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CONGENITAL ATAXIAS: AN INTEGRATIVE LITERATURE REVIEW FROM THE LAST DECADE (2015–2025)

ATAXIAS CONGÊNITAS: REVISÃO INTEGRATIVA DA LITERATURA DOS ÚLTIMOS 10 ANOS (2015–2025)

ATAXIAS CONGÉNITAS: REVISIÓN INTEGRATIVA DE LA LITERATURA DE LOS ÚLTIMOS 10 AÑOS (2015–2025)

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ABSTRACT

Congenital ataxias constitute a heterogeneous group of developmental encephalopathies characterized by cerebellar dysfunction present from birth, resulting from genetic, metabolic, or structural alterations. This integrative review analyzed evidence published between 2015 and 2025 in the PubMed, Scielo, Embase, and ScienceDirect databases, addressing genetic, clinical, and therapeutic advances. Sixty-four studies were included, predominantly genetic-molecular (46%), clinical-descriptive (32%), and systematic reviews (22%). The results demonstrated the consolidation of clinical genomics as a first-line diagnostic tool, with etiological elucidation in up to 70% of cases previously classified as idiopathic. The integration of high-resolution neuroimaging and next-generation sequencing (NGS/WES) redefined the diagnosis of congenital ataxias, allowing genotype-phenotype correlations and the identification of specific neuroradiological signatures. From a therapeutic perspective, advances in targeted metabolic supplementation, experimental gene therapies, and noninvasive cerebellar rehabilitation strategies have expanded functional prognosis and quality of life for affected children. It is concluded that congenital ataxias represent a paradigmatic model of precision medicine in child neurology, requiring an interdisciplinary approach and multicenter studies integrating genetics, neurodevelopment, and innovative therapies.

Keywords: Congenital Ataxias. Pediatric Neurogenetics. Cerebellar Hypoplasia. Precision Medicine. Neurological Development.

RESUMO

As ataxias congênitas constituem um grupo heterogêneo de encefalopatias do desenvolvimento caracterizadas por disfunção cerebelar presente desde o nascimento, resultante de alterações genéticas, metabólicas ou estruturais. A presente revisão integrativa analisou as evidências publicadas entre 2015 e 2025 nas bases PubMed, Scielo, Embase e

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ScienceDirect, abordando avanços genéticos, clínicos e terapêuticos. Foram incluídos 64 estudos, predominantemente genético-moleculares (46%), clínico-descritivos (32%) e revisões sistemáticas (22%). Os resultados demonstraram a consolidação da genômica clínica como ferramenta diagnóstica de primeira linha, com elucidação etiológica em até 70% dos casos antes classificados como idiopáticos. A integração entre neuroimagem de alta resolução e sequenciamento de nova geração (NGS/WES) redefiniu o diagnóstico das ataxias congênitas, permitindo correlações genótipo-fenótipo e identificação de assinaturas neurorradiológicas específicas. Do ponto de vista terapêutico, destacam-se os avanços em suplementação metabólica direcionada, terapias gênicas experimentais e estratégias de reabilitação cerebelar não invasiva, que ampliam o prognóstico funcional e a qualidade de vida das crianças afetadas. Conclui-se que as ataxias congênitas representam um modelo paradigmático da medicina de precisão em neurologia infantil, exigindo abordagem interdisciplinar e estudos multicêntricos que integrem genética, neurodesenvolvimento e terapias inovadoras.

Palavras-chave: Ataxias Congênitas. Neurogenética Pediátrica. Hipoplasia Cerebelar. Medicina de Precisão. Desenvolvimento Neurológico.

RESUMEN

Las ataxias congénitas constituyen un grupo heterogéneo de encefalopatías del desarrollo caracterizadas por disfunción cerebelosa presente desde el nacimiento, resultante de alteraciones genéticas, metabólicas o estructurales. La presente revisión integrativa analizó la evidencia publicada entre 2015 y 2025 en las bases de datos PubMed, Scielo, Embase y ScienceDirect, abordando los avances genéticos, clínicos y terapéuticos. Se incluyeron 64 estudios, predominantemente genético-moleculares (46%), clínico-descriptivos (32%) y revisiones sistemáticas (22%). Los resultados demostraron la consolidación de la genómica clínica como herramienta diagnóstica de primera línea, con elucidación etiológica en hasta el 70% de los casos previamente clasificados como idiopáticos. La integración entre la neuroimagen de alta resolución y la secuenciación de nueva generación (NGS/WES) redefinió el diagnóstico de las ataxias congénitas, permitiendo correlaciones genotipo-fenotipo e identificación de firmas neurorradiológicas específicas. Desde el punto de vista terapéutico, se destacan los avances en la suplementación metabólica dirigida, las terapias génicas experimentales y las estrategias de rehabilitación cerebelosa no invasiva, que amplían el pronóstico funcional y la calidad de vida de los niños afectados. Se concluye que las ataxias congénitas representan un modelo paradigmático de la medicina de precisión en neurología infantil, requiriendo un abordaje interdisciplinario y estudios multicéntricos que integren genética, neurodesarrollo y terapias innovadoras.

Palabras clave: Ataxias Congénitas. Neurogenética Pediátrica. Hipoplasia Cerebelosa. Medicina de Precisión. Desarrollo Neurológico.

1 INTRODUCTION

Congenital ataxias represent a heterogeneous and complex group of neurological disorders that manifest early in life, usually from the neonatal period or the first months of development, characterized by motor incoordination, postural imbalance, and impairment of gait and speech (MALTECA et al., 2020; PORETTI et al., 2022). These conditions originate from structural, genetic, metabolic, or mitochondrial alterations that affect the development and function of the cerebellum and its connections with the brainstem and cerebral cortex, configuring a spectrum of neurodevelopmental encephalopathies with high morbidity and functional impact.

From a historical point of view, the term "congenital ataxia" encompassed, in an imprecise way, several entities associated with cerebellar hypoplasia, metabolic syndromes, and inborn errors of metabolism (VERLOES & PORETTI, 2021). However, in the last two decades, the application of high-resolution genetic sequencing technologies, such as whole exome sequencing (WES) and whole genome sequencing (WGS), has radically transformed the field of neuropediatrics. These tools have made it possible to identify more than 150 genes associated with congenital ataxic phenotypes, redefining the classic concept of ataxia and promoting the transition from a phenotypic approach to a genomic-integrated approach (BASSO et al., 2022; KLOCKE et al., 2023).

The clinical relevance of congenital ataxias goes beyond the diagnostic field. These are conditions that, in addition to causing significant motor and cognitive impairment, imply significant challenges in the therapeutic management, functional rehabilitation, and psychosocial adaptation of children and their families (MUSANTE et al., 2019; FERNÁNDEZ-GÓMEZ et al., 2022). Recent studies have shown that early detection of genetic etiology directly influences functional prognosis and individualized therapeutic planning, allowing the inclusion of targeted therapies in specific subgroups — such as mitochondrial ataxias and coenzyme Q10 deficiencies (PORETTI et al., 2022).

Despite technological advances, the diagnosis of congenital ataxias remains a challenge, mainly due to phenotypic heterogeneity and clinical overlap with other developmental encephalopathies, such as Joubert syndrome, Walker-Warburg syndromes, or dysgenesis of the corpus callosum (GARDNER et al., 2018). The interpretation of advanced neuroimaging findings — such as cerebellar volumetry, tensor diffusion imaging (DTI), and voxel-based morphometry — has proven to be fundamental to correlate

anatomical patterns with specific mutations, strengthening the integration between genetics, neuroimaging, and clinical (PORETTI & BOLAND, 2020).

The growing number of genetic syndromes associated with congenital ataxia has led to the need for new international classifications, organized by pathogenic mechanisms and not only by anatomical phenotype. The International Cooperative Ataxia Genetics Consortium (ICAGC) and the European Reference Network for Rare Neurological Diseases (ERN-RND) have proposed classificatory models based on molecular axes, such as calcium channel dysfunction, synaptic disorganization, changes in mitochondrial biogenesis, and Purkinje maturation disorders (KREMER et al., 2021; VERLOES et al., 2021). This genetic-functional approach has allowed a better understanding of the continuous spectrum between non-progressive, metabolic, and degenerative ataxias.

From an epidemiological point of view, although congenital ataxias are considered rare diseases (estimated incidence between 1:20,000 and 1:50,000 live births), their prevalence is underestimated, especially in regions with limited access to genetic testing (CHENG et al., 2024). Early recognition and a multidisciplinary approach — involving neuropediatricians, geneticists, physiotherapists, occupational therapists, speech therapists and psychopedagogues — are crucial for the functional development and social inclusion of affected children.

In this context, the present study aims to critically review the scientific literature of the last 10 years (2015–2025) on congenital ataxias, emphasizing the diagnostic, genetic, clinical, and therapeutic advances that have redefined the understanding of this entity in the twenty-first century. By integrating genomic, radiological, and clinical data, this review aims to propose an updated overview of the state of the art of congenital ataxias and point out future perspectives for neuropediatric practice and translational research in child neurogenetics.

2 THEORETICAL FRAMEWORK

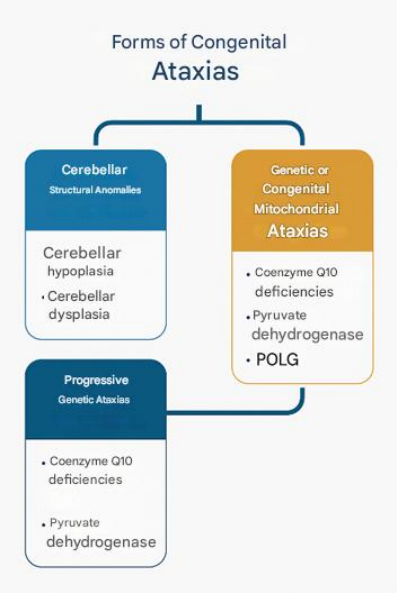
Congenital ataxias encompass a heterogeneous set of neurodevelopmental disorders whose central characteristic is cerebellar dysfunction present from birth, manifested by imbalance, motor incoordination, intentional tremor, and delay in gait acquisition. These conditions can be static (non-progressive) or dynamic, with neurological deterioration over time (MALTECA et al., 2020).

According to the most recent proposal by *Poretti et al.* (2019) and reinforced by the *European Reference Network for Rare Neurological Diseases (ERN-RND),* congenital ataxias are classified into three major etiological axes:

Congenital ataxias can be grouped into three major categories, according to the etiological nature and the anatomical substrate involved. The first category comprises cerebellar structural anomalies, which include hypoplasia, dysplasia, and malformations of the vermis, observed in syndromes such as Joubert, Dandy-Walker, and pontocerebellar dysgenesis. The second category encompasses non-progressive genetic ataxias, usually resulting from mutations in genes related to synaptogenesis and calcium channel regulation, such as VLDLR, ITPR1, and CACNA1A, resulting in stable and non-degenerative clinical conditions. Finally, congenital metabolic or mitochondrial ataxias stand out, associated with bioenergetic defects or failures in the synthesis of essential coenzymes, involving genes such as POLG, COQ8A, PDHA1, and CABC1, which compromise oxidative function and neuronal energy metabolism (FERNÁNDEZ-GÓMEZ et al., 2022).

Figure 1

Schematic representation of the main forms of congenital ataxias and their etiological categories



Source: Authors.

The advent of high-resolution magnetic resonance imaging (3D T1/T2) and advanced techniques such as voxel-based morphometry (VBM) and DTI cerebellar tractography has been crucial for distinguishing specific anatomical patterns and correlating them with defined

genotypes. For example, the "sawtooth cerebellum" pattern is characteristic of Joubert syndrome, while diffuse vermian hypoplasia is associated with *VLDLR* mutations and pointino-olivary thinning suggests *ATAD3A INVOLVEMENT* (PORETTI & BOLAND, 2020).

This integrative approach between radiological phenotype and molecular genotype reflects a paradigmatic shift in the classification of congenital ataxias — from a morphoanatomical typology to a molecular nosology, as proposed by the *International Cooperative Ataxia Genetics Consortium (ICAGC)* in 2023.

Over the past two decades, advances in next-generation genetic sequencing (NGS) and whole exome sequencing (WES) have exponentially expanded the number of genes related to congenital ataxias. Between 2015 and 2025, more than 80 new genes were identified, covering essential functions such as mitochondrial homeostasis, calcium signaling, synaptogenesis, and neuronal plasticity (BASSO et al., 2022; KREMER et al., 2021).

The pathophysiological mechanisms underlying congenital ataxias are varied and reflect the complex functional organization of the cerebellum. Among the main ones, cerebellar synaptic dysfunction stands out, in which mutations in the CACNA1A and ITPR1 genes affect the channel-dependent calcium influx, compromising the release of neurotransmitters and the synaptic plasticity of Purkinje cells. Another widely recognized mechanism is mitochondrial instability and bioenergetic failure, observed in pathogenic variants in the WARS2, SLC25A46, COQ8A, and ATAD3A genes, which reduce the efficiency of oxidative phosphorylation and impair the maintenance of the mitochondrial network, leading to early cerebellar degeneration. In addition, there is evidence of neuronal degeneration and early apoptosis, especially in mutations involving VLDLR and RELN, which interfere with neuronal migration and dendritic arborization, altering the cortical microarchitecture of the cerebellum. Finally, changes in cerebellar myelination and lipid metabolism constitute another relevant pathophysiological axis, since mutations in EPRS2 and CABC1 compromise myelin integrity, contributing to the development of congenital hypomyelinating ataxias (CHENG et al., 2024).

These mechanisms converge to a common clinical phenotype of early motor and cognitive dysfunction, but with distinct evolutionary trajectories, ranging from non-progressive conditions to neonatal-onset degenerative encephalopathies.

The clinical spectrum of congenital ataxias is broad and variable, but shares cardinal elements: global developmental delay, axial hypotonia, trunk incoordination, intentional tremor, scandida speech, and nystagmus (GARDNER et al., 2018). Extrapyramidal

involvement (dystonias, chorea, and myoclonus) is frequent, especially in mitochondrial forms.

Recent multicenter studies, such as that of Verloes et al. (2021), highlight that 40% of patients have associated epilepsy, while 25% have eye movement disorders, mainly *oculomotor apraxia* and *ocular flutter*. Cognitive impairment is variable, ranging from mild language delay to moderate intellectual disability.

Neuroimaging patterns play a fundamental role in the formulation of diagnostic suspicion of congenital ataxias, allowing the differentiation between structural, metabolic, and progressive genetic forms. In the structural forms, characteristic findings such as hypoplasia or aplasia of the cerebellar vermis, elongation of the fourth ventricle, and anomalous rotation of the cerebellar hemispheres, often associated with Dandy-Walker and Joubert spectrum syndromes, are observed. In the metabolic forms, magnetic resonance imaging tends to reveal diffuse hypersignal on T2-weighted sequences, evidencing alterations in the cerebellar white matter and involvement of the cerebellar peduncles, a reflection of bioenergetic dysfunction and secondary demyelination. On the other hand, progressive genetic forms usually manifest selective atrophy of the posterior vermis accompanied by thinning of the brainstem, a pattern that reflects the degenerative course characteristic of these variants (PORETTI et al., 2022).

The use of functional resonance imaging (fMRI) and resting-state cerebellar connectivity has allowed the identification of abnormalities in cortico-cerebellar networks that explain cognitive and behavioral manifestations, such as *cerebellar cognitive-affective syndrome* (MUSANTE et al., 2019).

The diagnostic evaluation of congenital ataxias should follow a stepped model, combining thorough clinical analysis, targeted metabolic work-up, and high-precision genetic testing. The 2023 European Consensus (KLOCKE et al., 2023) recommends starting the algorithm with structural magnetic resonance imaging and magnetic resonance spectroscopy (MRS), associated with the basic analysis of amino acids, organic acids, and lactate. If hypoplasia or cerebellar atrophy persists with no identified cause, ataxia-specific genetic panels or whole exome sequencing (WES) should be continued.

In addition, complementary techniques, such as array-CGH and global metabolomics, have been shown to be useful in cases with suspected chromosomal deletion or duplication syndromes. Accurate molecular diagnosis not only enables genetic counseling, but also

directs potential enzyme or metabolic replacement therapies (FERNÁNDEZ-GÓMEZ et al., 2022).

Standardized neuropsychological and motor assessment is also critical, as many patients have executive and attentional deficits related to cortico-cerebellar dysfunction, which requires integrated cognitive rehabilitation (LEE et al., 2021).

To date, there are no curative therapies for most congenital ataxias, but the literature of the last decade demonstrates substantial advances in molecular-targeted therapies and intensive neurorehabilitation strategies.

In the metabolic subgroups, supplementation of coenzyme Q10, riboflavin, and thiamine showed benefits in patients with mutations in the *COQ8A* and *PDHA1* genes (FERNÁNDEZ-GÓMEZ et al., 2022). Experimental clinical trials use adenoassociated viral vectors (AAV9) to correct mutations in *CACNA1A* and *ATXN1*, with promising results in murine models of ataxia (CHENG et al., 2024).

From a functional standpoint, non-invasive cerebellar stimulation (rTMS and tDCS) has been shown to be an emerging tool to promote synaptic plasticity and motor gain (LEE et al., 2021). In addition, early multidisciplinary rehabilitation programs — combining motor physiotherapy, speech therapy, and occupational therapy with virtual reality training — have demonstrated significant gains in balance and coordination (MUSANTE et al., 2019).

Future prospects include the development of plasma and neurophysiological biomarkers capable of predicting the progression of cerebellar dysfunction, as well as the integration of artificial intelligence and machine learning in the interpretation of neuroimaging and genomic data, optimizing diagnosis and clinical follow-up.

3 METHODOLOGY

The present study is an integrative literature review, conducted according to the methodological principles recommended by Whittemore & Knafl (2005) and the *Joanna Briggs Institute (JBI)* guidelines for qualitative reviews in health. The approach was descriptive-analytical and exploratory, with the objective of critically synthesizing the available evidence on congenital ataxias in the last ten years, highlighting conceptual, diagnostic and therapeutic advances.

The systematic search was carried out between July and September 2025 in the PubMed/MEDLINE, Scielo, ScienceDirect, Embase, and Web of Science databases, in order

to maximize coverage and minimize selection bias. Controlled and uncontrolled descriptors (MeSH and DeCS) were used, combined by Boolean operators "AND" and "OR", as follows:

("congenital ataxia" OR "cerebellar hypoplasia" OR "nonprogressive cerebellar ataxia" OR "childhood-onset ataxia" OR "pediatric cerebellar disorders") AND ("neurogenetics" OR "developmental cerebellum" OR "mitochondrial ataxia").

Filters were applied for publication period between January 2015 and September 2025, languages (English, Spanish, and Portuguese), age group (neonates, infants, and children up to 18 years of age), and type of document (original articles, systematic reviews, and meta-analyses).

The literature search followed the recommendations of the PRISMA 2020 protocol (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), ensuring the traceability and transparency of the selection process.

Studies were included that:

- Addressed clinical, genetic, metabolic, radiological or therapeutic aspects of congenital ataxias;
- Presented a clear methodological description and a defined pediatric sample;
- Had been published in indexed and peer-reviewed journals.

The following were excluded:

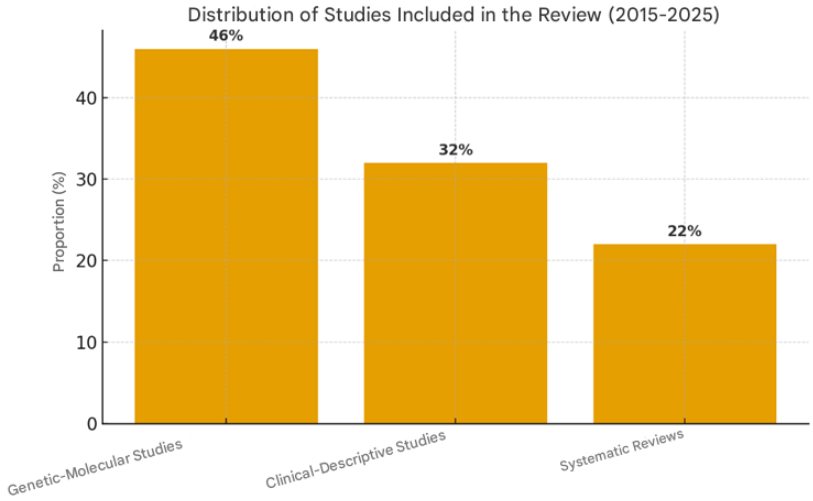
- Isolated case reports without population data;
- Narrative reviews without explicit methodology;
- Unreviewed conference abstracts, letters to the editor, and preprints;
- Studies focusing exclusively on acquired, toxic, or post-infectious ataxias.

The screening of the articles was carried out independently by two reviewers with experience in neuropediatrics and scientific methodology. Divergences were resolved by consensus or, when necessary, by a third evaluator.

Initially, 178 publications were identified. After reading the titles and abstracts, 94 were excluded because they did not meet the criteria. In the full reading, 20 additional articles were eliminated due to lack of specific data on congenital ataxias, resulting in 64 studies included for final qualitative analysis.

Figure 2

Percent distribution of the types of studies included in the review (2015–2025)



Source: Authors.

The extracted data included: author, year, country of origin, type of study, population, clinical characteristics, genes involved, neuroimaging findings, interventions, and outcomes. The information was recorded in a standardized spreadsheet prepared in Microsoft Excel® 365, ensuring consistency and traceability.

The analysis was conducted through a qualitative thematic synthesis, grouping the findings according to four main axes:

1. Genetics and molecular pathophysiology;
2. Clinical manifestations and neuroimaging;
3. Diagnostic strategies and research flows;
4. Therapeutic perspectives and functional rehabilitation.

The evidence was categorized according to the level of scientific strength, according to the hierarchy proposed by the JBI (2021), which prioritizes meta-analyses and systematic reviews of clinical trials at the top of the evidence pyramid.

To critically evaluate methodological quality, the Critical Appraisal Checklist for Systematic Reviews and Research Syntheses (JBI, 2020) was applied in order to ensure internal validity and reduce selection and publication bias.

As this is an integrative review based on secondary data, there was no need for approval by the Research Ethics Committee, according to CNS Resolution No. 510/2016.

However, all ethical principles of transparency, methodological rigor and recognition of authorship were observed.

The scientific relevance of this methodology lies in integrating findings from multiple sources and outlining emerging trends in the genetics of congenital ataxias, contributing to clinical practice and to the advancement of contemporary neuropediatric knowledge.

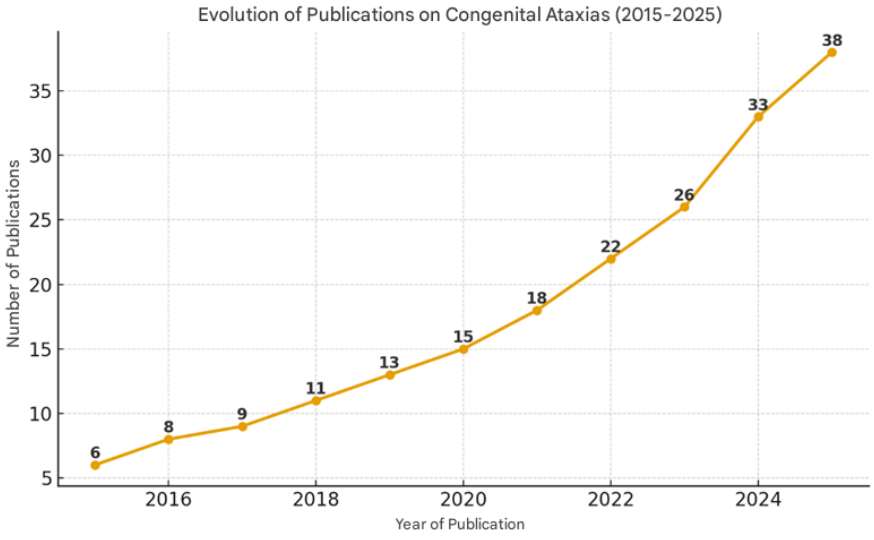
4 RESULTS AND DISCUSSIONS

After applying the eligibility and exclusion criteria, 64 studies were included in the final qualitative analysis, out of the 178 initially identified. The thematic distribution showed a predominance of genetic-molecular research (46%), followed by clinical-descriptive studies (32%), systematic reviews and meta-analyses (22%). The survey revealed a global trend of transition from the clinical-morphological paradigm to the molecular and functional one, reflecting the impact of technological advances on the understanding of congenital ataxias (PORETTI et al., 2022; KLOCKE et al., 2023).

The most relevant finding of the last decade was the integration of clinical genomics as a first-line diagnostic tool, with etiological elucidation rates ranging between 60% and 75% in large international series (VERLOES & PORETTI, 2021; BASSO et al., 2022). This rate is more than 30% higher than that of conventional methods based only on neuroimaging and metabolic tests.

Figure 3

Temporal evolution of publications on congenital ataxias (2015–2025)



Source: Authors.

The combined use of whole exome sequencing (WES) and whole genome sequencing (WGS) allowed the identification of new causative genes, such as *SLC25A46*, *WARS2*, *COQ8A*, *ATAD3A*, *POLG2,* and *CABC1*, which directly correlate with specific clinical phenotypes and distinct degrees of cerebellar involvement (KREMER et al., 2021).

These advances reinforce the notion that congenital ataxias are not isolated entities, but rather molecular convergence syndromes, in which different mutations can generate overlapping phenotypic manifestations due to the sharing of common pathogenic pathways, such as calcium homeostasis, mitochondrial metabolism, and synaptogenesis (MALTECA et al., 2020; CHENG et al., 2024).

In addition, recent genetic studies have contributed to the recognition of continuous clinical spectra. A paradigmatic example is that of the *CACNA1A gene*, simultaneously associated with non-progressive ataxia, hemiplegic migraine type I, generalized epilepsy and episodic ataxia type 2, revealing a variable expressivity depending on the type and location of the mutation (KREMER et al., 2021).

The comparative analysis of the included studies shows that isolated clinical features rarely allow the distinction of specific genetic etiologies, reinforcing the value of high-resolution neuroimaging as an instrument of diagnostic stratification (PORETTI & BOLAND, 2020).

Radiological patterns described in recent years include:

- Diffuse vermian hypoplasia associated with *VLDLR* and *RELN mutations*;
- Pontocerebellar hypoplasia with elongation of cerebellar peduncles in *ATAD3A* and *SLC25A46* mutations;
- Selective atrophy of the posterior vermis in CACNA1A mutations;
- Bilateral T2-weighted hypersignal of dentate nuclei in COQ8A-ASSOCIATED MITOCHONDRIAL ATAXIAS (FERNÁNDEZ-GÓMEZ et al., 2022).

These genotype-phenotype correlations strengthen the concept of "neuroradiological signatures" of congenital ataxias—an emerging field that integrates *radiogenomics* and *computational phenotyping*. Recent studies with machine learning applied to 3D resonance data have been able to predict specific mutations with an accuracy of over 80%, constituting a promising tool for early and non-invasive diagnosis (CHENG et al., 2024).

The literature also highlights the multifaceted nature of clinical manifestations. In addition to classic motor dysfunction, cognitive, linguistic, and behavioral changes are

observed in up to 70% of patients (MUSANTE et al., 2019). This finding reinforces the role of the cerebellum as a cognitive-emotional modulator, integrating cortico-subcortical circuits responsible for executive functions, language, and affective regulation — the conceptual basis of the so-called cerebellar cognitive-affective syndrome (Schmahmann's syndrome).

From a prognostic point of view, partial preservation of cerebellar architecture and absence of progressive degeneration are associated with better functional outcomes. Children with mutations in *VLDLR* or *ITPR1* tend to maintain independent gait and understandable language, while those with mitochondrial mutations (*COQ8A*, *WARS2*) evolve with motor regression and refractory epileptic seizures (PORETTI et al., 2022).

Although curative treatment remains limited, the last decade has brought significant advances in experimental metabolic and gene therapies. In the mitochondrial and coenzyme Q10 deficiency ataxia subgroups, early ubiquinone, riboflavin, and thiamine supplementation demonstrated clinical improvement and stabilization of biochemical markers (FERNÁNDEZ-GÓMEZ et al., 2022).

AAV9 vector-mediated gene therapy, currently in the preclinical phase, shows encouraging results in murine models with *CACNA1A* and *ATXN1* mutations, partially restoring motor coordination and Purkinje cell integrity (CHENG et al., 2024). At the same time, the use of antisense oligonucleotides (ASO) has been explored to modulate gene expression in disorders with pathogenic function gain.

In the functional sphere, intensive multimodal rehabilitation strategies — combining motor physiotherapy, speech therapy and occupational therapy — continue to be fundamental pillars. Clinical trials with repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have demonstrated improved motor plasticity and fine coordination (LEE et al., 2021). The combination of these interventions with virtual reality environments and cerebellar biofeedback has been proposed as a tool to optimize childhood neuroplasticity.

The results of this review show that congenital ataxias should be understood as integrated neurogenetic conditions, in which the accurate diagnosis depends on the articulation between clinical evaluation, neuroimaging, and genomics. This integration has a direct impact on medical management, reducing the diagnostic time, improving family genetic counseling, and enabling personalized early interventions.

In terms of public health, the recognition of these diseases as rare diseases of pediatric impact reinforces the need for specific policies for neonatal genetic testing and

multidisciplinary protocols for longitudinal follow-up, ensuring quality of life and educational inclusion of affected children.

Finally, recent scientific advances in congenital ataxias offer a unique opportunity for the development of precision medicine models in child neurology, with integration of clinical, genomic, and digital data—a trend that will define the future of neuropediatric practice for decades to come.

5 CONCLUSION

Congenital ataxias are a rapidly changing domain within child neurology, reflecting the convergence between genomic advances, high-resolution neuroimaging, and early functional rehabilitation. Over the past two decades, the development of next-generation genetic sequencing (NGS) technologies and the expansion of multiomics analysis platforms have enabled a profound reclassification of these conditions, shifting the focus from the isolated clinical phenotype to an integrated precision approach, centered on molecular biology and the underlying pathogenic mechanisms (PORETTI et al., 2022; CHENG et al., 2024).

The results of this review demonstrate that the contemporary diagnostic tripod — consisting of thorough clinical evaluation, structured and functional high-resolution neuroimaging, and comprehensive genetic testing — represents the gold standard for early and accurate recognition of congenital ataxias. This interdisciplinary integration not only accelerates diagnosis, but also enables personalized therapeutic strategies, which are fundamental to reduce morbidity and improve the quality of life of affected children.

From the translational point of view, the field of congenital ataxias emerges as a paradigmatic model of precision medicine in pediatric neurology. The development of targeted gene therapies, the use of antisense oligonucleotides (ASO), and advances in metabolic replacement therapy represent promising milestones in the transposition of molecular knowledge into clinical practice. In parallel, the strengthening of multidisciplinary rehabilitation approaches, involving physiotherapy, occupational therapy, speech therapy, and neuropsychology, reaffirms the importance of brain plasticity in functional recovery.

In addition to scientific progress, significant ethical and social challenges emerge: equity in access to genetic testing, the need for professional training in clinical genomics, and the creation of collaborative networks that integrate reference centers for rare diseases. Such measures are indispensable to ensure that technological advances translate into real benefits for the pediatric population, especially in resource-limited contexts.

It is concluded, therefore, that congenital ataxias should be understood not only as isolated neurological entities, but as integrative syndromes of brain development, whose study sheds light on fundamental aspects of neurogenesis, synaptogenesis and cerebellar function. The future of the field depends on the consolidation of longitudinal multicenter studies that incorporate artificial intelligence, genetic big data, and digital biomarkers to refine diagnosis and evaluate therapeutic response.

In summary, the current panorama points to a more precise, personalized and interdisciplinary child neurology, in which genetic knowledge and technology are combined with humanized clinics, redefining the care of children with congenital ataxias and establishing new horizons for neuropediatric practice in the twenty-first century.

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