Asian Journal of Pediatric Research

Volume 16, Issue 5, Page 1-9, 2026; Article no.AJPR.158485
ISSN: 2582-2950

Rare Genetic Ataxias in Childhood and Future Implications for Curing Gene Therapy Options

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/ajpr/2026/v16i5542

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://pr.sdiarticle5.com/review-history/158485

Minireview Article

Received: 18/03/2026
Published: 22/05/2026

Abstract

Rare genetic ataxias in childhood are usually progressive neurological disorders characterized by coordination problems (balance/gait instability, fine motor skills) due to damage to the cerebellum. Ataxias are movement disorders that mainly originate from the cerebellum and its connections, leading to a coordination disorder. The first symptom usually perceived by the patient is instability in standing and walking. As the condition progresses, speech and limb coordination disturbances occur, often manifesting as changes in fine motor skills. Speech becomes slow and slurred, and early eye movement disorders are common. Other neurological and non-neurological symptoms may also occur. Diagnosis relies on medical history, neurological examination, and cranial magnetic resonance imaging, followed by molecular genetic and possibly biochemical tests. The low prevalence and marked heterogeneity of ataxias complicate the diagnostic process.

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Cite as: *Bittmann, S., Luchter, E., & Moschüring-Alieva, E. (2026). Rare Genetic Ataxias in Childhood and Future Implications for Curing Gene Therapy Options . Asian Journal of Pediatric Research, 16(5), 1–9. https://doi.org/10.9734/ajpr/2026/v16i5542*

Ataxias can be classified into acquired ataxias (e.g., metabolic/toxic, immune-mediated), sporadic degenerative ataxias with cerebellar-type multisystem atrophy, or genetically inherited ataxias (e.g., Friedreich's ataxia, spinocerebellar ataxias). Early diagnosis is crucial to avoid unnecessary testing and provide appropriate patient counseling. Specific therapies are available for certain ataxias and symptoms, and rehabilitative therapies are essential components of treatment. In childhood, common forms include ataxia-telangiectasia, Niemann Pick type C, episodic and spinocerebellar ataxias. Diagnosis involves MRI, neurological examinations, and genetic tests, as therapies are rarely causative but increasingly gene-based research is being explored. Genetic ataxias are usually not curable, but research is focusing on gene therapies and molecular approaches. Occupational therapy, physiotherapy, and speech therapy are essential to maintain mobility and quality of life for as long as possible. This manuscript is an overview of rarely found ataxia types in childhood.

Keywords: Genetic ataxias; childhood; curing; gene therapy.

1. Introduction

Rare genetic ataxias in childhood, often referred to as early-onset ataxias, are a heterogeneous group of neurodegenerative diseases characterized by a progressive impairment of movement coordination (Ruano 2014, Rosenberg 1989, Paulson 2001, Bürk 2007, Bregant 2025, Alekseeva 2005, Spencer 2019, Bildirici 2023, Schöls 1997, Witek 2021). The cause is usually the degeneration of nerve cells in the cerebellum (Jayadev 2013, Eisel 2025, Bertrand 1952, Garcia 2022). Common forms in childhood are Friedreich's ataxia as the most common hereditary ataxia. It is inherited in an autosomal recessive manner and usually begins around puberty, but can also occur in early childhood (Parodi 2018, Krygier 2021). Typical symptoms include gait instability, sensory disturbances in the legs, and often a heart muscle disease (Arias-Merino 2017, Garces 2024)). Ataxia-telangiectasia is a congenital disease that usually manifests in early childhood. In addition to motor deterioration, dilated blood vessels in the eyes and immunodeficiency are often present (Pilotto 2024). Autosomal recessive cerebellar ataxias (ARCA) include a large group of very rare genetic defects that usually begin in childhood or young adulthood (Mahdieh 2024, Yigit 2022, Werdelin 1990). Spinocerebellar ataxias (SCA) are much less common in childhood than in adults. An exception is SCA7, which can be particularly severe in children due to "anticipation" and may be associated with retinopathy. Infantile spinocerebellar ataxia (IOSCA) is a very severe form that has mainly been described in Finnish families. Mitochondrial ataxias are inherited through the mother and can vary greatly in severity. In children, ataxias are often first noticed due to unusual clumsiness, such as in physical education class or frequent stumbling. Motor skills include insteady gait, problems with standing and fine motor skill disturbances. Slurred, slow speech and uncontrolled eye movements with nystagmus are often found. Genetic ataxias usually worsen gradually over time (de Silva 2019). The first step in case of suspicion is usually an MRI of the brain to visualize the cerebellum. Since there are hundreds of different genetic defects, specialized genetic diagnostics in ataxia centers such as are crucial. While most genetic forms are currently incurable, there are advances in gene therapy and symptomatic approaches such as physiotherapy and speech therapy to improve quality of life. Recent research focus on genetic treatment options for rare pediatric ataxias, where we focus on in this manuscript in detail.

2. Ataxia Telangiectactica

Louis-Bar syndrome, also known as Ataxia telangiectasia, is an inherited systemic disease classified as a phakomatosis and chromosomal breakage syndrome. In neurological classification, it is considered a hereditary ataxia, which refers to inherited movement coordination disorders. The disease is named after the Belgian physician Denise Louis-Bar. The inheritance pattern is autosomal recessive and involves the ATM gene located on chromosome 11 at locus q22.3. Approximately 0.5 to 1% of the population are healthy carriers of the mutation. About one in 40,000 newborns carries two defective gene copies, homozygous or compound heterozygous, and will develop Ataxia telangiectasia. The ATM gene encodes the serine-protein kinase ATM, which acts as a sensor of DNA damage from UV radiation and regulates DNA repair processes or programmed cell death. The diversity of symptoms in Louis-Bar syndrome is explained by the fact that many cell lines are affected by the mutation.

The first symptoms typically appear around the second to third year of life. Characteristic features include cerebellar ataxia with cerebellar atrophy, athetosis (dystonic movement disorder), eye movement disorders, and

physical and later cognitive developmental delay. Teleangiectasias (dilated small arteries) mainly on the face and conjunctiva of the eye, along with reduced immune competence due to a T-cell defect, leading to increased susceptibility to infections and a higher risk of developing leukemias and lymphomas compared to the general population. Patients also have an increased sensitivity to ionizing radiation and should avoid unnecessary X-rays. Other common symptoms include hypersalivation and hypogonadism. Diagnosis is often made clinically, with confirmation through imaging showing cerebellar atrophy, reduced immunoglobulin levels, and lymphopenia. Elevated alpha-1-fetoprotein levels are common. There is currently no curative treatment, with focus on managing pulmonary infections with antibiotics and ensuring proper vaccination, avoiding live vaccines. Life expectancy is significantly reduced due to recurrent lung infections and the increased risk of cancer. The median life expectancy is around 20 years, although there are cases of individuals with the syndrome living beyond their twenties, depending on the severity and course of the disease.

3. Niemann Pick Disease C

The estimated global birth prevalence of Niemann-Pick disease type C (NPDC) ranges between 1 in 45,000 and 1 in 286,000 live births. The disorder demonstrates marked clinical heterogeneity in both presentation and progression. NPDC is traditionally classified as a neurovisceral disorder, in which hepatosplenomegaly commonly precedes neurological manifestations and typically presents during infancy or childhood, although later onset has also been reported. Certain patients exhibit early pulmonary involvement, while a minority experience rapidly progressive hepatic or respiratory failure during early childhood. Neurological manifestations may emerge at any stage from early infancy to adulthood. Disease progression is generally characterised by dystonia, cerebellar ataxia, dysarthria, dysphagia, and progressive cognitive decline. Vertical supranuclear gaze palsy (VSGP) and cataplexy, with or without narcolepsy, are considered characteristic clinical features. Psychiatric manifestations are frequently observed in advanced stages of the disease.

Approximately 95% of affected individuals harbour pathogenic variants in the NPC1 gene, located on chromosome 18q11.2, which encodes a membrane-associated glycoprotein. The remaining cases are attributed to mutations in the NPC2 gene on chromosome 14q24.3, encoding a soluble lysosomal cholesterol-binding protein. Functional impairment of either protein disrupts intracellular cholesterol trafficking by preventing cholesterol egress from lysosomes, resulting in the accumulation of lipid membrane constituents, including unesterified cholesterol, glucosylceramide, and gangliosides, within the late endosomal–lysosomal compartment. Definitive diagnosis of NPDC relies on molecular genetic testing and, when required, confirmation by filipin staining, which detects unesterified cholesterol through its interaction with the fluorescent antibiotic filipin. Several biomarkers are currently employed, either individually or in combination, as first-line screening tools for NPDC, including oxysterols such as cholestan-3β,5α,6β-triol, lyso-SM-509, and lysosphingomyelin. Bone marrow examination frequently reveals the presence of foam cells and sea-blue histiocytes.

During the first two years of life, NPDC should be distinguished from other lysosomal and hepatic disorders, including Niemann-Pick disease type A, Niemann-Pick disease type B, Wolman disease, Gaucher disease type II, Gaucher disease type III, idiopathic neonatal hepatitis, and other causes of cholestatic jaundice. In older children and adults, differential diagnosis should include neurodegenerative and metabolic disorders such as mitochondrial diseases, Wilson disease, late-onset lysosomal storage disorders, Friedreich ataxia, Progressive supranuclear palsy, Huntington disease, Alzheimer disease, Pick disease, frontotemporal dementia, Amyotrophic lateral sclerosis, and primary psychiatric disorders. Acquired conditions, including pineal or midbrain tumours, attention-deficit disorders, learning disabilities, absence seizures, alternative causes of dementia, HIV encephalopathy, sleep disorders, and syncope, should also be considered.

Prenatal diagnosis should be offered to couples at increased genetic risk, with molecular genetic testing representing the preferred diagnostic approach. NPDC follows an autosomal recessive inheritance pattern; therefore, at-risk couples should receive genetic counselling regarding the 25% recurrence risk for each pregnancy. Current management remains predominantly symptomatic. Pharmacological therapy with the iminosugar inhibitor miglustat, which inhibits glucosylceramide synthase, has been approved in several countries for the management of neurological manifestations associated with NPDC. Additional therapeutic approaches currently under investigation include 2-hydroxypropyl-β-cyclodextrin and arimoclomol. Prognosis varies considerably, with survival ranging from only a few days in cases presenting with fetal hydrops to several decades in milder phenotypes. Mortality during early infancy is commonly attributable to hepatic or severe

pulmonary failure, typically occurring before 3–6 months of age. Severe early-onset neurological disease is frequently fatal between 3 and 5 years of age, whereas late-infantile neurological onset is generally associated with mortality between 7 and 12 years. Juvenile-onset neurological disease may permit survival from adolescence into the third decade of life.

4. Episodic Ataxias (EA)

EA are a group of rare autosomal dominant inherited disorders characterized by episodic balance and gait disturbances, as well as limb ataxia, caused by defects in ion channels (Jen 2008, Benatar 2000). The first description is believed to have been in 1975 by D. H. VanDyke and colleagues. The frequency is estimated to be 1 to 9 per 100,000, with autosomal dominant inheritance. Currently, the following different forms are known: EA-1, also known as episodic ataxia with myokymia, one of the two most common forms, mutation in the potassium channel gene KCNA1 on chromosome 12 locus p13. EA-2, also known as familial paroxysmal ataxia, is the second of the two most common forms, mutation in the calcium channel gene CACNA1A on chromosome 19 locus p13. EA-3 is known as episodic ataxia-vertigo-tinnitus-myokymia. EA-4 is known as periodic vestibulo-cerebellar ataxia (PATX). EA-5 is induced by a mutation in the CACNB4 gene on chromosome 2 at q23.3. EA-6 will be present by mutation in the SLC1A3 gene on chromosome 5 at p13.2. EA-8 is known as episodic ataxia with unclear speech. In EA-1, onset is in early childhood, triggered by fright, sudden movement, or physical exertion, ataxia lasts seconds to minutes, frequency decreases over time. Myokymia of facial and hand muscles is typical. In EA-2, onset between ages 2 and 20, triggered by stress and physical activity, ataxia lasts 15 minutes to several days, often accompanied by weakness, dizziness, nausea, vomiting, and migraine. Directional nystagmus is typical between episodes. Diagnosis can be made through genetic testing. Surface electromyography may show spontaneous repetitive discharges in EA-1, and brain MRI may show cerebellar atrophy in EA-2. Treatment involves avoiding triggering factors such as stress, alcohol, and nicotine, possibly stress management and learning relaxation techniques, and medication depending on the form, including acetazolamide (off-label use), potassium supplementation (more effective in EA-2 than EA-1), trial of 4-aminopyridine or sodium channel blockers, and carbamazepine.

5. Autosomal Dominant Spinocerebellar Ataxias (SCA)

Almost all known autosomal dominant spinocerebellar ataxias (SCA) are caused by the expansion of three base pairs, the trinucleotide repeat units, whose length is usually inversely proportional to the age of onset of the disease (Galatolo 2018, Boucher 1995). The pathomechanism leading to the degeneration of specific brain regions, mostly in adulthood, is uncertain (Nikali 2016). In the majority of affected genes, the elongation of a CAG trinucleotide repeat results in an extended polyglutamine chain in the aberrant protein with novel biochemical properties. Recently, inclusion bodies have been identified in the cell nuclei of neurons, predominantly in the affected brain areas. Thus, polyglutamine diseases share numerous similarities with neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and prion diseases. While protein precipitation is also discussed as a cause of these diseases, in contrast, the subcellular location of pathogenesis in CAG repeat diseases is predominantly localized in the cell nucleus. The intranuclear aggregates contain not only the mutated gene product but also other proteins such as heat shock proteins, ubiquitin, and proteasomes. The role of these protein complexes in the diseases is unclear.

6. Discussion

Ataxias are movement disorders that mainly originate from the cerebellum and its connections, leading to a coordination disorder.

The term "ataxia" is derived from the Greek word "a-taxia" meaning "lack of order." Ataxias refer to a range of rare diseases of the brain and spinal cord where the coordination of different muscle groups is disrupted. This leads to problems with balance and movement coordination. Activities such as walking, sitting, standing, speaking, hand movements, and eye movement control are affected. The gait becomes unsteady and wide-based, handwriting becomes illegible, and grasping and holding objects become difficult. Some individuals may not be able to sit or stand upright without support. Speech can also be affected, becoming unclear and slurred. Ataxias differ from Parkinson's disease and Amyotrophic Lateral Sclerosis (ALS) in that ataxias primarily involve disturbances in balance and coordination, while Parkinson's disease is characterized by a reduction and slowing of movements, tremors, and muscle stiffness, and ALS involves spasticity and paralysis. Ataxias can occur at

any age, including in children. It is estimated that around 16,000 people in Germany are affected, with equal numbers of men and women. Key players in the fine-tuning of movements are the cerebellum and spinal cord, as well as the connections between them and other parts of the brain. When communication is disrupted, coordination and execution of movements are affected. Acquired ataxias are usually due to damage in the cerebellum, which can have various causes. They may result from circulatory disorders, such as in a stroke, inflammatory or autoimmune diseases, infections or tumors, as well as malnutrition, injuries, poisoning, or alcohol abuse.

In addition, ataxias can be genetically determined. In hereditary ataxias, there are at least 200 different gene mutations that cause the disease. The cause of congenital, hereditary ataxias is a progressive degeneration of certain nerve cells in the cerebellum, for which different gene mutations are responsible depending on the subtype. Hereditary ataxias can be dominantly inherited, passed from one generation to the next. Patients often know that the disease runs in the family. If the parents are not affected, but their child or multiple siblings are, it is a recessively inherited ataxia: this means that both parents are carriers of the disease-causing genetic mutation, but the disease does not manifest in them. For the child to be affected, both parents must pass on the gene mutations. Among all recessive ataxias, Friedreich's ataxia is the most common. It begins in childhood or adolescence: the parents of the affected individuals are healthy, while the affected individuals, who previously developed normally for their age, experience balance and coordination problems. They have difficulty walking and may fall. As Friedreich's ataxia progresses, the children become dependent on a wheelchair. Currently, ataxias are not treatable with medication. Regular physiotherapy with active exercises to promote coordination can, however, provide long-term relief of symptoms. The first symptom usually perceived by the patient is instability in standing and walking. As the condition progresses, speech and limb coordination disturbances occur, often manifesting as changes in fine motor skills. Speech becomes slow and slurred, and early eye movement disorders are common. Other neurological and non-neurological symptoms may also occur. Adult-onset ataxias are etiologically heterogeneous diseases. Diagnosis relies on medical history, neurological examination, and cranial magnetic resonance imaging, followed by molecular genetic and possibly biochemical tests (Bernardi 2026). The low prevalence and marked heterogeneity of adult-onset ataxias complicate the diagnostic process. Ataxias can be classified into acquired ataxias (e.g.,metabolic/toxic, immune-mediated), sporadic degenerative ataxias (e.g., cerebellar-type multisystem atrophy), or genetically inherited ataxias (e.g., Friedreich's ataxia, spinocerebellar ataxias). An early diagnosis is crucial to avoid unnecessary testing and provide guidance to patients. Specific therapies are available for certain ataxias and symptoms, and rehabilitative therapies are essential components of treatment (Braga-Neto 2016). Present treatment options and possible future gene therapeutical options are described to each disease form in detail in Table 1. Most of these gene therapy options are in preclinical stage and the future will bring clesrer information about possible treatment options like gene editing, antisense oligonucleotides, gene silencing and CRISPR-CAS 9 technology for mutational repair. Overall, it will need many years to approve gene therapeutical options in these rare formas of ataxias, but it is important how to cure these diseases as best as possible for the future.

Table 1. Types of ataxia, their consequences and treatments

Type of Ataxia	Gene Defect	Consequences	Current Treatment	Future Treatment Options
Ataxia teleangiectasia (A-T) (Louis- Bar-Syndrom)	Chromosome 11q22.3, 1:40000, autosomal recessive, disorder of defective DNA repair, DNA damage response pathway, variant A-T: milder. Diverse exons, neurodegeneration, delayed immune dysdunction, cancer predisposition, sterility	Encoding of serine protein kinase ATM, first symptoms around 2-3 y of age Increased risk of cancer, T- and B-cell defect, risk for ionizised radiation, atrophy of cerebellum, developmental delay, cancer risk 100x, cerebellary ataxia Associated with: lymphoma, Hodgkin/Non Hodgkin, Breast CA,	No curative treatment Management of pulmonary infections	Preclinical stage

Type of Ataxia	Gene Defect	Consequences	Current Treatment	Future Treatment Options
		CML, Wilms TU Hepatocell CA, progressive unrelenting course, death from pulmonary infections and cancer, residual kinase activity with better outcome.		
Morbus Niemann Pick Type C „Childhood Alzheimer Disease“	Chromosome 18q11.2: NPC 1 gene (95%) Chromosome 14q24.3 NPC2 gene (5%) 1.45000-286000 Autosomal recessive	Blockage of exit of cholesterol ester in lysosomes Fat can not be removed from cells Lipid accumulation in organs (Spleen, liver, Brain) HSM, motoric delay, speech delay, ataxia, vertical ocular paresis dementia, depression	Miglustate Miplyffa (Arimoclomol) Aqneursa (Levacetylleucin)	Preclinical gene therapy options: AAV based gene delivery CRISP Cas9 technology “Gene therapy as soon as possible” BGT-NPC gene therapy candidate m-RNA therapy
Episodic Ataxias	In type 2: Chromosome 19p13 with CACNA1A mutation Found in CNS, presynaptic ends of neurons, Gain of Function mutation, coding of P/Q type Ca channels, autosomal dominant	Vertigo, ataxy, vomiting, stress induced, dysarthrie, diplopy, tinnitus, downbeat nystagmus.	Acetazolamide (carboanhydrase inhibition) 4-aminopyridin No stress/alcohol Carbamazepine Chlorzoxazone	Preclinical stage: CRISP CAS 9 technology Antisensse Oligonucleotides AAV Vectors
Spinocerebellar Ataxias	Example: Type 6: Gene ATXN2, SCA6 gain of function mutation.Chromosome 12, CAG repeat expansions, autos dominant	Gait ataxia, slow saccadic eye movements, dysarthria, muscle tremor, speech delay, muscle waste, parkinsonismus (Wan 2021), risk for amyothrophic lateral sclerosis	symptomatic	Gene silencing options (Santos 2023, Didonna 2016) RNa based therapy with antisense oligonucleotides (ASO), si RNA, viral vectors and gene editing options CRISP CAS9: cutting CAG repeats still difficult (preclinical stage)

7. Conclusion

Hereditary ataxias in childhood are rare, mostly autosomal recessive inherited neurodegenerative diseases that lead to progressive coordination disorders. Hereditary ataxias in childhood are a clinically and genetically heterogeneous group of rare, progressive neurological disorders. The primary hallmark symptom is a chronic-progressive coordination disorder, primarily based on dysfunction or degeneration of the cerebellum and its connecting pathways. Other key symptoms include gait/stance instability, coordination disorders, dysarthria, and oculomotor disturbances.

Consent

It is not applicable.

Ethical Approval

It is not applicable.

Disclaimer (Artificial Intelligence)

Author(s) hereby declare that no generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

Competing Interests

Authors have declared that no competing interests exist.

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