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Case Report

A novel pathogenic heterozygous mutation in the CDC42BPB gene: a case report of global developmental delay potentially associated with Chilton-Okur-Chung syndrome

Catarina Barros Azevedo[1]*, Lucinda Amorim Delgado[1], Maria Lopes Almeida[2], Sandra Rodrigues[3], André Almeida[4]

[1]Department of Pediatric, Unidade Local de Saúde de Alto Ave, Guimarães, Portugal
[2]Department of Human Genetics, Unidade Local de Saúde de Braga, Braga, Portugal
[3]Department of Pediatric, Unidade Local de Saúde de Tâmega e Sousa, Penafiel, Portugal
[4]Department of Neonatology, Unidade Local de Saúde de Alto Ave, Guimarães, Portugal

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***Correspondence:**
Dr. Catarina Barros Azevedo,
E-mail: catbazevedo8@gmail.com

ABSTRACT

Terminal deletions involving chromosome 14q32 are exceptionally rare and associated with variable neurodevelopmental phenotypes. We report a female child with fetal growth restriction, axial hypotonia, global developmental delay, delayed motor acquisition, and characteristic craniofacial dysmorphisms, including high forehead, downslanting palpebral fissures, retrognathia, sparse scalp hair, sparse eyebrows, and bilateral instep edema. Additional findings included patent ductus arteriosus, mild valvular insufficiency, and a globally thin corpus callosum on brain magnetic resonance imaging. Chromosomal microarray analysis identified a de novo 4.21Mb terminal heterozygous deletion at 14q32.31q32.33 encompassing multiple clinically relevant genes, including CDC42BPB, a gene associated with Chilton-Okur-Chung neurodevelopmental syndrome (CHOCNS). The deletion was classified as pathogenic according to ACMG/AMP criteria and supported by previously reported pathogenic alterations in DECIPHER. The patient demonstrated a relatively favorable developmental trajectory following early multidisciplinary intervention, achieving independent ambulation by 36 months with progressive cognitive and language acquisition. This report expands the phenotypic spectrum associated with distal 14q32 deletions involving CDC42BPB and highlights the importance of early diagnosis, longitudinal follow-up, and multidisciplinary intervention in rare neurodevelopmental disorders.

Keywords: CDC42BPB, Neurodevelopmental disorder, Chilton-Okur-Chung

INTRODUCTION

Facial dysmorphisms associated with genetic syndromes remain a cornerstone of the clinical evaluation of neurodevelopmental disorders, often representing some of the earliest observable indicators of disrupted developmental pathways.[1] Careful phenotypic characterization of craniofacial features has traditionally enabled clinicians to recognize and categorize rare syndromes, often guiding further diagnostic workup before molecular confirmation is established.[1,2] Despite the increasing availability of genomic technologies, the integration of thorough clinical examination with genetic data remains essential, particularly in conditions with marked phenotypic heterogeneity.[3]

Chilton-Okur-Chung neurodevelopmental syndrome (CHOCNS) is one such entity, an ultra-rare autosomal dominant disorder caused by heterozygous loss-of-function or missense variants in the CDC42BPB gene.[4,5]

Affected individuals typically present with a constellation of findings, including global developmental delay, intellectual disability, behavioral disturbances, and structural brain abnormalities, often accompanied by subtle yet clinically informative craniofacial features.[4] Although it shares part of its nomenclature with Okur-Chung neurodevelopmental syndrome, CHOCNS represents a distinct entity, caused by pathogenic variants in a different gene.[6]

Dysmorphic facial features are reported in approximately half of affected individuals and may include macrocephaly, abnormal head shape, a broad or high forehead, sparse scalp hair and eyebrows, low-set ears, and up or down slanting palpebral fissures.[4,5] Additional findings may comprise hypertelorism, a high nasal root, flat nasal bridge, broad nasal tip, short philtrum, large mouth, thin upper lip, and widely spaced teeth.[4]

Neuroimaging may reveal nonspecific structural brain abnormalities, most notably cerebellar vermis hypoplasia and agenesis or hypoplasia of the corpus callosum. Involvement of other organ systems has been reported in rare cases.[4,5]

Chilton et al first described a cohort of 14 unrelated individuals, aged between 2 and 29 years, all harboring de novo heterozygous variants in the CDC42BPB gene identified through exome sequencing.[4] Among these cases, one male fetus presented with cystic hygroma and progressive ventriculomegaly detected on prenatal ultrasound, leading to termination of pregnancy at 27 weeks of gestation. In contrast, one child exhibited normal development at 2.5 years of age. All remaining individuals demonstrated global developmental delay, frequently accompanied by intellectual disability, delayed speech acquisition, and behavioral disturbances, including attention-deficit/hyperactivity disorder, aggression, anxiety, and repetitive or stereotypic behaviors. Seizures and EEG abnormalities were documented in a subset of patients, as were ophthalmologic findings. Less frequent features included distal skeletal anomalies of the hands and feet, pectus deformities, cryptorchidism, micropenis, renal anomalies, sensorineural hearing loss, recurrent otitis media, constipation, and joint hypermobility.[4,5]

To date, no standardized clinical diagnostic criteria have been established for Chilton-Okur-Chung neurodevelopmental syndrome. Diagnosis is confirmed in individuals with suggestive clinical features and the identification of a heterozygous pathogenic variant in the CDC42BPB gene (OMIM #614062), located on chromosome 14q32.324. This gene encoding protein kinases have been increasingly implicated in a broad spectrum of neurodevelopmental disorders. These conditions are typically characterized by nonspecific clinical features and marked phenotypic variability, even among individuals harboring the same genetic variant. This heterogeneity likely reflects the wide range of downstream targets and biological processes regulated by kinase signaling pathways.[5]

In the cohort described by Chilton et al, a total of 12 heterozygous variants in CDC42BPB were identified across 14 unrelated individuals, all predicted to be deleterious.[4] These variants were confirmed to have arisen de novo in all cases for which parental DNA was available (11/14), further supporting a causal relationship. Notably, a high degree of phenotypic variability was observed, even among individuals carrying identical variants.

To date, fewer than twenty cases of CHOCNS have been reported in the literature, and both the genotypic and phenotypic spectrum of this condition remain incompletely characterized. The natural history of the disorder has yet to be fully elucidated. In this context, each additional case report contributes incrementally but meaningfully to the collective understanding of this ultra-rare syndrome, informing genotype-phenotype correlations, refining diagnostic criteria, and ultimately supporting more evidence-based, individualized therapeutic strategies. The present report describes and comprehensively characterizes a new case of Chilton-Okur-Chung Neurodevelopmental Syndrome, with particular emphasis on the craniofacial dysmorphic features, neurodevelopmental trajectory, and therapeutic interventions undertaken.

CASE REPORT

A 2-year-old girl, under Neonatology hospital follow-up due to fetal growth restriction, was submitted to genetics evaluation at 8 months of age due to axial hypotonia, delayed achievement of developmental milestones, and distinctive phenotypic features. She was born to non-consanguineous parents. The family history was unremarkable for neurodevelopmental disorders, although the mother had a solitary kidney.

The pregnancy was monitored late, and fetal growth restriction with evidence of blood flow redistribution was detected at 32 weeks of gestation, which prompted delivery by induction of labor at 36 weeks and 5 days. Delivery was performed by cesarean section due to a high risk of fetal hypoxia/acidosis, based on cardiotocographic findings interpreted according to International Federation of Gynecology and Obstetrics (FIGO) guidelines.[7] Apgar scores were 8, 9, and 10 at 1, 5, and 10 minutes, respectively.

Her body weight, length, and head circumference at birth were 2095g (-1.82 SDS), 44cm (-1.37 SDS), and 31.5cm (-1.08 SDS), respectively, according to Fenton's 2025 growth curves. Two days after birth, she required hospitalization in an intermediate neonatal care unit for a duration of 4 days, primarily due to thermal instability, feeding difficulties and jaundice, meeting the criteria for phototherapy, which she carried out for 24 hours. All

recommended neonatal screenings were conducted, and no abnormalities were reported, namely the National Early Diagnosis Program, Universal Neonatal Hearing Screening, Screening for Critical Congenital Heart Disease via Pulse Oximetry, and Neonatal Ophthalmological Screening (Red Reflex Test).

In accordance with the national protocol for late preterm infants, she underwent a transfontanellar ultrasound at birth, revealing mild bilateral periventricular hyper echogenicity, but a follow-up ultrasound at 6 months showed normalization of the findings. During medical follow-up, was noted high forehead, downslanting palpebral fissure, mandibular retrognathism, sparse scalp hair and eyebrows, hypotonia, poor muscle mass, single palmar crease, bilateral instep edema, and hallux in extension. Growth parameters, including weight, length, and head circumference, remained appropriate for age, consistently tracking around a z-score of 0 based on the WHO Child Growth Standards.

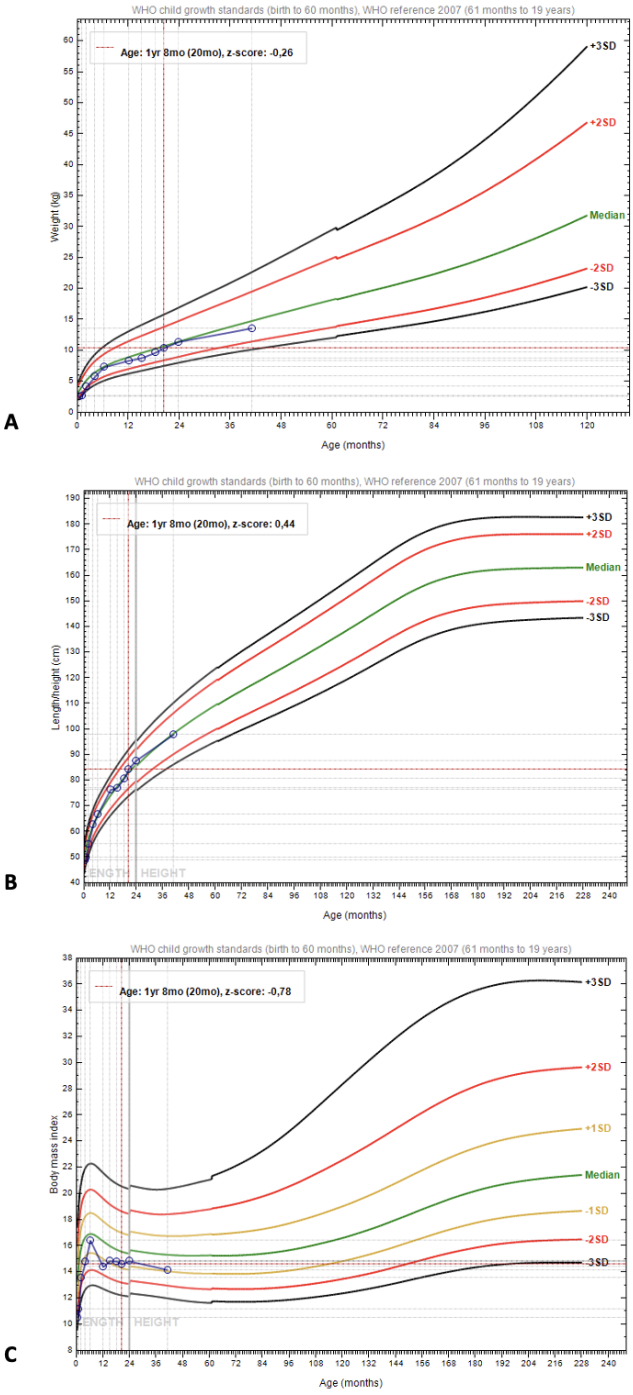

Figure 1: Growth charts according to WHO child growth standards (AnthroPlus).

Developmental delay became evident during infancy, predominantly affecting the gross motor domain. The patient was referred to Physical Medicine and Rehabilitation at 8 months and enrolled in a multidisciplinary early intervention program, including physical, occupational, and speech-language therapies. Caregivers reported generalized axial hypotonia and delayed head control, which was achieved at approximately 8 months of age. Independent sitting was attained at 10 months, consistent with delayed gross motor milestone acquisition. First meaningful words emerged at 16 months, indicating delayed expressive language development. At 20 months of age, she had not yet achieved independent ambulation, corresponding to persistent gross motor delay, although plantar weight-bearing and lower limb strength were preserved. By 24 months, she was able to stand independently and ambulate with a wide-based gait, suggestive of residual balance immaturity. At that time, social-communication skills were relatively preserved, with appropriate eye contact and emerging symbolic play. Receptive language included comprehension of simple commands, while expressive vocabulary comprised approximately 5-10 meaningful words. At 36 months of age, independent gait was fully established; however, impaired dynamic balance and motor coordination were evident, particularly during running. Fine motor and cognitive-adaptive skills showed progressive acquisition, including imitation of animal sounds, recognition of letters and colors, counting to five, and an expressive vocabulary of approximately 15-20 words, still below age expectations. A summary of neurodevelopmental milestones is presented in Table 1.

Table 1: Summary of neurodevelopmental milestones.

Age (in months)	Domain	Milestone achieved	Expected age range
8	Gross motor	Head control attained	2-4 months
10	Gross motor	Independent sitting	6-9 months
16	Language - expressive	First meaningful words	10-14 months
20	Gross motor	Plantar weight-bearing and lower limb strength preserved	12-15 months
24	Gross motor	Independent standing and ambulation with wide-based gait	12-15 months
24	Social communication	Appropriate eye contact; emerging symbolic play; comprehension of simple commands	18-24 months
24	Language - expressive	~5–10 meaningful words	~50 words by 24 months
36	Gross motor	Independent gait established; impaired dynamic balance and motor coordination, especially during running	12-15 months
36	Cognitive / fine motor	Imitation of animal sounds; letter and color recognition; counting to five	24-36 months
36	Language - expressive	~15–20 meaningful words	~200-1000 words by 36 months

Age of attainment compared to normative expectations (Denver Developmental Screening / WHO Motor Development milestones)

As part of the diagnostic workup, a comprehensive biochemical evaluation was performed to exclude inherited metabolic disorders, including analysis of organic acids, amino acids, acylcarnitine profile, lactate, and pyruvate; all results were within normal limits.

At 6 months of age, ophthalmologic evaluation revealed a centered Hirschberg reflex, bilateral normal red reflexes, and prominent epicanthal folds, consistent with pseudostrabismus. At the 2-year follow-up, mild astigmatism was identified, not requiring corrective lenses, and annual surveillance was recommended.

The patient was also referred to otorhinolaryngology at 20 months for further evaluation and exclude associated structural abnormalities. At 12 months, she was evaluated by pediatric cardiology, showing patent foramen ovale, mild mitral insufficiency, mild aortic insufficiency, and persistence of a restrictive patent ductus arteriosus on transthoracic echocardiogram. Therefore, was referred for percutaneous closure of the patent ductus arteriosus.

Brain magnetic resonance imaging (MRI), performed at 23 months of age, showed no significant abnormalities in brain parenchymal morphology or signal. The corpus callosum was structurally complete but globally thin, particularly at the isthmus.

Chromosomal microarray analysis identified a 4.21 Mb, terminal heterozygous deletion at 14q32.31q32.33. This region encompasses 16 genes with known or potential clinical relevance, including CDC42BPB, within the critical region associated with 14q32 microdeletion syndrome. Pathogenic heterozygous variants in CDC42BPB have been associated with Chilton-Okur-Chung syndrome and individuals with similar alterations classified as pathogenic have been described in the DECIPHER syndrome database.[9] Additionally, in the Franklin variant classification tool, based on the

ACMG/AMP guidelines, the alteration is classified as pathogenic.[10] Taken together, these findings support the clinical pathogenicity of the identified deletion and its likely contribution to the patient's phenotype. Genetic tests were performed on the parents, confirming that this was a de novo mutation.

The present case appears to fall within the more favorable end of the phenotypic spectrum. The patient's neurodevelopmental trajectory, supported by early and sustained therapeutic intervention, compares favorably with that reported in most previously described cases, providing cautious yet clinically meaningful optimism regarding prognosis in a subset of affected individuals.

These findings underscore the importance of early diagnosis and prompt multidisciplinary management, as the window of neuroplasticity in early childhood may represent a critical determinant of long-term functional outcomes in Chilton-Okur-Chung syndrome, consistent with observations across a broader range of rare monogenic neurodevelopmental disorders.

DISCUSSION

This case describes a child with a terminal heterozygous deletion at 14q32.31q32.33, presenting with a constellation of clinical features including fetal growth restriction, characteristic craniofacial dysmorphisms, generalized hypotonia, and global developmental delay, predominantly affecting the gross motor domain. The identified deletion encompasses genes within a region previously implicated in 14q32 microdeletion syndrome and overlaps with loci associated with Chilton-Okur-Chung syndrome, although the genotype-phenotype correlation remains incompletely understood. CHOCNS is an ultra-rare genetic disorder characterized by global development delay, intellectual disability, hypotonia, and occasional speech delay.[4]

Fewer than 20 cases have been reported in the literature.[5] Neurodevelopmental impairment represents the most prevalent clinical feature, described in 12 of 14 patients, and includes developmental delay, intellectual disability, and hypotonia, findings that are also present in our patient. Autism spectrum disorder has been reported with notable frequency; however, no features suggestive of this condition were identified in the present case. Despite the small number of reported cases, the available data indicate a broad phenotypic spectrum, ranging from mild to severe clinical presentations.[4,5] In this context, the patient's clinical presentation is broadly consistent with previously reported cases; however, the relatively favorable neurodevelopmental trajectory observed, particularly in the setting of early multidisciplinary intervention, adds to the expanding phenotypic spectrum and underscores the variability in clinical outcomes associated with this condition.

Dysmorphic features, although generally subtle, have been reported in more than half of the described individuals and are also present in our patient. The most frequently documented features include sparse scalp hair, variations in palpebral fissure orientation (both upslanting and downslanting), hypertelorism, a broad nasal tip, mandibular retrognathism, and instep edema, all of which were observed in the present case.

Structural brain abnormalities have been described in approximately half of reported individuals, including cerebellar vermis hypoplasia and thinning or agenesis of the corpus callosum. In our patient, brain MRI demonstrated a structurally complete corpus callosum, although globally thin, particularly at the isthmus, representing a milder manifestation within this spectrum.

Cardiac anomalies have been reported in a minority of cases, including patent foramen ovale and patent ductus arteriosus. Although a direct association with the syndrome remains uncertain, similar findings were identified in our patient, further contributing to the phenotypic characterization.

Given its ultra-rare nature, it is likely that a proportion of affected individuals remain undiagnosed or misdiagnosed, particularly in resource-limited settings with restricted access to genetic testing. Consequently, currently reported cases may represent only a fraction of the true disease burden. Furthermore, because the identified deletion encompasses multiple genes, the contribution of additional deleted loci to the observed phenotype cannot be excluded, further complicating genotype-phenotype correlations. These considerations underscore the need for further studies addressing both the clinical spectrum and epidemiology of this condition.

To date, no disease-specific pharmacological or curative therapy has been established for CHOCNS, consistent with the broader landscape of rare monogenic neurodevelopmental disorders, in which targeted molecular treatments remain largely unavailable. Clinical management is therefore supportive and symptom-directed, tailored to the individual's phenotypic profile and the severity of impairment across domains.[4,5] In this context, early initiation of multidisciplinary rehabilitative interventions represents the cornerstone of care, aligning with standard practice in children with global developmental delay, regardless of etiology.[10,11] Ongoing multidisciplinary follow-up, incorporating neurological, developmental, and behavioral assessments, is essential to monitor progression, optimize therapeutic strategies, and detect the emergence of associated complications, including structural brain abnormalities or involvement of additional organ systems.[4,5]

CONCLUSION

The long-term prognosis remains incompletely defined, reflecting the limited evidence base and the absence of

systematic longitudinal data. Available reports, however, highlight substantial phenotypic variability, with clinical severity ranging from profound developmental impairment and structural brain anomalies to comparatively favorable outcomes, including near-normal neurodevelopment in early childhood in isolated cases. Further research will be essential to better delineate the natural history and clarify the biological mechanisms underlying this variability.

This report adds to the emerging body of evidence on CDC42BPB-related disorders, contributing to improved recognition of the phenotypic spectrum and reinforcing the importance of early, multidisciplinary management in optimizing clinical outcomes.

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