1) is an autosomal dominant neurodegenerative disorder caused by CAG repeat expansion in ATXN1. Despite expanding knowledge on molecular mechanisms, clinical heterogeneity and limited therapeutic options persist.

Aim: To summarize the currently available evidence on spinocerebellar ataxia type 1 (SCA1), including its epidemiology, genetic determinants, clinical manifestations, rehabilitation strategies, and emerging therapeutic approaches.

Methods: A systematic literature search was conducted in PubMed, Scopus, and Web of Science for publications from 2010 – 2024. Inclusion criteria: studies on prevalence, genotype-phenotype correlations, clinical assessment, rehabilitation effectiveness, and experimental therapies in SCA1.

Results: Marked variability in prevalence and symptom severity was identified, with higher disease burden in regions with founder effects. Rehabilitation interventions demonstrated benefit in maintaining balance and functional independence, though evidence remains limited.

One of the methods aimed at reducing the spread of ataxias of various types is screening tests. In the future, genetic methods for correcting ataxic manifestations may appear in service.

Conclusions: Precision diagnostics, structured neurorehabilitation, and accelerated translational research are essential for improved outcomes in SCA1. Gene- and cell-based therapies may soon shift clinical management from symptomatic to disease-modifying intervention.

Key words: Ataxia. Hereditary neurodegenerative diseases. Spinocerebellar ataxia type 1. Symptomatic therapy.

ABSTRAKT

Východiská: Spinocerebelárna ataxia typu 1 (SCA1) je autozomálne dominantné neurodegeneratívne ochorenie spôsobené expanziou CAG opakovania v ATXN1. Napriek rozširujúcim sa poznatkom o molekulárnych mechanizmoch pretrváva klinická heterogenita a obmedzené terapeutické možnosti.

Ciele: Zhrnúť aktuálne dostupné dôkazy o spinocerebelárnej ataxii typu 1 (SCA1), vrátane jej epidemiológie, genetických determinantov, klinických prejavov, rehabilitačných stratégií a nových terapeutických prístupov.

Metódy: Systematické vyhľadávanie literatúry bolo vykonané v PubMed, Scopus a Web of Science pre publikácie v rokoch 2010 – 2024. Kritériá zaradenia: štúdie o prevalencii, korelá-ciách genotyp-fenotyp, klinickom hodnotení, účinnosti rehabilitácie a experimentálnych terapiách v SCA1.

Výsledky: Bola identifikovaná výrazná variabilita v prevalencii a závažnosti symptómov, s vyššou záťažou ochorenia v regiónoch s zakladateľskými efektmi. Rehabilitačné intervencie preukázali prínos pri udržiavaní rovnováhy a funkčnej nezávislosti, hoci dôkazy zostávajú obmedzené.

Jednou z metód zameraných na zníženie šírenia rôznych typov ataxií sú skríningové testy. V budúcnosti sa môžu objaviť genetické metódy na korekciu ataxických prejavov.

Záver: Presná diagnostika, štruktúrovaná neurorehabilitácia a zrýchlený translačný výskum sú nevyhnutné pre zlepšenie výsledkov SCA1. Terapie založené na génoch a bunkách môžu čoskoro presunúť klinické riadenie z symptomatických na intervencie modifikujúce priebeh ochorenia.

Kľúčové slová: Ataxia. Dedičné neurodegeneratívne ochorenia. Spinocerebelárna ataxia typu 1. Symptomatická terapia.

INTRODUCTION

Statodynamic disorders represent one of the most common clinical problems faced by neurologists, otolaryngologists and general practitioners (Brandt, 2000; Newman-Toker, et al., 2022). Dizziness and postural instability rank third among neurological symptoms after pain and fatigue, making them a major cause of disability, falls, and reduced quality of life in adults and older populations (Yardley, et al., 1998; Mueller, et al., 2020). Large epidemiological surveys indicate that 20 – 30 % of individuals experience significant imbalance at least once in their lifetime, while approximately 5 – 7 % report persistent or recurrent disequilibrium annually (Neuhauser, et al., 2009; Cnyrim, et al., 2008; Kaski, 2021).

Among neurological disorders affecting balance and coordination, ataxias constitute a highly heterogeneous group with both acquired and hereditary etiologies. Hereditary ataxias, and particularly cerebellar ataxias, remain one of the most complex and

dynamically developing fields of clinical neurology and neurogenetics (Klockgether, et al., 2019; Rossi, et al., 2022). Historically, ataxia as a clinical sign was first characterized by Duchenne de Boulogne in patients with tabes dorsalis, while later in-depth investigation of hereditary cerebellar degeneration was carried out by Charcot, Marie, Friedreich, Strümpell and their successors (Paulson, 2009).

Hereditary ataxias constitute one of the most common groups of inherited disorders of the nervous system, second in prevalence only to hereditary neuromuscular diseases. The estimated global prevalence of all forms of hereditary ataxia ranges from 3 to 10 cases per 100,000 population (Winborn, et al., 2008).

More than 40 autosomal dominant spinocerebellar ataxias (SCAs) have been identified to date, with a combined prevalence of 1-5 cases per 100,000 population. Among them, SCA1, SCA2, SCA3, SCA6, and SCA7 account for the majority of cases. SCA3 (Machado–Joseph disease) represents 25-50% of all dominant forms, followed by SCA2 (13-18%), SCA6 (13-15%), and SCA7. SCA1 accounts for approximately 10% of cases worldwide (Bhandari, et al., 2025; Krysa, et al., 2016).

The distribution of individual SCA subtypes varies considerably across populations, likely influenced by founder effects, historical migration patterns, and genetic drift (Krysa, et al., 2016).

The highest SCA1 prevalence has been reported in South Africa (up to 41% of all SCAs), as well as in Japan, India, Italy, and Australia, whereas it is less common in Portugal, Brazil, and Central Japan (Klockgether, 2019; Sato, et al., 2009; Sulek, et. al., 2004; Barca, et al., 2019).

Several notable high-prevalence clusters have been documented (Paulson, 2009):

- Central Poland – SCA1 constitutes up to 68 % of autosomal dominant ataxias,
- Tamil Nadu, India – in isolated villages up to 7.2 % of residents may be affected,
- Northern Honshu, Japan (Tohoku region) – 24.8 % of SCAs are SCA1,
- Yakutia (Eastern Siberia) – prevalence reaches 46 cases per 100,000 rural population.

The increased concentration of SCA1 in genetically isolated populations such as the Yakuts appears to reflect both founder mutations and high survival and functional capacity in preclinical stages, which facilitate transmission to subsequent generations. Thus, although the overall frequency of SCA1 globally is relatively low (approximately 1 per 100,000 population), significant geographic and ethnic variation underscores the need for population-specific genetic screening and epidemiological surveillance. Table 1 shows statistical data on spinocerebellar ataxia type 1 in different countries.

Table 1 Statistical data on spinocerebellar ataxia type 1 in different countries

Average age of disease onset, years	Number of observations	Duration of the disease, years	Length of pathological CAG expansion	Length of CAG normal allele	Source
38.0±9.2	53	14.8±7.3	48.7±4.8	30.2±3.4	Russia, Yakutia 2015
38.43±10.14	21	5.43±5.13	50.14±6.27	-	Thailand, 2014
37.1±11.2	20	6.1±4.7	46.7	29.6	Brazil, 2014
40.41±11.40	60	-	-	-	USA, 2013
34.8±10	21	-	52.0±3.8	-	Sri Lanka, 2013
37.0±10.6	117	-	47.4±5.2	28.9±1.7	EUROSCA, 2011
37.5±11.0	206	-	49.6±5.8	-	Poland, 2010
30±10	57	-	42-72	-	India, 2007
33.3±8.0	33	-	-	-	Serbia, 2006
30-57	17	-	40-48	-	India, 2005
36.3±16.6	6	-	70.4±25.9	-	South Korea, 2003
36.6±12.5	18	-	-	29-37	Netherlands, 2002
37.3±4.3	12	-	-	-	China, 2001
28.50±13.41	7	3.63±3.07	-	-	China, 2000
38	60	7	-	-	England, 1998
36.5	36	-	-	-	Germany, 1998
35.6±9.4	126	-	45-55	-	Japan, 1995

According to modern views, the development of the disease can be predicted with mathematical accuracy by the length of CAG repeats (Tezenas du Montcel, 2014). In this regard, it is appropriate to note that in some cases, patients live to old age in the presence of pathological CAG repeats of the Ataxin 1 gene without obvious signs of disease development (Goldfarb, 1996), and in some cases, the onset of the disease was noted at the age of over 70 years (Schöls, et al., 2004).

The exact prevalence of various genetic forms of autosomal dominant SCA in the population is difficult to estimate, since the number of detailed epidemiological studies of autosomal dominant SCA for the most common types is still insufficient, and rare forms have been identified in isolated families (Bohannon, 1989).

Unfortunately, the available literature does not contain any information on the life expectancy of patients with the same number of CAG repeats. Due to the rare occurrence of the disease, mortality rates of patients have not been sufficiently analyzed. Clarification of this issue will allow us to search for risk factors and protection of degenerative changes in the brain.

Based on the above, the aim of study is to investigate and summarize the currently available evidence on spinocerebellar ataxia type 1 (SCA1), including its epidemiology, clinical manifestations, genetic characteristics, and prospects for gene- and cell-based therapies.

METHODOLOGY

The study included a comprehensive analysis of scientific literature in the field of clinical neurology and neurogenetics, with an emphasis on current data on spinocerebellar ataxia type 1 (SCA1). The publications devoted to the prevalence, pathogenesis, molecular diagnostics and clinical course of SCA1, as well as works on neurorehabilitation in degenerative diseases of the central nervous system, were studied.

The methodological basis was: analysis and synthesis of current medical literature (including publications in journals indexed in Scopus and Web of Science); systematization and generalization of practical experience data on issues of symptomatic therapy and physical rehabilitation of patients with SCA1; formal logical methods of scientific research applied in interpreting data, developing conclusions and formulating recommendations.

The approach was predominantly theoretical and analytical with elements of evidence-based medicine and a multidisciplinary approach.

RESULTS

Spinocerebellar ataxia type 1 (SCA1) belongs to a broader class of polyglutamine spinocerebellar ataxias, whose epidemiology and genetic diversity have just recently been re-examined across Europe. (De Mattei, et al; 2023) A large 2023 systematic review of autosomal-dominant spinocerebellar ataxias (SCAs) confirmed more than 40 genetically distinct SCA subtypes (Klockgether, et al., 2025).

Typical clinical features of SCA1 – progressive cerebellar ataxia, dysarthria, and oculomotor dysfunction – persist irrespective of geographic background, although phenotype severity and age at onset vary, highlighting the influence of both genetic and environmental modifiers.

So, the disease generally presents in early to mid-adulthood, most commonly between 30 and 40 years of age, although earlier onset in adolescence has also been documented. The course of SCA1 is relentlessly progressive, leading to severe functional decline, and life expectancy following symptom onset is typically estimated at approximately 10 – 30 years (Zoghbi, et al. 2009; Colucci, 2025).

To further clarify the spectrum of SCA1, we examined its specific clinical and genetic features

Clinical and genetic characteristics of spinocerebellar ataxia type 1

Patients with SCA1 have a mutation in the ATXN1 gene (Figure 1) on chromosome 6p22.3. The mutation is an uncontrolled increase in the number of trinucleotide CAG repeats in the coding region of ATXN1 from 25-32 to 39-72 with the loss of the CAT "bridge", which presumably prevents pathological expansion of the trinucleotide tract. The number of uninterrupted CAG triplets in the ATXN1 gene correlates with the age of onset and severity of the disease. nstability of the CAG segment length is manifested in meiosis: the number of CAG repeats in the mutant ATXN1 gene increases when transmitted from a paternal carrier by an average of 3.04 repeats and from a maternal carrier by 0.182 repeats. Transmission from one generation to another in the population occurs on average by +1.614 repeats, which explains the increase in SCA1 incidence. Patients from three spatially remote regions of Yakutia have the same haplotype

when examined with informative markers, which confirms the origin of the mutation from a common ancestor approximately 37 generations ago. SCA1 patients in Mongolia and China have a different haplotype. To determine the tendency for further spread of SCA1, the fertility rates of ATXN1 mutation carriers were examined and the Crow selection intensity index was calculated. The obtained estimate of 0.19 indicates that the mutation has little chance of being eliminated from the population without targeted preventive measures (Koeppen, 2011; Rüb, 2012; Orr, et al., 2007; Eisel, et al., 2024; Kerkhof, et. al., 2023).

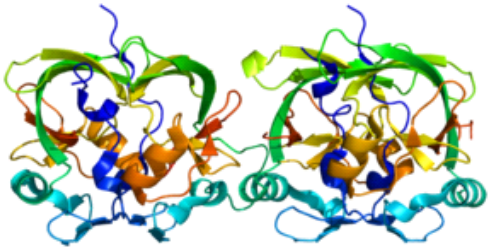

Figure 1. Spinocerebellar ataxia type 1 (SCA1), Jester's disease; *ATXN1* gene (Slatkin, 2000; Gouriev, 2004).

As follows, SCA1 displays clear founder effects in selected populations and demonstrates an expansion-driven increase in disease prevalence through paternal transmission.

Since SCA1 belongs to the wider group of autosomal dominant spinocerebellar ataxias (ADSCAs), comparative analysis helps distinguish its specific phenotype and inheritance characteristics.

Clinical characteristics of autosomal dominant spinocerebellar ataxias

More than 50 % of all autosomal dominant spinocerebellar ataxias are SCA types 1, 2, 3, 6, 7. The prevalence of different SCA types varies greatly from population to population (Daroff, 2016; Delatycki, et al., 2000; Koeppen, 2011; Schmitz-Hübsch, et. al., 2008). SCA 1, 2, 3, 6, 7 are inherited in an autosomal dominant manner, that is, there is a 50% risk of developing the disease in offspring. All of the listed SCAs, except for type 6 SCAs, are characterized by the phenomenon of anticipation (MacIver, et al., 2020; Soong, et al., 2018; Bhandari, et. al., 2025).

The clinical manifestations of autosomal dominant spinocerebellar ataxias of individual SCA types are very nonspecific and it is impossible to establish the ataxia type based on clinical signs and instrumental examination data. Validated scales such as the Spinocerebellar Ataxia Composite Score (SACS) are increasingly used to quantify disease progression and monitor therapeutic outcomes (Potashman, et al., 2025). The only way to confirm the SCA type is molecular genetic analysis. All SCA are characterized by slowly progressive cerebellar dysfunction. Some SCA are more characterized by certain clinical manifestations than other ataxia types (Menon, et al., 2013; Platonov, et al., 2016; Colucci, 2025). A brief description of the clinical features of SCA1, 2, 3, 6, 7 types is presented in Table 2.

The first manifestations of SCA1 typically occur in the fourth decade of life, although juvenile and very late-onset cases have been documented; affected families frequently demonstrate genetic anticipation (earlier onset in successive generations). The clinical phenotype is dominated by progressive cerebellar ataxia accompanied by hyperreflexia, hypermetric saccades, nystagmus and dysarthria with mild dysphonia. In later stages patients commonly develop slow saccades, upward gaze palsy, hypotonia and muscle atrophy with reduced tendon reflexes, loss of joint-position and vibration sense, as well as cognitive deficits (notably frontal-executive

Table 2 Clinical features of individual forms of spinocerebellar ataxia (SCA)

Form SCA	Age of manifestation, years	Predominant neurological signs
SCA1	4 – 74	Ataxia, pyramidal signs, neuropathy, slow/hypermetric saccades, cognitive decline
SCA2	6 – 67	Marked saccadic slowing, neuropathy, amyotrophy
SCA3	5 – 65	Nystagmus, parkinsonism, spasticity, dystonia, neuropathy
SCA6	19 – 77	Isolated cerebellar syndrome, positional nystagmus
SCA7	0.1 – 76	Ataxia with retinal degeneration

dysfunction and verbal memory impairment), chorea, dystonia, bulbar signs, optic atrophy, ophthalmoparesis and maculopathy. (Giocondo, et al., 2018; Rüb, et al., 2012; Cui, et al., 2024; Klockgether, et al., 2025).

Although SCA1 can present with a broad neuropsychiatric spectrum, several large contemporary cohorts report a relatively spared global cognitive profile in many patients compared with other SCA subtypes (e.g., SCA6), while domain-specific executive and memory deficits are nevertheless observed in a subset of cases (Seidel, et al., 2012; Martins, et al., 2017; De Mattei, et al., 2023).

So, while ADSCA subtypes share core features of cerebellar dysfunction, SCA1 demonstrates a distinctive combination of oculomotor, pyramidal, peripheral neuropathy, and selective cognitive findings.

Genetics of spinocerebellar ataxia type 1 (SCA1)

Spinocerebellar ataxia type 1 (SCA1) is a polyglutamine (polyQ) neurodegenerative disease caused by an autosomal dominant CAG-repeat expansion in the ATXN1 gene located on chromosome 6p22.3. ATXN1 encodes ataxin-1, a nuclear protein highly expressed in cerebellar Purkinje cells, where it regulates transcription, RNA processing, and synaptic signaling (Shimobayashi, et al., 2018; Shimobayashi, et al., 2018). Region-specific BDNF alterations have also been documented in SCA1, reflecting selective vulnerability of cerebellar circuits (Andreska, et al., 2023). In healthy individuals, the polyQ tract contains ≤38 glutamines, whereas ≥39 uninterrupted repeats result in pathogenic misfolding of ataxin-1 and aggregation within neuronal nuclei. The repeat length strongly correlates with earlier onset, greater disease severity, and accelerated neurodegeneration (Wild, et al., 2023). Accordingly, SCA1 exhibits genetic anticipation, whereby one generation with the disease exhibits an earlier onset and more rapid progression than the previous generation (Matilla-Dueñas, et al., 2008). This is commonly extended by intergenerational polyglutamine studies and case reports of paternal inheritance

Interruptions by histidine residues within the CAG tract are increasingly recognized as a natural protective modifier: they reduce toxicity, slow repeat expansion, and shift the clinical threshold for disease onset (Choi, et al., 2024). Genetic counseling must consider this repeat structure, not only repeat number.

SCA1 displays genetic anticipation, most frequently with paternal transmission, leading to earlier onset and faster progression in subsequent generations (Paulson, 2009; Rossi, et al., 2023).

A growing body of work emphasizes the role of DNA mismatch-repair dysfunction in modulating repeat instability, particularly during paternal transmission, thereby explaining anticipation and enabling molecular-targeted therapeutic development (McMurray, 2010; Bhandari, 2025).

This is explained by germline repeat instability caused by secondary DNA structures (hairpins, R-loops) that impair mismatch and base-excision DNA repair (Kang, et al., 2009; McMurray, 2010; Bhandari, 2025). Somatic mosaicism arising from progressive expansions in vulnerable neuronal populations contributes to phenotype progression (Ricca, 2023).

Together, these mechanisms highlight SCA1 as a prime model for precision-therapy development, targeting transcriptional dysregulation, RNA-binding dysmetabolism, and DNA repair pathway modulation.

Modern neurogenetic studies confirm that hereditary ataxias are transmitted through four major inheritance patterns:

- Autosomal dominant transmission – a single pathogenic allele inherited from either parent is sufficient for disease manifestation, with a 50% recurrence risk in offspring regardless of biological sex (Coarelli, 2023).
- Autosomal recessive transmission – both parents are asymptomatic carriers of a pathogenic variant, and the probability of disease in offspring is 25% (Rossi, 2023).
- X-linked transmission – the mutant gene is located on the X chromosome, most often transmitted by a healthy female carrier, with predominantly male clinical expression due to hemizygosity (Ricca, 2023).
- Mitochondrial (maternal) inheritance – pathogenic variants in mtDNA are passed exclusively through the maternal line, presenting with multisystem neurological impairment including progressive ataxia (Naini, 2021).

The schematic overview in Figure 2 represents our conceptual synthesis, highlighting the sequential interplay of genetic, molecular, and cellular

events that drive SCA1 progression toward cerebellar neurodegeneration and motor dysfunction.

Thereby, scientists have determined that structured primary and secondary prevention strategies – including genetic counseling, carrier and presymptomatic testing, reproductive planning, lifestyle interventions, and longitudinal monitoring – are essential to reducing disability, improving functional outcomes and increasing life expectancy in patients with SCA1 (Kacher, 2024; Klockgether, 2025).

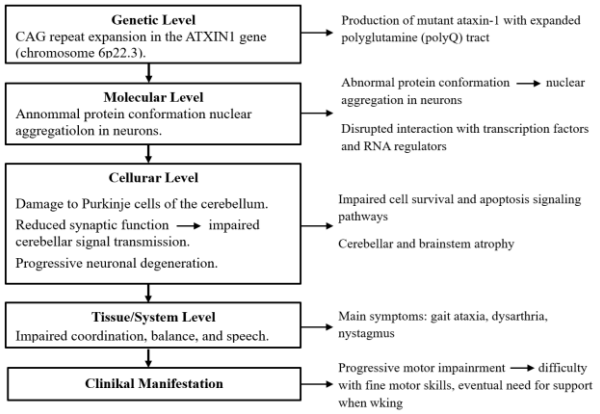

Fig. 2. Schematic representation of the major pathogenic mechanisms in Spinocerebellar Ataxia Type 1 (SCA1).

DISCUSSION

The results of our analysis of clinical, genetic, and epidemiological data on spinocerebellar ataxia type 1 (SCA1) demonstrate the critical importance of early molecular-genetic testing for precise diagnosis, disease onset prediction, and risk stratification. Quantification of expanded CAG repeats in the ATXN1 gene remains the strongest predictor of age at symptom onset and progression severity, which is essential for patient counseling and reproductive decision-making (Orr, 2007; van de Warrenburg, 2014, 2020; Shimobayashi, et al., 2018).

Recent European epidemiological studies show substantial heterogeneity in SCA1 prevalence, reflecting founder mutations, genetic drift, and differences in access to genetic diagnostics (Kacher, 2024; Rossi, 2023). High-frequency clusters such as in Poland, Yakutia, Northern Honshu, and South India indicate that haplotype-based population tracking is required for accurate surveillance and early detection strategies (Klockgether, 2019; Paulson, 2009; Barca, et al., 2019).

Clinically, SCA1 manifests with a broad spectrum of neurological impairments involving cerebellar, brainstem, motor, oculomotor, and, in selected cases, cognitive domains. Despite polyglutamine SCAs commonly causing cognitive involvement, recent findings confirm that SCA1 demonstrates a relatively preserved cognitive profile compared to SCA2, SCA3 and especially SCA6, though subtle executive dysfunction persists (Colucci, 2025; Wild, 2023; Rossi, 2023). These diverse clinical phenotypes, even among individuals with comparable CAG lengths, highlight the influence of epigenetic regulators, somatic mosaicism, and DNA repair polymorphisms (Kang, 2009).

A growing body of work emphasizes the role of DNA mismatch-repair dysfunction in modulating repeat instability, particularly during paternal transmission, thereby explaining anticipation and enabling molecular-targeted therapeutic development (McMurray, 2010; Bhandari, 2025).

Although no curative therapy currently exists, recent advances in personalized neurorehabilitation – including stabilometric biofeedback, intensive balance training, task-specific physiotherapy, and cerebellar-focused neuromodulation – have demonstrated measurable impact on functional performance and gait stability (Bonanno, et. al., 2024; Ilg, 2009; Schmitz-Hübsch, et. al., 2008; Colucci, 2025; Klockgether, 2025; Graciani, et. al., 2024).

The convergence of genetic diagnostics, biomarker development, and precision therapeutics supports a paradigm shift from purely symptomatic care toward future neuroprotective interventions (Cui, 2024; Klockgether, 2025; Wild, 2023).

Taken together, the evidence supports the necessity for a multidisciplinary management model integrating neurogenetics, advanced rehabilitation technologies, and structured monitoring of cognitive and motor function.

CONCLUSIONS

Spinocerebellar ataxia type 1 (SCA1) is a rare autosomal dominant neurodegenerative disorder characterized by progressive damage to the cerebellar cortex, brainstem structures, and associated neural pathways, resulting in significant motor and cognitive decline. Owing to its relentless progression and diverse clinical manifestations, SCA1 requires a multidisciplinary, personalized approach to diagnosis and management. Molecular genetic testing remains the gold standard for confirming the diagnosis, determining repeat expansion size, anticipating clinical trajectory, and designing

individualized monitoring strategies. Nevertheless, the broad clinical polymorphism, anticipation phenomenon, and population-specific variability of SCA1 demand expanded genomic research, including high-precision genotype-phenotype correlations, large-scale epidemiological surveillance, and development of prediction models for disease onset and progression.

Currently, physical therapy and symptomatic management remain the main approaches that can help preserve functional independence and improve quality of life. However, high-quality randomized clinical trials evaluating the comparative effectiveness of next-generation rehabilitation modalities – such as virtual and augmented reality, robot-assisted therapy, stabilometric balance training, non-invasive cerebellar stimulation, and exergaming – are still limited and urgently needed.

At the same time, fundamental advances in gene-targeted therapies open real opportunities to modify the disease course or even prevent onset in pre-symptomatic carriers. Integration of biomarkers, wearable digital phenotyping, and artificial intelligence in monitoring could accelerate therapeutic development and improve individualized clinical decision-making.

Therefore, expanding international cooperation, patient registries, biobanking, and longitudinal cohort studies is crucial to accelerate the translation of scientific discoveries into effective treatments and ultimately reduce the global burden of SCA1.

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