Clinical and Genetic Characterization of a Cohort of Brazilian Patients With Congenital Ataxia

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Abstract

Background and Objectives
Congenital ataxias are rare hereditary disorders characterized by hypotonia and developmental motor delay in the first few months of life, followed by cerebellar ataxia in early childhood. The course of the disease is predominantly nonprogressive, and many patients are incorrectly diagnosed with cerebral palsy. Despite significant advancements in next-generation sequencing in the past few decades, a specific genetic diagnosis is seldom obtained in cases of congenital ataxia. The aim of the study was to analyze the clinical, radiologic, and genetic features of a cohort of Brazilian patients with congenital ataxia.

Methods
Thirty patients with a clinical diagnosis of congenital ataxia were enrolled in this study. Clinical and demographic features and neuroimaging studies were analyzed. Genetic testing (whole-exome sequencing) was also performed.

Results
A heterogeneous pattern of genetic variants was detected. Eighteen genes were involved: *ALDH5A1, BRF1, CACNA1A CACNA1G, CC2D2A, CWF19L1, EXOSC3, ITPR1, KIF1A, MME, PEX10, SCN2A, SNX14, SPTBN2, STXBP1, TMEM240, THG1L,* and *TUBB4A*. Pathogenic/likely pathogenic variants involving 11 genes (*ALDH5A1, CACNA1A, EXOSC3, MME, ITPR1, KIF1A, STXBP1, SNX14, SPTBN2, TMEM240,* and *TUBB4A*) were identified in 46.7% of patients. Variants of uncertain significance involving 8 genes were detected in 33.3% of patients. Congenital ataxias were characterized by a broad phenotype. A genetic diagnosis was more often obtained in patients with cerebellar-plus syndrome than in patients with a pure cerebellar syndrome.

Discussion
This study re-emphasizes the genetic heterogeneity of congenital ataxias and the absence of a clear phenotype-genotype relationship. A specific genetic diagnosis was established in 46.7% of patients. Autosomal dominant, associated with sporadic cases, was recognized as an important genetic inheritance. The results of this analysis highlight the value of whole-exome sequencing as an efficient screening tool in patients with congenital ataxia.

Introduction

The term "congenital ataxia" was first used in 1893 by Freud and in 1903 by Batten to describe a heterogeneous group of rare hereditary ataxias characterized by motor developmental delay in the first months of life followed by cerebellar ataxia in early childhood.[1] Because many affected

Glossary

PCH = pontocerebellar hypoplasia; **SCAs** = spinocerebellar ataxias; **VUS** = variants of uncertain significance; **WES** = whole-exome sequencing.

patients do not progress to neurodegeneration over time, the disease is supposed to be nonprogressive.[2-4] Congenital ataxia is often misdiagnosed as cerebral palsy.[1-5]

Congenital ataxias have been described a long time ago. Still, little progress has been made in the elucidation of their genetic causes. In the past decade, advancements in next-generation sequencing have increased the frequency of genetic diagnosis of a large number of neurologic disorders. However, only a few genes have been implicated in a small number of cases of congenital ataxias.[2,4] This study was designed to enhance our understanding of congenital ataxias. Phenotypic features, neuroimaging findings, and inheritance patterns determined by whole-exome sequencing were analyzed in a cohort of Brazilian patients with congenital ataxia.

Methods

Clinical Protocol and Brain Imaging

Thirty patients previously diagnosed with congenital cerebellar ataxia of unknown genetic origin were examined at the Ataxia Unit of the Federal University of São Paulo (UNIFESP) between 2018 and 2022.

Inclusion criteria were as follows: patients with the typical phenotype of congenital ataxia (very early onset of cerebellar ataxia, up to 3 years of age, preceded by hypotonia and/or motor developmental delay, and nonprogressive disease). Patients with clinical and neuroimaging findings of pontocerebellar hypoplasia (a congenital ataxia subtype with a complex neurologic phenotype, which may include ataxia, other movement disorders, epilepsy, microcephaly, spinal amyotrophy, and pontocerebellar hypoplasia on brain imaging) were also included. Patients with acquired causes of cerebellar ataxia, such as prematurity, perinatal hypoxia, prenatal infections, exposure to teratogens, and metabolic disorders or leukoencephalopathies, were excluded. Data on sex, first symptoms, and clinical and neurologic signs were collected. Brain MRI data were gathered from 29 of 30 patients (one patient had not been submitted to brain imaging). Routine digital brain MRI sequences, including at least T1 and T2-weighted, diffusion-weighted, and fluid-attenuated inversion recovery images, were retrospectively analyzed. Brain imaging studies performed at different centers were also reviewed.

Whole-Exome Sequencing

Buccal swabs were obtained from all patients (n = 30) for whole-exome sequencing (WES). Samples were sent for automated genomic DNA extraction (QIAsymphony DNA kits, QIAGEN). Target regions were captured using a custom library preparation kit (Illumina). Variant calling was then performed and retrieved variants analyzed using Varstation.[6] Variants were classified as per the American College of Medical Genetics and Genomics.[6]

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from all participants. This project was approved by the institutional ethics committee.

Data Availability

The data are not publicly available to protect the privacy of participants.

Results

Clinical and Demographic Features

Thirty patients (16 male and 14 female patients aged 9 months to 53 years) from 28 families and diagnosed with congenital ataxia participated in this study. Except for 2 families with affected non-twin siblings, all patients were sporadic.

Hypotonia and/or motor developmental delay were the most common first symptoms in 66.7% (20/30) of patients. Cerebellar ataxia signs were the first manifestation in 6 patients (20%). Seizures were the first symptom in 3 patients (10%) and oculomotor abnormalities (oculomotor apraxia) in one patient (3.3%).

Isolated cerebellar ataxia or pure cerebellar syndrome was observed in 56.7% (17/30) of patients. Thirteen of 30 patients (43.3%) had cerebellar-plus syndrome, a complex congenital ataxia phenotype characterized by epilepsy, pyramidal signs, and movement disorders other than cerebellar dysfunction. Seven patients (23.3%) had ataxia and epilepsy. Of these, one had seizures, motor stereotypies, and autism spectrum disorder, and one had epilepsy associated with oromandibular dystonia. Three patients (10%) had cerebellar ataxia and a pyramidal syndrome. One of these patients also had upper and lower motor neuron dysfunction. Other movement disorders were observed in 16.7% (5/30) of patients. These included hyperkinetic syndrome (2 brothers), dystonia (one patient), choreoathetosis in distal limbs (one patient), and motor stereotypies (one patient). Most patients had ataxia with no other movement abnormalities.

External eye movement abnormalities such as nystagmus, convergent strabismus, bilateral horizontal ophthalmoplegia,

Figure 1 Phenotype Features and Cerebellar Pattern on Brain MRI in Brazilian Patients With Congenital Ataxia
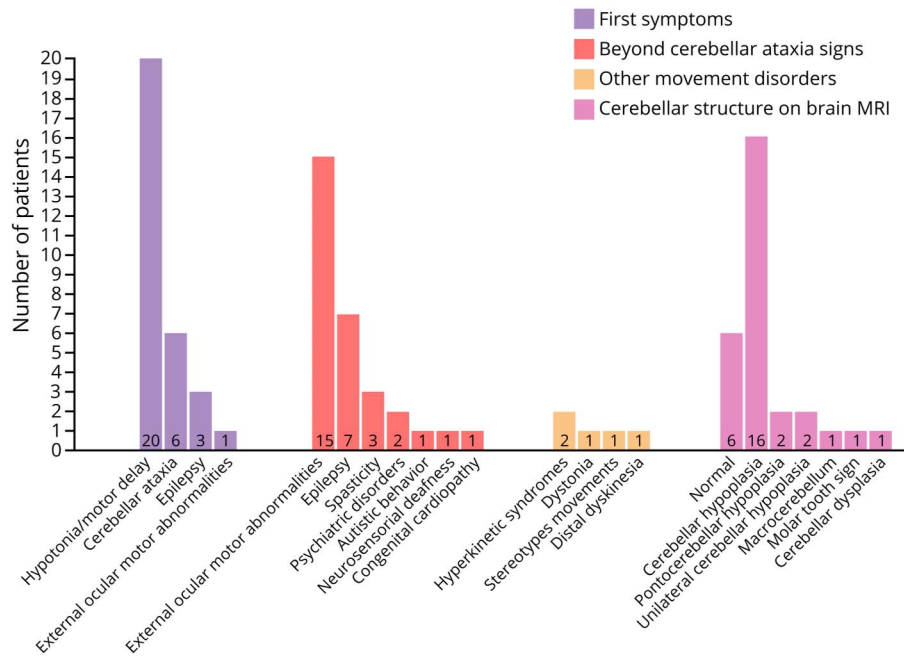
square-wave jerks, and saccades were observed in 50% (15/30) of patients.

Brain Imaging

Brain MRI was normal in 20.7% (6/29) of patients. One patient had not been submitted to brain imaging but met clinical criteria for congenital cerebellar ataxia and was, therefore, included in the study.

Isolated global cerebellar hypoplasia was the most common neurologic finding on brain MRI (16 of 29 patients; 55.2%). Other cerebellar structural abnormalities included unilateral hypoplasia, isolated macrocerebellum, molar tooth sign associated with macrocerebellum, and cerebellar dysplasia. Pontocerebellar hypoplasia was observed in 2 patients. Clinical examination and brain imaging findings of patients with congenital ataxia are displayed in Figure 1.

Supratentorial anomalies were rare. One patient had agenesis of the corpus callosum, one arachnoid cyst in the temporal lobe, and fusion of the basal ganglia associated with cerebellar dysplasia. Corpus callosum and pontocerebellar hypoplasia were also observed in one patient. Brain MRI findings in patients with congenital ataxia are shown in Figure 2.

Whole-Exome Sequencing

Whole-exome sequencing revealed a heterogeneous genotypic spectrum. Eighteen genes were identified: *ALDH5A1*, *BRF1*, *CACNA1A*, *CACNA1G*, *CC2D2A*, *CWF19L1*, *EXOSC3*, *ITPR1*, *KIF1A*, *MME*, *PEX10*, *SCN2A*, *SNX14*, *SPTBN2*, *STXBP1*, *TMEM240*, *THG1L*, and *TUBB4A*. Pathogenic/likely pathogenic variants were identified in

46.7% (14/30) of patients. Variants of uncertain significance (VUS) were found in 33.3% (10/30) of patients. Only 20% (6/30) of patients had normal WES results.

Pathogenic variants were found in 11 genes: *TUBB4A*, *ALDH5A1*, *MME*, *TMEM240*, *KIF1A*, *STXBP1*, *CACNA1A*, *SNX14*, *SPTBN2*, *EXOSC3*, and *ITPR1*. The autosomal-dominant pattern of inheritance prevailed in patients with a genetic diagnosis established in this study. These patients had no family history (sporadic cases). Only 3 patients had biallelic variants in the *ALDH5A1*, *EXOSC3*, and *SNX14* genes. New variants (not reported in population databases such as gnomAD and ABraOM) were limited to 3 genes: *TUBB4A*, *MME*, and *TMEM240*. Relationships between cerebellar structural abnormalities on brain MRI and genetic features of patients with congenital ataxia are shown in Figure 3.

Phenotypic and genetic data of patients with congenital ataxia are presented in the Table.

Discussion

Congenital ataxias are a group of clinically and genetically heterogeneous disorders. Despite advancements in neurogenetics over the past few decades, the genetic etiology of congenital ataxias cannot be determined in a large number of patients.[2,3] A specific genetic diagnosis was established in 46.7% of cases in this cohort of Brazilian patients with congenital ataxia. Autosomal dominant, associated with sporadic cases, was the most common genetic inheritance. Patient phenotype was characterized by pure cerebellar ataxia or
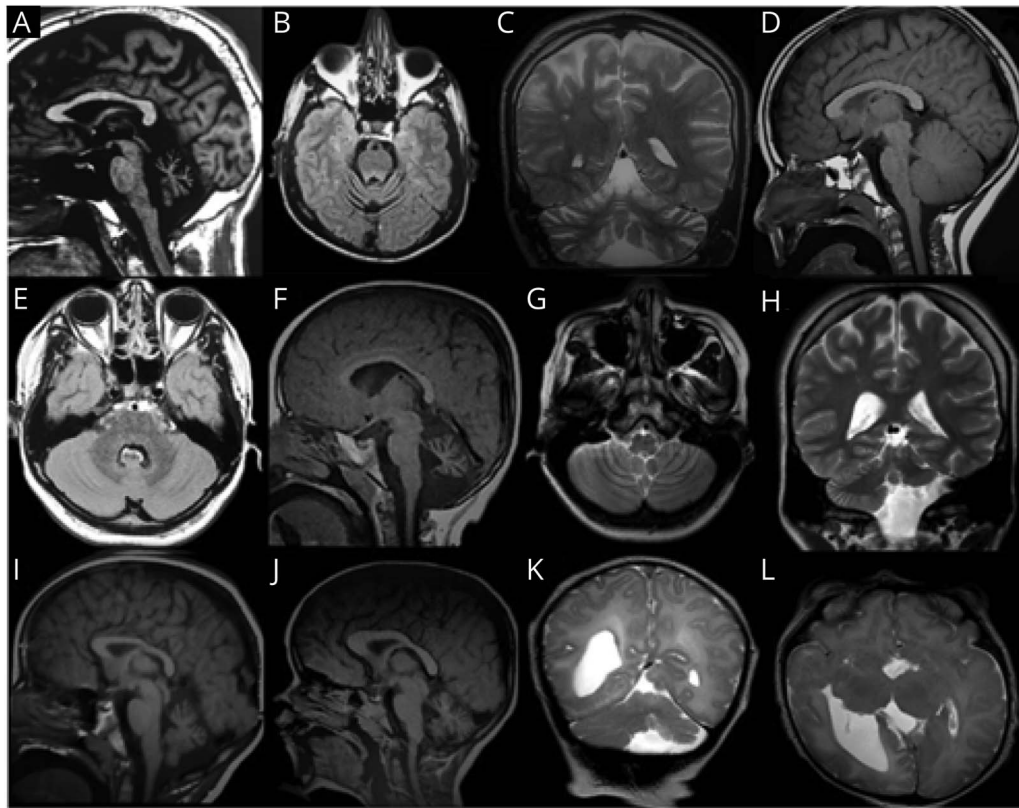
(A) Sagittal T1-weighted showing global cerebellar hypoplasia in a patient with a pathogenic heterozygous mutation in the ITPR1 gene. (B) Axial FLAIR-weighted and (C) coronal T2-weighted showing global cerebellar hypoplasia in a patient with a pathogenic homozygous mutation in the ALDH5A1 gene. (D) Sagittal T1-weighted and (E) axial FLAIR-weighted showing global cerebellar hyperplasia in a patient with unknown genetic etiology. (F) Sagittal T1-weighted showing global cerebellar hypoplasia in a patient with a VUS in the THG1L gene. (G) Axial T2-weighted showing normal cerebellar structure in a patient with unknown genetic etiology. (H) Coronal T2-weighted brain MRI showing unilateral cerebellar hemisphere hypoplasia in a patient with unknown genetic etiology. (I) Sagittal T1-weighted showing global cerebellar hypoplasia in a patient with a monoallelic pathogenic mutation in the KIF1A gene. (J) Sagittal T1-weighted showing global cerebellar hypoplasia in a patient with a VUS in the SCN2A gene. (K) Coronal T2-weighted showing cerebellar dysplasia, followed by hypoplasia of the left cerebellar hemisphere and cortical polymicrogyria in a patient with a novel pathogenic monoallelic mutation in the MME gene. (L) Axial T2-weighted showing abnormal fusion of the basal ganglia, cortical polymicrogyria, and cerebellar dysplasia in patient with a pathogenic mutation in the MME gene. FLAIR = fluid-attenuated inversion recovery.

cerebellar-plus syndrome associated with a broad genotype. This study emphasizes the challenges involved in the establishment of phenotype-genotype relationships in congenital ataxias.

Congenital ataxias are classified into 4 subtypes according to clinical features, disease course, and neuroimaging findings: syndromic, cerebellar malformation, congenital cerebellar hypoplasia, and pontocerebellar hypoplasia (PCH).[1] In this series, 14 patients had congenital cerebellar hypoplasia, 4 patients had cerebellar malformations (congenital isolated macrocerebellum, cerebellar dysplasia, and unilateral hemispheric cerebellar hypoplasia, one, one, and 2 patients, respectively), 3 patients had syndromic congenital ataxia (Joubert syndrome, cerebello-facio-dental syndrome or Uner Tan syndrome, one patient each), and one patient had PCH. Seven patients had no cerebellar structural abnormalities on brain MRI and/or no features suggestive of specific syndromic congenital ataxias and hence did not meet the criteria for any of the aforementioned subtypes. A fifth subtype of congenital

ataxia may, therefore, be suggested: cerebellar syndrome with or without clinical features other than cerebellar dysfunction and no cerebellar atrophy or structural abnormalities on brain imaging. The congenital ataxia classification of patients in this series is summarized in the Table.

It is often difficult to establish the etiology of congenital ataxias because of marked genetic heterogeneity and variable inheritance. X-linked, autosomal dominant, and autosomal recessive inheritance patterns have been described.[1,2] Genetic findings in this study were heterogeneous. Pathogenic variants were identified in 11 genes involved in cerebellar ataxia.[1,2,7-11] Different patients had variants in different genes. The only exceptions were variants in the *SPTBN2*, *CACNA1A*, and *ITPR1* genes, which were found in more than one patient. This finding emphasizes the role of these genes in the etiology of congenital ataxias.

Pathogenic homozygous variants were found in 3 genes: *ALDH5A1*, *EXOSC3*, and *SNX14*. The *ALDH5A1* gene is

Figure 3 Relationships Between Cerebellar Structural Abnormalities on Brain MRI and Genetic Features of Brazilian Patients With Congenital Ataxia
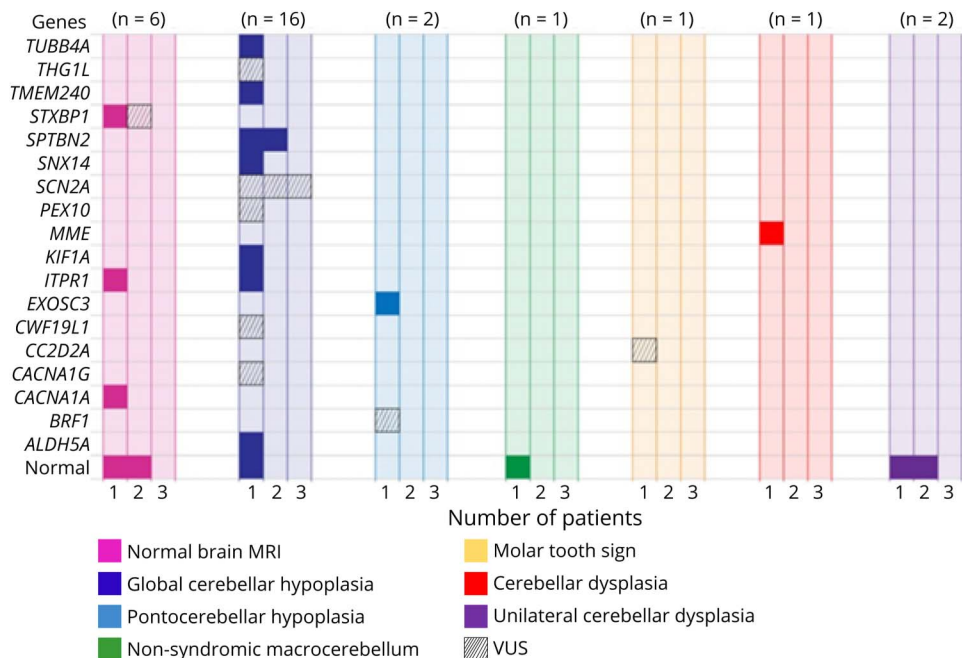
associated with succinic semialdehyde dehydrogenase deficiency (OMIM 271980), a rare autosomal recessive neurologic disorder caused by a defect in the GABA degradative pathway and characterized by mental retardation, cerebellar ataxia, seizures, behavioral disorders, and sleep disturbances.[12-14] Variants in the *SNX14* gene are linked to autosomal recessive spinocerebellar ataxia 20 (SCAR 20), a neurodevelopmental disorder characterized by severe psychomotor developmental delay and early cerebellar dysfunction.[15] These disorders may be associated with a congenital ataxia phenotype.

Pontocerebellar hypoplasia is a rare subtype of congenital ataxia characterized by prenatal-onset neurodegenerative disorders.[1,16-18] Seventeen types of PCH have been described to date. In this sample, 1 patient classified as having PCH (patient 21) had pathogenic homozygous variants in the *EXOSC3* gene, indicative of PCH type 1B. Spinal amyotrophy associated with pontocerebellar hypoplasia on brain imaging is one of the distinguishing characteristics of PCH type 1.[16-18]

Monoallelic pathogenic variants prevailed in this cohort of Brazilian patients with congenital ataxia. Spinocerebellar ataxias (SCAs) tend to manifest in adult life. However, in some SCAs, the first symptoms may appear during childhood. Heterozygous variants in the *SPTBN2* gene, involved in SCA5, have recently been recognized as a relevant cause of nonprogressive, very early-onset ataxia.[4,8,19-23] Likewise, *ITPR1*, the causative gene of SCA15 and SCA29, and *TMEM240*, a gene involved in SCA21, have been implicated as causes of congenital ataxia.[4,9,24-27] These data are supported

by findings of this study (i.e., identification of 5 patients with a congenital ataxia phenotype associated with monoallelic variants in the aforementioned genes). One patient (patient 27) with a monoallelic mutation in the *ITPR1* gene was diagnosed with Uner Tan syndrome (quadrupedal gait, cognitive impairment, speech impairment, and cerebellar ataxia), expanding the phenotype of *ITPR1*-related disorders.[28] The same variant detected in the *ITPR1* gene using GeneMatcher[28] has been identified in one pair of siblings from the Netherlands diagnosed with Gillespie syndrome (unpublished data).

Identification of novel monoallelic variants in the *TUBB4A* and *MME* genes expands the phenotypic expression of related disorders. Mutations in the *TUBB4A* gene are associated with DYT-TUBB4A (OMIM 128101), hypomyelinating leukodystrophy-6 (OMIM 612438), and cerebral malformations with structural abnormalities in the cerebellum and basal ganglia.[29] One patient (patient 1) with a pathogenic variant in the *TUBB4A* gene was classified as having congenital cerebellar hypoplasia with no other structural brain abnormalities, expanding the spectrum of *TUBB4A*-related disorders. The *MME* gene has been implicated as the causative of SCA43, a typical adult-onset SCA.[30] Another patient (patient 20) with a novel monoallelic variant in the same gene and a congenital ataxia phenotype extended the phenotypic spectrum of disorders related to the *MME* gene.

CACNA1A mutations are thought to be an important etiology in patients with congenital ataxia.[10,31-33] Seizures and migraine are often associated with cerebellar dysfunction in

Table Clinical, Neuroimaging, and Genetic Features of Brazilian Patients With Congenital Ataxia

Patients	Sex	First symptoms	Other neurologic signs	Brain structure on MRI	Congenital ataxia classification[a]	Variants	Classification of ACMG 2015[b]
1	M	Hypotonia, developmental delay	Pyramidal syndrome, strength proximal decreased, sensorineural deafness	Global cerebellar hypoplasia	Congenital cerebellar hypoplasia	TUBB4A:c.1096A>G; p.(Thr366Ala) Monoallelic	Likely pathogenic
2	F	Tremor (ataxia)	Hypermetric saccades, deep hyporeflexia	Normal	Unclassified	STXBP1:c.169+5G>A;p.? Monoallelic	VUS
3	M	Hypotonia, developmental delay	Deep hyporeflexia, bilateral convergent strabismus	Global cerebellar hypoplasia	Congenital cerebellar hypoplasia	ALDH5A1:c.803G>A; p.Gly268Glu Biallelic	Pathogenic
4	F	Oculomotor ataxia	Oculomotor ataxia	Molar tooth sign, macrocerebellum	Congenital ataxia syndrome (Joubert syndrome)	1) CC2D2A:c.2102T>G; p.Leu701Arg2 2) CC2D2A:c.3725T>C; p.Ile1242Thr Biallelic	1) VUS 2) VUS
5	M	Hypotonia, developmental delay	Bilateral convergent strabismus, some coffee au lait spots, epilepsy	Macrocerebellum	Congenital cerebellar malformation (macrocerebellum)	Not found	Nothing found
6	F	Hypotonia, developmental delay	Horizontal ophthalmoplegia	Unilateral hypoplasia of the left cerebellar hemisphere	Congenital cerebellar malformation (unilateral cerebellar hypoplasia)	Not found	Nothing found
7	M	Hypotonia, developmental delay	Isolated ataxia cerebellar syndrome	Global cerebellar hypoplasia	Congenital cerebellar hypoplasia	Not found	Nothing found
8	F	Hypotonia, developmental delay	Isolated ataxia cerebellar syndrome	Unilateral hypoplasia of the left cerebellar hemisphere	Congenital cerebellar malformation (unilateral cerebellar hypoplasia)	Not found	Nothing found
9	M	Cerebellar ataxia	Convergent strabismus	Global cerebellar hypoplasia	Congenital cerebellar hypoplasia	CACNA1G:c.3309G>C; p.Trp1103Cys Monoallelic	VUS
10	M	Seizures	Axial hypotonia, hypertonia of appendages, and epilepsy	Cerebellar dysplasia, corpus callosum agenesis, arachnoid cyst, basal ganglia fusion	Congenital cerebellar malformation (cerebellar dysplasia)	MME:c.838G>T; p.Glu280Ter Monoallelic	Likely pathogenic
11	M	Tremor (ataxia)	Deep areflexia, horizontal nystagmus	Global cerebellar hypoplasia	Congenital cerebellar hypoplasia	PEX10:c.851C>T; p.Thr284Ile Monoallelic	VUS
12	F	Hypotonia, developmental delay	Square-wave jerks, head tremor (titubation)	Global cerebellar hypoplasia	Congenital cerebellar hypoplasia	TMEM240:c.305G>A; p.Trp102Ter Monoallelic	Likely pathogenic
13	F	Gait ataxia	Pyramidal syndrome	Global cerebellar hypoplasia	Congenital cerebellar hypoplasia	KIF1A:c.760C>T; p.Arg254Trp Monoallelic	Pathogenic
15	M	Hypotonia, developmental delay	Slight appendage hypertonia, facial dysmorphism	Pontocerebellar hypoplasia	Congenital ataxia syndrome (syndrome cerebello-facio-dental)	BRF1:c.878C>T; p.Ser293Leu Biallelic	VUS
16 17[c]	M F	Seizures	Hyperkinetic syndrome, axial hypotonia, multidirectional nystagmus, deep hyporeflexia	Normal	Unclassified	Not found	Nothing found
18	F	Head tremor (ataxia)	Hypometric saccades, nystagmus in all directions	Normal	Unclassified	CACNA1A:c.4988G>A; p.Arg1663Gln Monoallelic	Pathogenic
19	F	Hypotonia, developmental delay	Oculomotor apraxia, deep areflexia, dystonia in lower limbs and oral region, epilepsy	Global cerebellar hypoplasia	Unclassified	SNX14:c.1108G>T; p.Glu370Ter Biallelic	Pathogenic

Continued

Patients	Sex	First symptoms	Other neurologic signs	Brain structure on MRI	Congenital ataxia classification[a]	Variants	Classification of ACMG 2015[b]
20	F	Hypotonia, developmental delay	Epilepsy, psychiatric disorder (schizophrenia)	Global cerebellar hypoplasia	Unclassified	SPTBN2:c.1307T>C; p.Met436Thr Monoallelic	Likely pathogenic
21	F	Hypotonia, developmental delay	First and second neuron syndrome, bilateral horizontal nystagmus, and a craniofacial disproportion	Pontocerebellar hypoplasia	Pontocerebellar hypoplasia congenital ataxia	EXOSC3:c.395A>C; p.Asp132Ala Biallelic	Pathogenic
22 23 24[c]	M F F	Hypotonia, developmental delay	Isolated ataxia cerebellar syndrome	Global cerebellar hypoplasia	Congenital cerebellar hypoplasia	SCN2A:c.2749G>A; p.Asp917Asn Monoallelic	VUS
25	M	Hypotonia, developmental delay	Deep hyperreflexia and mild facial telangiectasias	Global cerebellar hypoplasia	Congenital cerebellar hypoplasia	SPTBN2:c.1310G>A; p.Arg437Gln Monoallelic	Pathogenic
26	F	Cerebellar ataxia	Profound hyporeflexia, cephalic titubation, mild thoracolumbar scoliosis	Global cerebellar hypoplasia	Congenital cerebellar hypoplasia	CWF19L1:c.24-1G>C;p.? Biallelic	VUS
27	M	Gait delay	Quadrupedal ataxia	Global cerebellar hypoplasia	Congenital ataxia syndrome (Uner Tan syndrome)	ITPR1:c.7952G>A; p.Gly2651Glu Monoallelic	Pathogenic
28	M	Bilateral ptosis and motor delay	Dyskinetic movements in hands and feet, bilateral ptosis and presence of 3 café au lait spots, and congenital heart disease (pulmonary stenosis)	Normal	Unclassified	ITPR1:c.731A>G; p.His244Arg Monoallelic	Likely pathogenic
29	M	Hypotonia, developmental delay	Global hypotonia, horizontal nystagmus, deep hyporeflexia, epilepsy	Global cerebellar hypoplasia	Congenital cerebellar hypoplasia	1) THG1L:c.164T>C; p.Val55Ala 2) THG1L:c.287A>T; p.Asp96Val Biallelic	1) Pathogenic 2) VUS
30	F	Hypotonia, developmental delay	Hypotonia and oculomotor apraxia	MRI not performed	CACNA1A: c4991G>A.p.Arg1664Gln	CACNA1A: c4991G>A.p.Arg1664Gln Monoallelic	Pathogenic

F = female; M = male.
[a] Congenital cerebellar ataxia classification proposed by Raslan IR et al.[1]
[b] ACMG: American College of Medical Genetics and Genomics.
[c] Siblings.

these cases.[33] In 2 patients in this sample (Patients 28 and 30), different monoallelic pathogenic mutations in the *CACNA1A* gene were associated with a congenital ataxia phenotype. Of interest, the father of patient 30 had the same variant and suffered from hemiplegic migraine.

STXBP1 gene variants, an important cause of early-onset epileptic encephalopathies,[34,35] and *KIF1A* gene variants implicated in autosomal dominant mental retardation 9 (OMIM 614255), hereditary sensory neuropathy type II C (OMIM 614213), and spastic paraplegia type 30 (OMIM 610357) play an important role in the etiology of congenital ataxias.[36-39] The current clinical spectrum of *STXBP1*-related disorders is not limited to the epileptic phenotype.[35] In this study, a monoallelic pathogenic mutation in the *STXBP1* gene was implicated as the cause of congenital ataxia with cerebellar-plus syndrome and normal brain structure on MRI. Although patients with the congenital ataxia phenotype associated with monoallelic

variants in the *KIF1A* gene may have pyramidal signs, these are not the prevailing clinical characteristic. Extrapyramidal symptoms, epilepsy, and peripheral neuropathy are also uncommon[38] in these cases, as seen in patient 18.

Variants of unknown significance were identified in 33.3% of patients in this cohort and involved 8 genes. In some patients, the phenotype was consistent with the genotype (patients with variants in *STXBP1*, *CC2D2A*, *CACNA1G*, *BRF1*, *THG1L*, and *CWF19L1* genes). Although the phenotype is indicative of pathogenicity in these cases, complementary diagnostics such as parental segregation studies or functional biochemical tests are needed to confirm a deleterious effect.

This study contributes to the understanding of the clinical and genetic aspects of congenital ataxias. However, small sample size, analysis of neuroimages obtained at different centers using different protocols, lack of cognitive function tests, and

complementary diagnostics such as microarray testing and whole-genome sequencing in patients with VUS and patients with normal WES results are potential limitations of this study.

This study highlights the value of WES as an efficient screening tool in patients with congenital ataxia. In this cohort of Brazilian patients with congenital ataxia, genetic variants were identified in 80% of patients and a specific genetic diagnosis obtained in 46.7% of cases. Accurate diagnosis of congenital ataxia requires a comprehensive approach including prenatal and postnatal history, physical examination, neuroimaging, and laboratory testing. Whole-exome sequencing represents another important step in this process.

The genetic diagnosis of congenital ataxia is often challenging because of the diversity of clinical and genetic features. This study re-emphasizes the genetic heterogeneity of congenital ataxias, confirms monoallelic variants as an important inheritance pattern, expands the genotype associated with this disorder, and underscores the difficulties involved in establishing phenotype-genotype relationships.

Despite significant advancements in neurogenetic technology, in many cases of congenital ataxia the genetic etiology cannot be determined. Further research is needed to understand the complex and unexplored field of congenital ataxia. Genetic testing abbreviates the difficult diagnostic process, optimizes patient management, and facilitates accurate recurrence risk and prenatal counseling, with significant effects on the life of patients and their families.

Study Funding

Disclosure

The authors report no relevant disclosures. Go to Neurology.org/NG for full disclosures.

Publication History

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Name	Location	Contribution
Ivana R. Raslan, MD	Department of Ataxia Unit of the Federal University of São Paulo (UNIFESP), Brazil	Major role in the acquisition of data; study concept or design; analysis or interpretation of data
Thiago Yoshinaga Tonholo Silva, MD	Department of Ataxia Unit of the Federal University of São Paulo (UNIFESP), Brazil	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data

Appendix (continued)

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Marcondes C. França Jr, MD, PHD	Department of Neurology, Universidade de Campinas (UNICAMP), Brazil	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
Orlando G. Barsottini, MD, PhD	Department of Ataxia Unit of the Federal University of São Paulo (UNIFESP), Brazil	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
José Luiz Pedroso, MD, PhD	Department of Ataxia Unit of the Federal University of São Paulo (UNIFESP), Brazil	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

References

1. Raslan IR, Barsottini OG, Pedroso JL. A proposed clinical classification and a diagnostic approach for congenital ataxias. *Neurol Clin Pract.* 2021;11(3):e328-e336. doi:10.1212/CPJ.0000000000000966
2. Bertini E, Zanni G, Boltshauser E. Nonprogressive congenital ataxias. *Handb Clin Neurol.* 2018;155:91-103. doi:10.1016/B978-0-444-64189-2.00006-8
3. Pinchefsky EF, Accogli A, Shevell MI, Saint-Martin C, Srour M. Developmental outcomes in children with congenital cerebellar malformations. *Dev Med Child Neurol.* 2019;61(3):350-358. doi:10.1111/dmcn.14059
4. Parolin Schnekenberg R, Perkins EM, Miller JW, et al. De novo point mutations in patients diagnosed with ataxic cerebral palsy. *Brain.* 2015;138(Pt 7):1817-1832. doi:10.1093/brain/awv117
5. Valence S, Cochet E, Rougeot C, et al. Exome sequencing in congenital ataxia identifies two new candidate genes and highlights a pathophysiological link between some congenital ataxias and early infantile epileptic encephalopathies. *Genet Med.* 2019;21(3):553-563. doi:10.1038/s41436-018-0089-2
6. Faria ACO, Caraciolo MP, Minillo RM, et al. Varstation: a complete and efficient tool to support NGS data analysis. *bioRxiv.* 2019:833582. biorxiv.org/content/10.1101/833582v1%0
7. Aldinger KA, Timms AE, Thomson Z, et al. Redefining the etiologic landscape of cerebellar malformations. *Am J Hum Genet.* 2019;105(3):606-615. doi:10.1016/j.ajhg.2019.07.019
8. Zonta A, Brussino A, Dentelli P, Brusco A. A novel case of congenital spinocerebellar ataxia 5: further support for a specific phenotype associated with the p.(Arg480Trp) variant in SPTBN2. *BMJ Case Rep.* 2020;13(12):e238108. doi:10.1136/bcr-2020-238108
9. Das J, Lilleker J, Shereef H, Ealing J. Missense mutation in the ITPR1 gene presenting with ataxic cerebral palsy: description of an affected family and literature review. *Neurol Neurochir Pol.* 2017;51(6):497-500. doi:10.1016/j.pjnns.2017.06.012
10. Travaglini L, Nardella M, Bellacchio E, et al. Missense mutations of CACNA1A are a frequent cause of autosomal dominant nonprogressive congenital ataxia. *Eur J Paediatr Neurol.* 2017;21(3):450-456. doi:10.1016/j.ejpn.2016.11.005

11. Aldinger KA, Doherty D. The genetics of cerebellar malformations. *Semin Fetal Neonatal Med.* 2016;21(5):321-332. doi:10.1016/j.siny.2016.04.008

12. DiBacco ML, Pop A, Salomons GS, et al. Novel ALDH5A1 variants and genotype: phenotype correlation in SSADH deficiency. *Neurology.* 2020;95(19):e2675-e2682. doi:10.1212/WNL.0000000000010730

13. Akaboshi S, Hogema BM, Novelletto A, et al. Mutational spectrum of the succinate semialdehyde dehydrogenase (ALDH5A1) gene and functional analysis of 27 novel disease-causing mutations in patients with SSADH deficiency. *Hum Mutat.* 2003; 22(6):442-450. doi:10.1002/humu.10288

14. Blasi P, Palmerio F, Caldarola S, et al. Succinic semialdehyde dehydrogenase deficiency: clinical, biochemical and molecular characterization of a new patient with severe phenotype and a novel mutation. *Clin Genet.* 2006;69(3):294-296. doi: 10.1111/j.1399-0004.2006.00579.x

15. Thomas AC, Williams H, Setó-Salvia N, et al. Mutations in SNX14 cause a distinctive autosomal-recessive cerebellar ataxia and intellectual disability syndrome. *Am J Hum Genet.* 2014;95(5):611-621. doi:10.1016/j.ajhg.2014.10.007

16. Ivanov I, Atkinson D, Litvinenko I, et al. Pontocerebellar hypoplasia type 1 for the neuropediatrician: genotype-phenotype correlations and diagnostic guidelines based on new cases and overview of the literature. *Eur J Paediatr Neurol.* 2018;22(4): 674-681. doi:10.1016/j.ejpn.2018.03.011

17. Bilge S, Mert GG, Hergüner Ö, et al. Clinical, radiological, and genetic variation in pontocerebellar hypoplasia disorder and our clinical experience. *Ital J Pediatr.* 2022; 48(1):169. doi:10.1186/s13052-022-01349-9

18. Schottmann G, Picker-Minh S, Schwarz JM, et al. Recessive mutation in EXOSC3 associates with mitochondrial dysfunction and pontocerebellar hypoplasia. *Mitochondrion.* 2017;37:46-54. doi:10.1016/j.mito.2017.06.007

19. Mizuno T, Kashimada A, Nomura T, et al. Infantile-onset spinocerebellar ataxia type 5 associated with a novel SPTBN2 mutation: a case report. *Brain Dev.* 2019;41(7): 630-633. doi:10.1016/j.braindev.2019.03.002

20. Al-Muhaizea MA, AlMutairi F, Almass R, et al. A novel homozygous mutation in SPTBN2 leads to spinocerebellar ataxia in a consanguineous family: report of a new infantile-onset case and brief review of the literature. *Cerebellum.* 2018;17(3):276-285. doi:10.1007/s12311-017-0893-2

21. Sancho P, Andrés-Bordería A, Gorría-Redondo N, et al. Expanding the β-III spectrin-associated phenotypes toward non-progressive congenital ataxias with neurodegeneration. *Int J Mol Sci.* 2021;22(5):2505. doi:10.3390/ijms22052505

22. Gouvêa LA, Raslan IR, Rosa ABR, et al. Spinocerebellar ataxia type 5 (SCA5) mimicking cerebral palsy: a very early onset autosomal dominant hereditary ataxia. *Cerebellum.* 2023;22(2):316-318. doi:10.1007/s12311-022-01380-w

23. Nicita F, Nardella M, Bellacchio E, et al. Heterozygous missense variants of SPTBN2 are a frequent cause of congenital cerebellar ataxia. *Clin Genet.* 2019;96(2):169-175. doi:10.1111/cge.13562

24. Zambonin JL, Bellomo A, Ben-Pazi H, et al. Spinocerebellar ataxia type 29 due to mutations in ITPR1: a case series and review of this emerging congenital ataxia. *Orphanet J Rare Dis.* 2017;12(1):121. doi:10.1186/s13023-017-0672-7

25. Synofzik M, Helbig KL, Harmuth F, et al. De novo ITPR1 variants are a recurrent cause of early-onset ataxia, acting via loss of channel function. *Eur J Hum Genet.* 2018; 26(11):1623-1634. doi:10.1038/s41431-018-0206-3

26. van der Put J, Daugeliene D, Bergendal Å, Kvarnung M, Svensningsson P, Paucar M. On spinocerebellar ataxia 21 as a mimicker of cerebral palsy. *Neurol Genet.* 2022;8(3): e668. doi:10.1212/NXG.0000000000000668

27. Riso V, Galatolo D, Barghigiani M, et al. A next generation sequencing-based analysis of a large cohort of ataxic patients refines the clinical spectrum associated with spinocerebellar ataxia 21. *Eur J Neurol.* 2021;28(8):2784-2788. doi:10.1111/ene.14868

28. Raslan IR, França MC Jr, Oliveira JB, et al. Quadrupedal gait and cerebellar hypoplasia, the Uner Tan syndrome, caused by ITPR1 gene mutation. *Parkinsonism Relat Disord.* 2021;92:33-35. doi:10.1016/j.parkreldis.2021.10.008

29. Purnell SM, Bleyl SB, Bonkowsky JL. Clinical exome sequencing identifies a novel TUBB4A mutation in a child with static hypomyelinating leukodystrophy. *Pediatr Neurol.* 2014;50(6):608-611. doi:10.1016/j.pediatrneurol.2014.01.051

30. Depondt C, Donatello S, Rai M, et al. MME mutation in dominant spinocerebellar ataxia with neuropathy (SCA43). *Neurol Genet.* 2016;2(5):e94. doi:10.1212/NXG.0000000000000094

31. Indelicato E, Boesch S. From genotype to phenotype: expanding the clinical spectrum of *CACNA1A* variants in the era of next generation sequencing. *Front Neurol.* 2021;12: 639994. doi:10.3389/fneur.2021.639994

32. Izquierdo-Serra M, Fernández-Fernández JM, Serrano M. Rare CACNA1A mutations leading to congenital ataxia. *Pflugers Arch.* 2020;472(7):791-809. doi:10.1007/s00424-020-02396-z

33. Naik S, Pohl K, Malik M, Siddiqui A, Josifova D. Early-onset cerebellar atrophy associated with mutation in the CACNA1A gene. *Pediatr Neurol.* 2011;45(5): 328-330. doi:10.1016/j.pediatrneurol.2011.08.002

34. Gburek-Augustat J, Beck-Woedl S, Tzschach A, Bauer P, Schoening M, Riess A. Epilepsy is not a mandatory feature of STXBP1 associated ataxia-tremor-retardation syndrome. *Eur J Paediatr Neurol.* 2016;20(4):661-665. doi:10.1016/j.ejpn.2016.04.005

35. Değerliyurt A, Kesen GG, Ceylaner S. Ataxia, tremor, intellectual disability: a case of STXBP1 encephalopathy with a new mutation. *Turk J Pediatr.* 2019;61(5):757-759. doi:10.24953/turkjped.2019.05.015

36. Aguilera C, Hümmer S, Masanas M, et al. The novel KIF1A missense variant (R169T) strongly reduces microtubule stimulated ATPase activity and is associated with NESCAV syndrome. *Front Neurosci.* 2021;15:618098. doi:10.3389/fnins.2021.618098

37. Nemani T, Steel D, Kaliakatsos M, et al. KIF1A-related disorders in children: a wide spectrum of central and peripheral nervous system involvement. *J Peripher Nerv Syst.* 2020;25(2):117-124. doi:10.1111/jns.12368

38. Ohba C, Haginoya K, Osaka H, et al. De novo KIF1A mutations cause intellectual deficit, cerebellar atrophy, lower limb spasticity and visual disturbance. *J Hum Genet.* 2015;60(12):739-742. doi:10.1038/jhg.2015.108

39. Boyle L, Rao L, Kaur S, et al. Genotype and defects in microtubule-based motility correlate with clinical severity in *KIF1A*-associated neurological disorder. *HGG Adv.* 2021;2(2):100026. doi:10.1016/j.xhgg.2021.100026