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# A Brief Review on Spinocerebellar Ataxia and its Treatment

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## ABSTRACT

Ataxia is defined as a neurological sign including the lack of muscle movement coordination particularly of gait abnormality, talking changes, and also abnormality in eye actions. In ataxia, a part of nervous system is dysfunction which is also coordinate movement such as the cerebellum. In adults, ataxia can be acquired or genetic disorder. The Spinocerebellar ataxia is hereditary, progressive, degenerative, genetic disease or often fatel. There are no effective treatment and cure for Spinocerebellar ataxia (SCA). Spinocerebellar ataxia is a progressive disorders in which the cerebellum slowly degenerates. An average results estimated that 150,000 peoples in the United States have a diagnosis of Spinocerebellar ataxia (SCA) at any given time periods. Spinocerebellar ataxia (SCA) can affects anybody persons of at all ages.A current systemic review shows that the global prevalence of Spinocerebellar ataxia (SCA) is 3 in 100,000 people. However, a wide regional variation exists. SCA3 is common subtype around the world, SCA2 is additional prevalent in Cuba than SCA3 whilst SCA7 is the most frequent subtype in Venezuela due to strong founder's effect. SCA6 is 1 of the most general ADCA in the North of England, with a global prevalence of 5.2/100,000.There are many different types of spinocerebellar ataxia (SCA) and each may have unique signs and symptoms. And these includes: Problems with coordination and balance (ataxia), Uncoordinated walk, poor hand eye coordination, Abnormal speech, Involuntary eye movement, Vision problems, Difficulty processing, Learning and remembering information. The hereditary ataxias are categorized by mode of inheritance and causative gene or chromosomal locus. The hereditary ataxias can be inherited in an autosomal dominant, autosomal recessive,or X-linked manner. Some types of SCA inherited in an autosomal dominant manner are caused by trinucleotide repeat expansions. A trinucleotide repeat is a segment of DNA that is repeated a number of times. It is normal for these repeats to exist and they typically do not cause any problems. Some Spinocerebellar ataxia SCAs remain unspecified and cannot be precisely diagnosed, but in the previous decades genetic testing has permissible precise identification of dozens of different SCAs and extra tests are being added each year. The spinocerebellar ataxia are classified SCA1 to SCA35for the treatment of SCA. There are no effective and cure treatment available for the spinocerebellar ataxia (SCA). But there are some methods; therapies and treatment are available which will be fruitful for the SCA. And these included the following: Meditation, Zolpidem, N-acetyl leucine, Rehabilitation.

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## Introduction

Ataxia is defined as a neurological sign including the lack of muscle movement coordination particularly of gait abnormality, talking changes, and also abnormality in eye actions. In ataxia, a part of nervous system is dysfunction which is also coordinate movement such as the cerebellum. In adults, ataxia can be acquired or genetic disorder. The Spinocerebellar ataxia is hereditary, progressive, degenerative, genetic disease or often fatel. There are no effective treatment and cure for Spinocerebellar ataxia (SCA). Spinocerebellar ataxia is a progressive disorders in which the cerebellum slowly degenerates.A average results estimated that 150,000 peoples in the United States have a diagnosis of Spinocerebellar ataxia (SCA) at any given timeperiods. Spinocerebellar ataxia (SCA) can affects anybody persons of at all ages [1-5].

## Epidemiology

A current systemic review shows that the global prevalence of Spinocerebellar ataxia (SCA) is 3 in 100,000 people. However, a wide regional variation exists. SCA3 is common subtype around the world. SCA2 is additional prevalent in Cuba than SCA3 whilst SCA7 is the most frequent subtype in Venezuela due to strong founder's effect. SCA6 is 1 of the most general ADCA in the North of England, with a global prevalence of 5.2/100,000 [6-12]. There are a variety of mutations described in SCA, although repeat expansions still account for nearly half of SCA diagnosis in European cohort. In 412 undiagnosed autosomal dominant cerebellar ataxia (ADCA) without recognized repeat expansion, 59 individuals (14.3%) were found to harbor pathogenic variants. 35 of these variants (8.5%) belong to channel genes. In contrast, conventional mutations in channel genes are very rare in Han Chinese cohort. In another cohort of 194 individuals with undiagnosed ADCA, SCA14 accounts for 6.7% of the studied population[13-15].

## Molecular Pathophysiology of Spinocerebellar Ataxia

The autosomal dominant spinocerebellar ataxias (SCAs) are a group of neurodegenerative diseases, clinically and genetically heterogeneous, characterized by loss of balance and motor coordination due to dysfunction of the cerebellum and its afferent and efferent connections. Despite a well-described clinical and pathological phenotype, the molecular and cellular events that underlie neurodegeneration are still poorly understood. Compelling evidence points to major aetiological roles for interference with transcriptional regulation, protein aggregation and clearance, the ubiquitin-proteasome system and alterations of calcium homeostasis in the neuronal loss observed during the neurodegenerative process. But novel molecular routes that might be disrupted during disease progression are also being identified. These pathways could act independently or, more likely, interact and enhance each other, triggering the accumulation of cellular damage that eventually leads to dysfunction and, ultimately, the demise of neurons through a series of multiple events. This suggests that simultaneous targeting of several pathways might be therapeutically necessary to prevent neurodegeneration and preserve neuronal function. Understanding how dysregulation of these pathways mediates disease progression is leading to the establishment of effective therapeutic strategies in vivo, which may prove beneficial in the treatment of SCAs. Herein, we review the latest evidence for the proposed molecular processes to the pathogenesis of dominantly inherited spinocerebellar ataxias and the current therapeutic strategies.

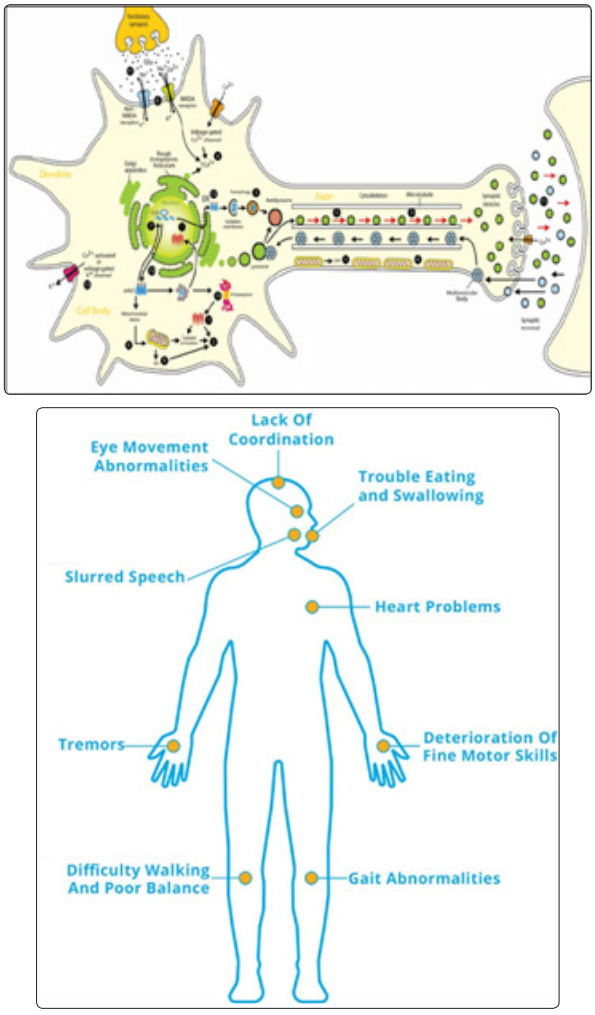



**Figure 1:** Molecular mechanisms of neurodegeneration in spinocerebellar ataxia

## Sign and Symptoms

There are many different types of spinocerebellar ataxia (SCA) and each may have unique signs and symptoms. And these includes [16-17].

A. Problems with coordination and balance (ataxia)
B. Uncoordinated walk
C. Poor hand-eye coordination
D. Abnormal speech (dysarthria)
E. Involuntary eye movement
F. Vision problems
G. Difficulty processing, learning, and remembering information


## Causes of Spinocerebellar ataxia

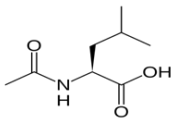
The hereditary ataxias are categorized by mode of inheritance and causative gene or chromosomal locus. The hereditary ataxias can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. Mutations in many different genes are known to cause the different types of spinocerebellar ataxia (SCA). For some types, the gene known to cause it has been identified, while in others, the genetic cause is still unknown (about 40% to 25% of the cases). Some types of SCA inherited in an autosomal dominant manner are caused by trinucleotide repeat expansions. A trinucleotide repeat is a segment of DNA that is repeated a number of times. It is normal for these repeats to exist and they typically do not cause any problems. However, a greater than normal number of repeats can interfere with the function of the gene, resulting in a genetic condition. Trinucleotide repeats are unstable and can change in length when passed from parent to child. An increased number of repeats often leads to an earlier age of onset and more severe disease[18-19].

**Classification of Spinocerebellar ataxia**

| SCA Type | Average Onset (in Yrs) | Average Duration ( in Yrs) | What the patient experiences | Common origin | Problems with DNA |
|---|---|---|---|---|---|
| SCA1(ATXN1) | 4th decade (<10 to >60) | 15 years (10–35) | Hypermetric saccades, slow saccades, upper motor neuron (note: saccades relates to eye movement) | Z | CAG repeat, 6p (Ataxin 1) |
| SCA2 (ATXN2) | 3rd–4th decade (<10 to >60) | 10 years (1–30) | Diminished velocity saccades areflexia (absence of neurologic reflexes) | Cuba | CAG repeat, 12q |
| SCA3 (MJD) (ATXN3) | 4th decade (10–70) | 10 years (1–20) | Also called Machado-Joseph disease (MJD)[11] Gaze-evoked nystagmus (a rapid, involuntary, oscillatory motion of the eyeball) upper motor neuron slow saccades | Azores (Portugal) | CAG repeat, 14q |
| SCA4 (PLEKHG4) | 4th–7th decade (19–72) | Decades | Areflexia (absence of neurologic reflexes) | | Chromosome 16q |
| SCA5 (SPTBN2) | 3rd–4th decade (10–68) | >25 years | Pure cerebellar | | Chromosome 11 |
| SCA6 (CACNA1A) | 5th–6th decade (19–71) | >25 years | Downbeating nystagmus, positional vertigo Symptoms can appear for the first time as late as 65 years old. | | CAG repeat, 19p Calcium channel gene |
| SCA7 (ATXN7) | 3rd–4th decade (0.5–60) | 20 years (1–45; early onset correlates with shorter duration) | Macular degeneration, upper motor neuron, slow saccades | | CAG repeat, 3p (Ataxin 7) |
| SCA8 (IOSCA) | 39 yrs (18–65) | Normal lifespan | Horizontal nystagmus (a rapid, involuntary, oscillatory motion of the eyeball), instability, lack of coordination | | CTG repeat,[15] 13q |
| SCA10 (ATXN10) | 36 years | 9 years | ataxia, seizures | Mexico | Chromosome 22q linked pentanucleotide repeat |
| SCA11 (TTBK2) | 30 yrs (15–70) | Normal lifespan | Mild, remain ambulatory (able to walk about on one's own) | | 15q |
| SCA12 (PPP2R2B) | 33 yrs (8–55) | | Head and hand tremor, akinesia (loss of normal motor function, resulting in impaired muscle movement) | | CAG repeat, 5q |
| SCA13(KCNC3) | Childhood or adulthood depending on mutation | Depending on KCNC3 (a kind of gene) | Mental retardation | | 19q |
| SCA14 (PRKCG) | 28 yrs (12–42) | Decades (1–30) | Myoclonus (a sudden twitching of muscles or parts of muscles, without any rhythm or pattern, occurring in various brain disorders) | | 19q |
| SCA16 (ITPR1) | 39 yrs (20–66) | 1–40 years | Head and hand tremor | | 8q |
| SCA17 (TBP) | | | | | CAG repeat, 6q (TATA-binding protein) |
| SCA19, SCA22(KCND3) | | | Mild cerebellar syndrome, dysarthria | | |
| SCA25 | 1.5–39 yrs | Unknown | Ataxia with sensory neuropathy, vomiting and gastrointestinal pain. | | 2p |
| SCA27 (FGF14) | 15–20 yrs | Unknown | ataxia with poor cognition, dyskinesias and tremor | | FGF14 13q34 |

| | | | | | |
|---|---|---|---|---|---|
| SCA35 | 40–48 years | Unknown | gait and limb ataxia, dysarthria, ocular dysmetria, intention tremor, pseudobulbar palsy, spasmodic torticollis, extensor plantar responses, reduced proprioception and hyperreflexia | China | transglutaminase 6 (TGM6) located at chromosome 20p13 |

Others include SCA18, SCA20, SCA21, SCA23, SCA26, SCA28, and SCA29.[20-37]



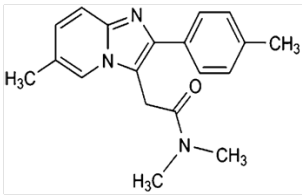
It is an orally administered drug. N-Acetyl-Leucine has been granted multiple orphan drug designations from the U.S.FDA for the treatment of various genetic diseases including the SCA. And a multinational clinical trial investigating the N-Acetyl-L-Leucine for the treatment of a related inherited cerebellar ataxia, Ataxia-Telangiectasia, beganin 2019 [42].

**Rehabilitation**

Physical therapists can assist patients in maintaining their level of independence through therapeutic exercise programmes. In general, physical therapy emphasises postural balance and gait training for ataxia patients. A randomised clinical trial revealed that an intensive rehabilitation program with physical and occupational therapies for patients with degenerative cerebellar diseases can significantly improve functional gains in ataxia, gait, and activities of daily living. Occupational therapists may assist patients with incoordination or ataxia issues through the use of adaptive devices [43-44].

**Zolpidem**

Zolpidem is N, N,6-trimethyl-2-p-tolylimidazo[1,2-a] pyridine-3-acetamide L-(+)tartrate (2:1). Zolpidem tartrate is a white to off-white crystalline powder that is sparingly soluble in water, alcohol, and propylene glycol.



One report described some improvement in the symptoms with zolpidem 10 mg infour out of five family members with SCA type 2, and a trial of 20 patients with SCA3 foundthatvarenicline led to improvement in some, but not all of the symptoms[45].

**Conclusion**

Tremendous scientific progresshas occurred in the understanding of spinocerebellarataxia. Next-generation sequencing has helped improve the diagnostic accuracy of SCAsand discover new disease mechanisms. New technologies such as nanoporeandExpansionHunter may help improve diagnosis of known and new SCAs with repeatexpansions in future. As outlined, evidence suggests that genes in DNA repair pathwaysappear to play a modifying role. An international GWAS of repeat expansion ataxiawould be worthwhile to pursue these potential therapeutic targets. Meanwhile, emerging therapies for neurogenetic diseases such as ASOs also provide physicians and patients of SCA hopes of effective treatments in the near future.

**References**

1. DystaxiaNd (2014)the American Heritage Stedman's Medical Dictionary, Retrieved from ictionary.comwebsite: https://www.dictionary.com/browse/dystaxia.
2. Bird TD (2002) Approaches to the patient with neurogenesis disease, Neurologic clinics 20: 619-626.
3. Nance MA (2003) Genetic testing in inherited ataxias. Seminars in pediatric neurology. 10: 223-231.
4. Taroni F, Di Donato S (2004) Pathways to motor in coordination: the inherited ataxias. Nat Rev Neurosci5: 641-655.
5. Rossi M, Perez-Lloret, SDoldan, LCerquetti, DBalej et al (2014). Autosomal dominant cerebellar ataxias: A systematic reviewofclinicalfeatures. European Journal of Neurology 21: 607-615.
6. Ruano L, Melo C, Silva MC, Coutinho P (2014). The global epidemiology ofhereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. Neuroepidemiology 42:174-183.
7. De Castilhos RM, Furtado GV, Gheno TC, Schaeffer P, Russo A, et al(2014)Spin cerebellar ataxias in Brazil–frequencies and modulating effects of related genes, Cerebellum 13:17-28.
8. Coutinho P, Ruano L, Flourier JL, Cruz VT, Barros J, et al (2013)hereditary ataxia and spastic paraplegia in Portugal: a population-based prevalence study. JAMA Neurol 70:746-755.
9. Zaltzman R, Sharony R, Klein C, Gordon CR (2016) Spin cerebellar ataxia type 3in Israel: phenotype and genotype of a Jew Yemenite subpopulation. J Neurol 263:2207-2214.
10. Gonzalez-Zaldivar Y, Vazquez-Mojena Y, Laffita-Mesa JM, Almaguer-Mederos LE,Rodriguez-Labrada R, et al (2015) Epidemiological, clinical, and molecular characterization of Cuban families with spin cerebellar ataxia type 3/Machado–Joseph disease. Cerebellum Ataxias 2:1.
11. Paradisi I, Ikonomu V, Arias S (2016) spin cerebellar ataxias in Venezuela: genetic epidemiology and their most likely ethnic descent. J Hum Genet 61: 215-222.
12. Bargiela D, Yu-Wai-Man P, Keogh M, Horvath R, Chinnery PF (2015) Prevalence of neurogenetic disorders in the North of England. Neurology 85: 1195-1201.
13. Coutelier M, Coarelli G, Monin ML, Konop J, Davoine CS, et al (2017) A panel study on patients with dominant cerebellar ataxia highlights the frequency of channelopathies. Brain 140:1579-1594.
14. Chen Z, Wang P, Wang C, Peng Y, Hou X, et al (2018) Updated frequency analysis of spin cerebellar ataxia in China. Brain 14:e22.
15. Chelban V, Wiethoff S, Fabian-Jessing BK, Haridy NA, Khan A, et al. (2018) Genotype phenotype correlations, dystonia and disease progression inspinocerebellar ataxia type 14. MovDisord.
16. Opal P,Zoghbi (2010)HY.TheSpinocerebellar Ataxias. UP TO Date. http://www.uptodate.com/contents/the spinocerebellar ataxia.
17. Autosomal Dominant Hereditary Ataxia. NORD. April2014;http://rarediseases.org/raredisease-information/

rare-diseases/byID/674/viewFullReport. (http://rarediseases.org/raredisease-information/rarediseases/byID/674/viewFullReport).
18. Usdin K, House NS, freudenriech CH (2015). Repeat instability during DNA repair: Insights from model systems. Crit. Rev. Biochem. Mol. Biol. 50: 142 167.
19. Autosomal Dominant Hereditary Ataxia.NORD. April2014; http://rarediseases.org/raredisease-information/rare-iseases/byID/674/viewFullReport. http://rarediseases.org/rarediseaseinformation/rare-diseases/byID/674/viewFullReport).
20. Orr HT, Zoghbi HY (2007) Trinucleotiderepeat disorders. Annual review of neuroscience30:575–621.
21. Taroni F, DiDonato S (200) Pathways to motor incoordination: the inherited ataxias. NotreNeurosci 5: 641–655.
22. Paulson HL (2007) dominantly inherited ataxias: lessons learned from Machado-Joseph disease/spin cerebellar ataxia type 3. Seminars in neurology 27:133-142.
23. Ikeda Y, Dick KA, Weatherspoon MR, Gincel D, Armbrust KR, et al. (2006) Spectrum mutations cause spin cerebellar ataxia type 5. Nature genetics 38: 184-190.
24. Kordasiewicz HB, Gomez CM (2007) Molecular pathogenesis of spin cerebellar ataxia type 6.Neurotherapeutics. 4: 285-294.
25. Garden GA, La Spade AR (2008) Molecular pathogenesis and cellular pathology of spin cerebellar ataxia type 7 neurodegeneration. Cerebellum (London, England) 7: 138-49.
26. Day JW, Schut LJ, Moseley ML, Durand AC, Ranum LP (2000) Spin cerebellar ataxia type 8: clinical features in a large family. Neurology 12: 649-657.
27. Matsuura T, Yamagata T, Burgess DL, Rasmussen A, Grewal RP, et al. (2000) large expansion of the ATTCT pent nucleotide repeat in spin cerebellar ataxia type 10. Nature genetics 26:191-194.
28. Houlden H, Johnson J, Gardner-Thorpe C, Lashley T, Hernandez D, et al. (2007) Mutations inTTBK2, encoding a kinase implicated in tau phosphorylation, segregate with spin cerebellar ataxia type 11. Nature genetics 39: 1434-1436.
29. Holmes SE, Hearn EO, Ross CA, Margolis RL (2001) SCA12: an unusual mutation leads to anunusualspinocerebellar ataxia. Brain research bulletin 56:397-403.
30. Waters MF, Minassian NA, Stevanin G, Figueroa KP, Bannister JP, et al. (2006) Mutations involtage-gated potassium channel KCNC3 cause degenerative and developmental central nervous system phenotypes. Nature genetics 38:447-451.
31. Chen DH, Brkanac Z, Verlinde CL, Tan XJ, Bylenok L, et al. (2003) Missense mutations in the regulatory domain of PKC gamma: a new mechanism for dominant no episodic cerebellar ataxia. American journal of human genetics72: 839-849.
32. Dalski A, Mitulla B, Burk K, Schattenfroh C, Schwinger E, et al. (2006) Mutation of the highly conserved cysteine residue 131 of the SCA14 associated PRKCG gene in a family with slow progressive cerebellar ataxia. Journal of neurology. 253:1111–1112.
33. Iwaki A, Kawano Y, Miura S, Shibata H, Matsuse Det al. (2008) Heterozygous deletion of ITPR1,but not SUMF1, in spin cerebellar ataxia type 16. Journal of medical genetics 45:32-35.
34. Nakamura K, Jeong SY, Uchihara T, Anno M, Nagashima K, et al. (2001) SCA17, a novel autosomal dominant cerebellar ataxia caused by an expanded polyglutamine in TATA-binding protein.Huanmolecular genetics10:1441-1448.
35. Knight MA, Hernandez D, Diede SJ, Dauwerse HG, Rafferty I, et al. (2008) a duplication at chromosome 11q12.2-11q12.3 is associated with spin cerebellar ataxia type 20. Human molecular genetics 17:3847-3853.
36. Van Swieten JC, Brusse E, de Graaf BM, Krieger E, van de Graaf R, et al. (2003) A mutation in the fibroblast growth factor 14 gene is associated with autosomal dominant cerebellar ataxia. American journal of human genetics 72: 191-199.
37. Perlman, Susan L. (2016). Evaluation and Management of Ataxic Disorders: An Overview for Physicians. Minneapolis: National Ataxia Foundation. 6:14-24.
38. OpalP,Zoghbi, HY (2016) the spin cerebellar ataxia. Up To Date http://www.uptodate.com/contents/the-spinocerebellar-taxias.www.uptodate.com/contents/the-spinocerebellar-ataxias).
39. Autosomal Dominant Hereditary Ataxia. NORD. April (2014) http://rarediseases.org/raredisease-information/rare-diseases/byID/674/ viewFullReport(http://rarediseases.org/rarediseaseinformation/rare-diseases/byID/674/viewFullReport).
40. Cruts Marc, EmgelborghsSebastiaan, van der zee Julie, Van Broeckhoven, (1993) Christine "C9orf72-Related Amyotrophic Lateral Sclerosis and Front temporal Dementia. Gene Reviews® [Internet]. Seattle (WA): University of Washington.
41. N Acetyl, L Leucine (2019) for Ataxia-Telangiectasia (A-T)-Full Text View- ClinicalTrials.gov". Clinical trials.gov. Retrieved 08 011.
42. Marsden J, Harris C (2011) Cerebellar ataxia: Pathophysiology and rehabilitation. Clinical Rehabilitation. 25: 195 216.
43. Miyai I, ITO M, Hattori N, Mihara M, Hatakenaka M,et al.(2011) Crebellar ataxia rehabilitation realists collaboration Cerebellar ataxia rehabilitation trials in degenerative cerebellar diseases,. Neurorehabilitation and Neural Repair 26: 515 522.
44. Opal P, Zoghbi HY (2016) the Spin cerebellar Ataxias. Up-to-date.
45. Duenas AM, Goold R, Giunti P (2006) Molecular pathogenesis of spin cerebellar ataxias. Brain 129:1357-1370.