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Investment memorandum

11 Jun 2026

First-generation therapy forecast:

Spinocerebellar ataxia type 3

Categories: rare genetic diseases, rare neurological diseases

Gene therapies

Forecast for the first gene therapies based drug for the disease.

Disease landscape:

Orphan designations: **1**

Approved drugs: **0**

De-risked by AI:

Top 1.0%
of research

Highest probability of becoming an approved therapy from the research stage.

Disease overview

AI-generated summary. Verify critical details against original sources.

Spinocerebellar ataxia type 3

Synonyms: Azorean disease of the nervous system, MJD, Machado disease, Machado-Joseph disease, Nigro-spino-dentatal degeneration with nuclear ophthalmoplegia, SCA3.

Spinocerebellar Ataxia Type 3 (SCA3/MJD) is an autosomal dominant neurodegenerative disorder caused by a CAG repeat expansion in the ATXN3 gene, producing toxic polyglutamine aggregates. It manifests with progressive cerebellar ataxia, dysarthria, pyramidal signs, oculomotor abnormalities, and peripheral neuropathy. Non-motor features include sleep disorders (REM sleep behavior disorder), neuropathic pain, and psychiatric comorbidities. Symptom onset typically occurs in adulthood (2nd–5th decade), with progressive disability leading to wheelchair dependence within 10–20 years. Anticipation correlates with longer CAG repeats [1] [6] [16].

Population

- Prevalence: 1–9/100,000 globally, with hotspots in Portugal, Brazil, and China [6] [12]
- Most common inherited ataxia worldwide (20–50% of dominant cases) [5] [17]
- Onset ranges from childhood to late adulthood (median 30–40 years) [2] [6]

Current Therapeutic Strategies

- Symptomatic management: Pharmacotherapy for spasticity (baclofen), Parkinsonism (levodopa), and neuropathic pain (antidepressants) [6] [8]
- Rehabilitative support: Physical/occupational therapy to maintain mobility; speech therapy for dysphagia/dysarthria [18] [20]
- Experimental approaches: Antisense oligonucleotides, CRISPR-based gene silencing, and HDAC inhibitors in clinical trials [3] [13] [16]

Burden of the Disease

- High fall risk (80% annual incidence) with injuries in 85% of fallers [2] [9]
- Progressive dysphagia increases aspiration pneumonia risk (leading mortality cause) [4] [6]
- 60% report depression/suicidal ideation; 100% require caregiver support within 10–15 years [2] [9] [17]

Literature overview

Most influential articles for LLM-classifier prediction.

14.2% influence 14 Jun 2019

Restoring brain cholesterol turnover improves autophagy and has therapeutic potential in mouse models of spinocerebellar ataxia.

Spinocerebellar ataxias (SCAs) are devastating neurodegenerative disorders for which no curative or preventive therapies are available. Deregulation of brain cholesterol metabolism and impaired brain cholesterol turnover have been associated with several neurodegenerative diseases. SCA3 or Machado-Joseph disease (MJD) is the most prevalent ataxia worldwide. We show that cholesterol 24-hydroxylase (CYP46A1), the key enzyme allowing efflux of brain cholesterol and activating brain cholesterol turnover, is decreased in cerebellar extracts from SCA3 patients and SCA3 mice. We investigated whether reinstating CYP46A1 expression would improve the disease phenotype of SCA3 mouse models. We show that administration of adeno-associated viral vectors encoding CYP46A1 to a lentiviral-based SCA3 mouse model reduces mutant ataxin-3 accumulation, which is a hallmark of SCA3, and preserves neuronal markers. In a transgenic SCA3 model with a severe motor phenotype we confirm that cerebellar delivery of AAVrh10-CYP46A1 is strongly neuroprotective in adult mice with established pathology. CYP46A1 significantly decreases ataxin-3 protein aggregation, alleviates motor impairments and improves SCA3-associated neuropathology. In particular, improvement in Purkinje cell number and reduction of cerebellar atrophy are observed in AAVrh10-CYP46A1-treated mice. Conversely, we show that knocking-down CYP46A1 in normal mouse brain impairs cholesterol metabolism, induces motor deficits and produces strong neurodegeneration with impairment of the endosomal-lysosomal pathway, a phenotype closely resembling that of SCA3. Remarkably, we demonstrate for the first time both in vitro, in a SCA3 cellular model, and in vivo, in mouse brain, that CYP46A1 activates autophagy, which is impaired in SCA3, leading to decreased mutant ataxin-3 deposition. More broadly, we show that the beneficial effect of CYP46A1 is also observed with mutant ataxin-2 aggregates ...

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12.2% influence 7 Dec 2021

miRNA-Mediated Knockdown of ATXN3 Alleviates Molecular Disease Hallmarks in a Mouse Model for Spinocerebellar Ataxia Type 3.

Open article

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Spinocerebellar ataxia type 3 (SCA3) is a neurodegenerative disorder caused by the expansion of a CAG repeat in the ATXN3 gene. This mutation leads to a toxic gain of function of the ataxin-3 protein, resulting in neuronal dysfunction and atrophy of specific brain regions over time. As ataxin-3 is a dispensable protein in rodents, ataxin-3 knockdown by gene therapy may be a powerful approach for the treatment of SCA3. In this study, we tested the feasibility of an adeno-associated viral (AAV) vector carrying a previously described artificial microRNA against ATXN3 in a striatal mouse model of SCA3. Striatal injection of the AAV resulted in good distribution throughout the striatum, with strong dose-dependent ataxin-3 knockdown. The hallmark intracellular ataxin-3 inclusions were almost completely alleviated by the microRNA-induced ATXN3 knockdown. In addition, the striatal lesion of dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32) in the SCA3 mice was rescued by ATXN3 knockdown, indicating functional rescue of neuronal signaling and health upon AAV treatment. Together, these data suggest that microRNA-induced ataxin-3 knockdown is a promising therapeutic strategy in the treatment of SCA3.

9.1% influence 22 Feb 2025

CAG-targeted brain-permeable therapy tested in biallelic humanized polyQ mouse models.

Open article

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In polyglutamine (polyQ) diseases, including Huntington disease (HD) and spinocerebellar ataxia type 3 (SCA3), targeting the mutant CAG tract in mRNA could be a therapeutic strategy for lowering pathogenic protein. We explored the viability of this therapeutic strategy in vivo at the level of the reagent design, toxicity, systemic delivery, brain regions transduction, silencing efficiency, and allele preference. We designed a series of CAG-directed short hairpin RNAs (shRNAs) based on a previous A2 reagent, allele selective in vitro. Humanized HD (Hu128Q/21Q) and SCA3 (Ki150Q/21Q) mice with mutant ~100 CAGs and normal 21 CAGs alleles were used to simulate biallelic conditions occurring in patients. We administered AAV-PHP.eB shRNAs-encoding vectors into the blood as an equivalent of non-invasive CAG-directed brain-targeted therapy crossing the blood-brain barrier. We demonstrate that optimized

CAG-targeted A4(P10) and A4(P10,11) shReagents can lower mutant huntingtin and ataxin-3 protein and its aggregates by targeting brain regions selectively and with diminished toxicity compared to other tested shRNAs. The important considerations of the approach are the silencing efficiency depending on the transduction region and careful dose adjustment. Moreover, the CAG approach could be suitable to target somatic expansion. Our work paves the way toward developing the therapy for polyQ diseases, potentially shortening drug development.

8.8% influence 2 Oct 2025

rAAV-Delivered Bicistronic Artificial microRNAs for Allele-Specific Silencing Improve Motor and Molecular Outcomes in Spinocerebellar Ataxia Type 3

ABSTRACT Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease, is an autosomal dominant neurodegenerative disorder caused by the expansion of CAG trinucleotide repeats in the ATXN3 gene. This mutation induces a toxic gain-of-function of the ATXN3 protein, leading to neurodegeneration, particularly in the cerebellum and brainstem. Despite extensive research, no disease-modifying treatments are available for SCA3 patients. In this study, we developed and tested a novel therapeutic strategy using recombinant adeno-associated virus (rAAV) to deliver bicistronic artificial microRNAs designed to selectively silence the mutant ATXN3 allele. Through in vitro screening, we identified a lead construct (miATXN3-I0x2) that effectively and specifically silenced the mutant allele by targeting of a single nucleotide polymorphism (SNP) associated with the repeat expansion. This construct was packaged into rAAV9 and delivered via intra-cerebellar administration into two mouse models of SCA3, resulting in robust suppression of mutant ATXN3 in the cerebellum. To assess long-term efficacy, we performed intra-cisterna magna (ICM) injections of rAAV9-miATXN3-I0x2 in a severe SCA3 transgenic mouse model. Widespread distribution of viral vectors and miATXN3 copies was observed in disease-relevant brain regions. Treated animals exhibited significant and sustained improvements in motor function at 5, 8, and 11 weeks post-injection. Histological analyses showed a reduction in mutant ATXN3 aggregates and a trend toward preventing shrinkage of cerebellar molecular layer. These findings were supported by dose-dependent reductions in mutant ATXN3 mRNA levels and decreased expression of neuroinflammatory markers in the cerebellum. Additionally, a significant increase of the neuronal marker NeuN was also observed in treated animals. Finally, transcriptomic profiling of the cerebellum demonstrated that treated transgenic animals ...

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7.3% influence 5 Aug 2025

Differential impact of mutant Ataxin-3 in hindbrain regions: further evidence of white matter loss as a core pathological feature.

Spinocerebellar ataxia type 3 (SCA3) is a devastating neurodegenerative disorder that belongs to the family of polyglutamine disorders. Although the CAG repeat expansion underlying SCA3 was discovered 30 years ago, there is still no cure or treatment able to delay its progression. One of the reasons for this lag may be attributed to the phenotypic and neuropathological heterogeneity among individuals. To overcome this gap, we aimed to delve into the specific contributions of hindbrain regions that have been consistently reported to be the most degenerated in SCA3 patients, the cerebellar cortex, namely lobules IV-V, VIII and IX, deep cerebellar nuclei and the pons. For this purpose, we used lentiviral vectors to deliver the SCA3-causing gene, mutant Ataxin-3, to these specific regions in mice. We observed that the overexpression of mutant Ataxin-3 in different hindbrain regions led to the formation of Ataxin-3 aggregates in neuronal cells and mild motor impairments. Neurons in the pons were more vulnerable to mutant Ataxin-3 overexpression than in the cerebellum. There was also an increase in astrocytes and microglia recruitment that may explain myelin damage and, consequently, white matter loss in the cerebellum. Indeed, cerebellar white matter loss was the most broadly observed pathological feature upon overexpression of mutant Ataxin-3 in different regions of the hindbrain. In conclusion, we confirm that cerebellar white matter changes are a consistent feature of SCA3 neuropathology, and demonstrate that the region-specific lentiviral models offer a valuable platform to study early, selective pathological mechanisms and support future therapeutic testing.

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Related companies

AI-generated summary of companies related to the forecast. Verify critical details against original sources.

Company	Lead candidate	Stage
uniQure (Lexington, MA / Amsterdam, NL)	**AMT-150** AAV5-delivered microRNA (miQURE™) gene-silencing candidate designed to lower ATXN3 (non-allele-specific) via intrathecal/cisterna magna delivery. Presented preclinical proof-of-concept (mouse, NHP) showing mutant ataxin-3 lowering.	Preclinical / IND-enabling (pre-clinical data presented; IND/CTA-enabling studies reported). [1] [2] [3]
Vico Therapeutics (Leiden, Netherlands)	**VO659** Antisense oligonucleotide (ASO) that targets expanded CAG repeat transcripts to reduce mutant polyQ proteins (designed to engage multiple polyglutamine diseases including SCA3). Administered intrathecally in a first-in-human Phase 1/2a trial.	Clinical — Phase 1/2a (first patient dosed; NCT05822908 recruiting/ongoing updates). [1] [2] [3]
Cure Rare Disease (CRD) (Boston, USA)	**Unspecified ASO clinical candidate (CRD SCA3 program)** Non-profit biotech developing an antisense oligonucleotide therapy targeting ATXN3 for SCA3; program progressed through in-vivo studies and non-GLP tox to identify a clinical candidate and is funded to complete IND-enabling manufacturing/toxicology and submit an IND.	Preclinical / IND-enabling (CIRM grant awarded to complete IND-enabling work and prepare clinical trial submission). [1] [2]
Arrowhead Pharmaceuticals / Sarepta Therapeutics (Pasadena, CA / Cambridge, MA)	**ARO-ATXN3 (Arrowhead TRiM™ RNAi program; licensed to Sarepta)** siRNA/RNAi program (Arrowhead TRiM platform) designed to reduce ATXN3 expression for SCA3. Program is preclinical under Arrowhead and was licensed to Sarepta for further development/manufacture.	Preclinical (preclinical candidate ARO-ATXN3; partnership/licensing to Sarepta with plans to progress toward CTA/IND readiness). [1] [2] [3]

SineuGene Therapeutics (Beijing, PRC)	**SG-006 (ATXN3 program listed by company)** Company webpage and pipeline listings indicate an ASO (and/or AAV/ASO approaches) discovery program targeting ATXN3/SCA3; described as preclinical discovery/development work to selectively reduce mutant ATXN3.	**Preclinical / discovery.** [1] [2]
Biogen (Cambridge, MA)	**BIIB132** Intrathecal antisense candidate (BIIB132) was being developed for SCA3 (MERA study) but the program was halted after nonclinical safety and pharmacodynamic assessment.	**Clinical program stopped / withdrawn (Phase 1 MERA study stopped/withdrawn).** [1] [2]

Drug discovery timeline

Orphan designations and approvals related to the disease.

Drug	Therapy type		Orphan designation	Approval	Sponsor
trehalose	small molecules	FDA	2014-11-17	nan	Seelos Therapeutics, Inc.