ISSN: 2584-0355
DOI: doi.org/10.51219/MCCRJ/Daniela-Ramírez-Pertuz/455

URF PUBLISHERS
connect with research world

Medical & Clinical Case Reports Journal

https://urfpublishers.com/journal/case-reports

Vol: 4 & Iss: 1

Case Report

New Truncating variant in CUL4B gene in a Colombian family with Cabezas Syndrome

Daniela Ramírez Pertuz[1]*, Nelly Silva[1], Margarita Vega[1], Victoria Leal[2] and Awadalla Shokery[2]

[1]Fellow in Pediatric Endocrinology at Fundación Universitaria de Ciencias de la Salud, Bogotá, Colombia

[2]Pediatric Endocrinologist, Professor at Fundación Universitaria de Ciencias de la Salud, Bogotá, Colombia

Citation: Pertuz DR, Silva N, Vega M, Leal V, Shokery A. New Truncating variant in CUL4B gene in a Colombian family with Cabezas Syndrome. *Medi Clin Case Rep J* 2026;4(1):1659-1661. DOI: doi.org/10.51219/MCCRJ/Daniela-Ramírez-Pertuz/455

Received: 13 March, 2026; **Accepted:** 16 March, 2026; **Published:** 18 March, 2026

***Corresponding author:** Daniela Ramírez Pertuz, Fellow in Pediatric Endocrinology at Fundación Universitaria de Ciencias de la Salud, Bogotá, Colombia

ABSTRACT

Variants in the CUL4B gene are associated with Cabezas syndrome, a rare X-linked disorder characterized by intellectual disability and a variable spectrum of neurological and systemic manifestations including seizures, hypogonadism, behavioral abnormalities and distinctive facial features. Clinical Case: its report two brothers from a Colombian family presenting with intellectual disability, short stature, behavioral abnormalities and dysmorphic facial features. Whole-exome sequencing identified a new truncating variant in the CUL4B gene, predicted to result in loss of protein function. Segregation analysis supported X-linked inheritance within the family.

Keywords: CUL4B; Cabezas syndrome; X-linked disorder

Introduction

The CUL4B gene, located on chromosome Xq24, consists of 22 exons and encodes 913 amino acids scaffolding protein that forms part of the cullin 4B-RING ubiquitin ligase (E3) complexes (CRL4B). This complex participates in the ubiquitination of multiple substrate proteins, thereby regulating various essential cellular processes, including cell cycle control, proteasome-mediated protein degradation, DNA repair by nucleotide excision, embryonic development and response to DNA damage[1-3]. Alteration of the ubiquitination and proteasomal degradation pathway has been associated with multiple human genetic disorders[4].

Loss-of-function variants in CUL4B can affect the assembly or catalytic activity of CRL4B-dependent E3 ligase complexes, generating abnormal interactions between the complex and its substrate proteins. As a result, key cellular processes are disrupted, which can manifest clinically with a broad phenotypic spectrum, probably related to specific effects depending on the cell type and tissue affected[5,6].

In 2000, Cabezas, et al. described six affected individuals belonging to two generations and four families connected through female carriers. These patients presented intellectual disability, short stature, small testicles, muscle atrophy in the lower limbs, kyphosis, joint hyperlaxity, abnormal gait, tremor,

impaired fine motor coordination and a prominent lower lip[7,8].

To date, fewer than 100 patients with pathogenic variants in CUL4B have been described, including missense, frameshift, splicing and truncating variants. The case of a child carrying a nonsense variant in the CUL4B gene, was identified in the context of a Colombian family with several siblings affected by intellectual disability. Molecular analysis of the family identified a frameshift variant in the same gene in another sibling. This report contributes to broadening the phenotypic spectrum associated with pathogenic variants in CUL4B and highlights the importance of genetic testing in families with suspected X-linked intellectual disability **(Figure 1)**.

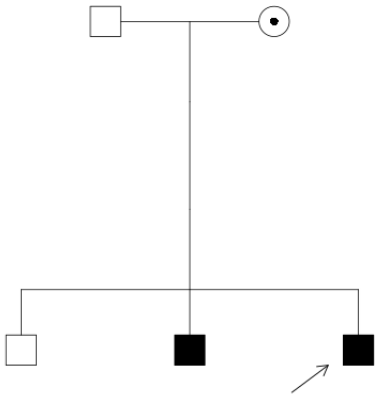

Figure 1: Familial pedigree of the CUL4B variant.

Clinical Case

A 5-year-old boy, the youngest of three brothers with intellectual disabilities, is the son of healthy, non-consanguineous Colombian parents. He was born at 39 weeks gestation by cesarean section due to severe oligohydramnios. His birth weight and height were appropriate for his gestational age and the neonatal period was uneventful.

Developmental delay became apparent at 18 months of age, when he was able to sit independently. Subsequently, at 3 years of age, he was still unable to walk without assistance and his language was limited to a few words until 4 years of age. At the current evaluation, his weight was 14 kg (-3.1 SD), height was 101.5 cm (-2.3 SD) and head circumference was 53 cm, indicating short stature with relative macrocephaly. Physical examination revealed distinctive facial features, including a broad forehead, slightly depressed nasal bridge, short philtrum, thin upper lip and relatively prominent lower lip, as well as micrognathia. Neurological examination revealed no focal motor or sensory deficits.

Pituitary hormonal function was normal. Whole exome sequencing (WES) was performed, identifying a heterozygous nonsense variant c.1026dup p.(Glu343Ter) in the CUL4B gene (NM_001079872.2), a finding consistent with Cabezas syndrome. Additionally, his 7-year-old brother has similar clinical manifestations, characterized by global developmental delay, learning difficulties and persistent sialorrhea. Duo WES analysis identified a heterozygous frameshift variant c.1026dupT p.(Glu343fs) in the same gene, inherited maternally.

Discussion

Pathogenic variants in the CUL4B gene are associated with an X-linked neurodevelopmental disorder characterized primarily by intellectual disability and facial dysmorphic features. This condition was initially described by David A. Cabezas[9] and afterwards, Tarpey, et al., expanded its clinical characterization by demonstrating its association with additional manifestations such as aggressive behavior, seizures, relative macrocephaly, central obesity, hypogonadism, pes cavus and tremor[10]. These findings contributed to a more precise definition of the clinical spectrum of the disorder and highlighted the role of ubiquitin-proteasome system dysfunction in neurological development.

From a clinical perspective, patients with pathogenic variants in CUL4B present a broad phenotypic spectrum. The most common manifestations include varying degrees of intellectual disability, hypotonia, delayed language development and characteristic facial features, including a broad forehead, depressed nasal bridge, prominent lower lip and micrognathia. Neuromotor disorders, behavioral problems, short stature and, in some cases, endocrine abnormalities have also been described[2,3]. In line with these findings, our patient presents with global developmental delay, short stature and facial dysmorphic features consistent with those previously described in patients with Cabezas syndrome. Similar phenotypes have also been described in individuals with complete deletions of the CUL4B gene. For example, Isidor et al. reported a child with a deletion of this gene who presented with intellectual disability, short stature, hypogonadism, ataxia and minor facial features, supporting the critical role of CUL4B loss of function in the pathophysiology of this syndrome and reinforcing the consistency of the phenotype associated with the alteration of this gene[9].

This case takes on additional relevance due to the limited number of reports from Latin American populations. Most of the cases described in the literature correspond to European or Asian cohorts, so the description of patients from other regions contributes to expanding knowledge about the phenotypic and genetic variability of this disorder in different populations. In this context, the clinical and molecular characterization of this Colombian family provides additional information on the clinical spectrum associated with pathogenic variants in CUL4B and highlights the importance of molecular diagnosis for genetic counseling and clinical management of families with suspected X-linked intellectual disability.

Conclusion

This case expands our knowledge of the clinical spectrum of Cabezas syndrome associated with truncating variants in the CUL4B gene and highlights the importance of recognizing both neurological and endocrine manifestations for a comprehensive diagnosis.

Acknowledgments

The authors thank the patient and his family for their cooperation and for granting consent for the publication of this report for academic purposes.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Funding

This study did not receive external financial support.

Contribuciones de los autores

SA and VL participated in the clinical evaluation of the patient

and in the initial drafting of the manuscript. MV supervised the clinical work and critically reviewed the intellectual content of the manuscript. DR and NS contributed to the literature review and editing of the manuscript. All authors read and approved the final version of the manuscript.

Ethical Approval

Written informed consent was obtained from the patient's legal guardians for participation in this study and publication of clinical information. In accordance with institutional policies, approval from an ethics committee was not required for the publication of a single case report with anonymous information.

References

1. Liu L, Yin Y, Li Y, et al. Essential role of the CUL4B ubiquitin ligase in extra-embryonic tissue development during mouse embryogenesis. Cell Res 2012;22(8):1258-1269.
2. Londin ER, Adijanto J, Philp N, et al. Donor splice-site mutation in CUL4B is likely cause of X-linked intellectual disability. Am J Med Genet A 2014;164(9):2294-2299.
3. Lin L, Yang Q, Zhang S, et al. Case Report: Cabezas syndrome caused by CUL4B gene mutations in two unrelated Chinese boys. Front Neurosci 2025;19:1600852.
4. Jiang YH, Beaudet AL. Human disorders of ubiquitination and proteasomal degradation. Curr Opin Pediatr 2004;16(4):419-426.
5. Stier A, Gilberto S, Mohamed WI, et al. The CUL4B-based E3 ubiquitin ligase regulates mitosis and brain development by recruiting phospho-specific DCAFs. EMBO J. 2023 Sep 4;42(17):e112847.
6. Kerzendorfer C, Hart L, Colnaghi R, et al. CUL4B-deficiency in humans: understanding the clinical consequences of impaired Cullin 4-RING E3 ubiquitin ligase function. Mech Ageing Dev 2011;132(8-9):366-373.
7. Cabezas DA, Slaugh R, Abidi F, et al. A new X linked mental retardation (XLMR) syndrome with short stature, small testes, muscle wasting and tremor localises to Xq24-q25. J Med Genet. 2000 Sep;37(9):663-668.
8. Zou Y, Liu Q, Chen B, et al. Mutation in CUL4B, which encodes a member of cullin-RING ubiquitin ligase complex, causes X-linked mental retardation. Am J Hum Genet 2007;80(3):561-566.
9. Isidor B, Pichon O, Baron S, et al. Deletion of the CUL4B gene in a boy with mental retardation, minor facial anomalies, short stature, hypogonadism and ataxia. Am J Med Genet A 2010;152(1):175-180.
10. Tarpey PS, Raymond FL, O'Meara S, et al. Mutations in CUL4B, which encodes a ubiquitin E3 ligase subunit, cause an X-linked mental retardation syndrome associated with aggressive outbursts, seizures, relative macrocephaly, central obesity, hypogonadism, pes cavus and tremor. Am J Hum Genet 2007;80(2):345-352.