CASE REPORT

Rippling associated with a variant in the *CAV3* gene in a Peruvian child: a case report

Peggy Carol Martínez-Esteban[1], Maira Saavedra Ruiz[2], Edoardo Malfatti[3,4], J. Andoni Urtizberea[5]

[1] Research and Technological Innovation Subunit, Instituto Nacional de Salud del Niño San Borja, Lima 15037, Peru.
[2] Department of Neurology, Hospital Nacional Guillermo Almenara Irigoyen, Lima 15033, Peru.
[3] APHP, Centre de Référence de Pathologie Neuromusculaire Nord-Est-Ile-de-France, Henri Mondor University Hospital, Créteil, France.
[4] Université Paris-Est Créteil, U955 INSERM, IMRB, Créteil 94010, France.
[5] Institut de Myologie, AFM-Téléthon, Paris, France.

ABSTRACT

Background: Caveolinopathies are diseases primarily caused by variants in the *CAV3* gene (caveolin-3), affecting skeletal muscle, cardiac muscle, or both.
Case description: We describe the case of a 6-year-old Peruvian boy who presented with muscle stiffness, myalgia, rippling, and hyperCKemia. Clinical examination revealed calf hypertrophy, Achilles tendon contractures, and toe walking. Next-generation sequencing analysis identified the previously reported heterozygous pathogenic variant c.99C>G (p.Asn33Lys) in *CAV3*. Segregation studies in affected family members were consistent with an autosomal dominant inheritance pattern.
Conclusions: This case illustrates the phenotypic variability of caveolinopathies and highlights the importance of considering this diagnosis in patients with myalgia and rippling beginning in the first decade of life. Although clinical findings guide the diagnosis, genetic confirmation is necessary to provide timely family counseling.

Keywords: Caveolin-3; Muscle Rigidity; Myalgia; Muscular Diseases (Source: MeSH)

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Corresponding author:
Peggy Carol Martínez-Esteban
Telephone: +51 999887130
Email:
peggy.martinez.esteban@gmail.com

ORCID iDs
Peggy Carol Martínez-Esteban
https://orcid.org/0000-0002-2513-5839
Maira Saavedra Ruiz
https://orcid.org/0000-0002-3984-6092
Edoardo Malfatti
https://orcid.org/0000-0001-7871-8600
J. Andoni Urtizberea
https://orcid.org/0000-0002-7077-6344

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Rippling relacionado a una variante en el gen *CAV3* en un niño peruano: reporte de caso

RESUMEN

Antecedentes: Las caveolinopatías son enfermedades causadas principalmente por variantes en el gen *CAV3* (caveolina-3), que afectan el músculo esquelético, el músculo cardíaco o ambos.
Descripción del caso: Se describe el caso de un niño peruano de 6 años que presentó rigidez muscular, mialgias, *rippling* e hiperCKemia. El examen clínico evidenció hipertrofia de pantorrillas, retracciones del tendón de Aquiles y marcha en puntillas. El análisis de secuenciación de nueva generación identificó la variante patogénica heterocigota c.99C>G (p.Asn33Lys), previamente descrita en el gen *CAV3*. Los estudios de segregación en familiares afectados fueron compatibles con un patrón de herencia autosómica dominante.
Conclusiones: Este caso ilustra la variabilidad fenotípica de las caveolinopatías y resalta la importancia de considerar este diagnóstico en pacientes con mialgias y *rippling* que inician en la primera década de vida. Aunque los hallazgos clínicos orientan el diagnóstico, el diagnóstico genético es necesario para brindar un asesoramiento familiar oportuno.

Palabras clave: Caveolina-3; Rigidez Muscular; Mialgia; Enfermedades Musculares (Fuente: DeCS)

INTRODUCTION

Caveolinopathies comprise a group of neuromuscular diseases mainly associated with variants in the gene *CAV3*, which encodes caveolin-3. Caveolins constitute a family of structural proteins of the plasma membrane that are expressed in skeletal, smooth, and cardiac muscle. Three isoforms exist (CAV-1, CAV-2, CAV-3), encoded by three different genes (*CAV1, CAV2, CAV3*). Caveolin-3 is the isoform specific to skeletal and cardiac muscle and is located

in structures known as caveolae, which correspond to non-coated invaginations located on the cytoplasmic surface of the sarcolemma. Within the sarcolemma, caveolin-3 forms part of the dystrophin-glycoprotein complex, which establishes a link between the cytoskeleton and the extracellular matrix and is essential for providing stability to the muscle fiber membrane (1).

Pathogenic variants in the gene *CAV3* are associated with a broad spectrum of muscular and cardiac disorders, including limb-girdle muscular dystrophy type 1C, characterized by progressive proximal weakness and elevated creatine kinase (2); idiopathic hyperCKemia; hereditary rippling muscle disease, characterized by the rippling phenomenon; distal myopathy; familial hypertrophic cardiomyopathy; arrhythmogenic long QT syndrome; and sudden infant death syndrome (3–8). Therefore, preservation of caveolin-3 is essential for normal muscle development and skeletal muscle function (1). Some cases present combinations of these phenotypes. Conversely, the same variant of *CAV3* may give rise to any of these clinical conditions.

In patients carrying variants in *CAV3*, various cardiovascular alterations have also been identified, including arrhythmias (such as atrial fibrillation), cardiac hypertrophy, and myocardial damage following ischemia–reperfusion (2,3).

In this context, we describe the first genetically confirmed case in Peru of rippling associated with variants in *CAV3*.

CASE DESCRIPTION

We report the case of a 6-year-old boy born to non-consanguineous parents, with a history of mild and transient language delay that improved with therapy. He achieved independent walking at 14 months and progressively developed toe walking over the years, along with a sensation of stiffness and mild, transient pain in the calves upon standing in the morning; occasionally, he experienced mild pain in the same region after exercise, which prompted neurological consultation.

The initial neurological examination at 6 years of age revealed toe walking, bilateral shortening of the Achilles tendons, mild weakness of the lower limb girdle (4+/5 according to the Medical Research Council scale), and bilateral calf hypertrophy (Figure 1); deep tendon reflexes were preserved. Serum creatine kinase (CK) levels were 1,143 IU/L (normal range <218 IU/L), while electrolytes (sodium, potassium, and chloride) were within normal ranges. In addition, a cardiological evaluation was performed using electrocardiography and echocardiography, with no evidence of cardiovascular pathology at that time.

The maternal grandfather, aged 66 years, and the mother, aged 41 years, exhibited a similar disease phenotype with onset in childhood, characterized by calf hypertrophy, stiffness, and lower limb pain upon awakening (Figure 2). The mother also reported toe walking and exercise-induced pain during childhood. Currently, she presents rippling in the legs upon awakening in the morning, which limits walking for a few seconds (Video 1). CK levels were elevated (1,092 IU/L; normal range <218 IU/L), and electromyography showed hyperexcitability in the anterior tibial muscle, with continuous discharge of a single motor unit at rest (Video 2). In both relatives, symptoms remained mild and stable with aging, without functional limitations in daily life.

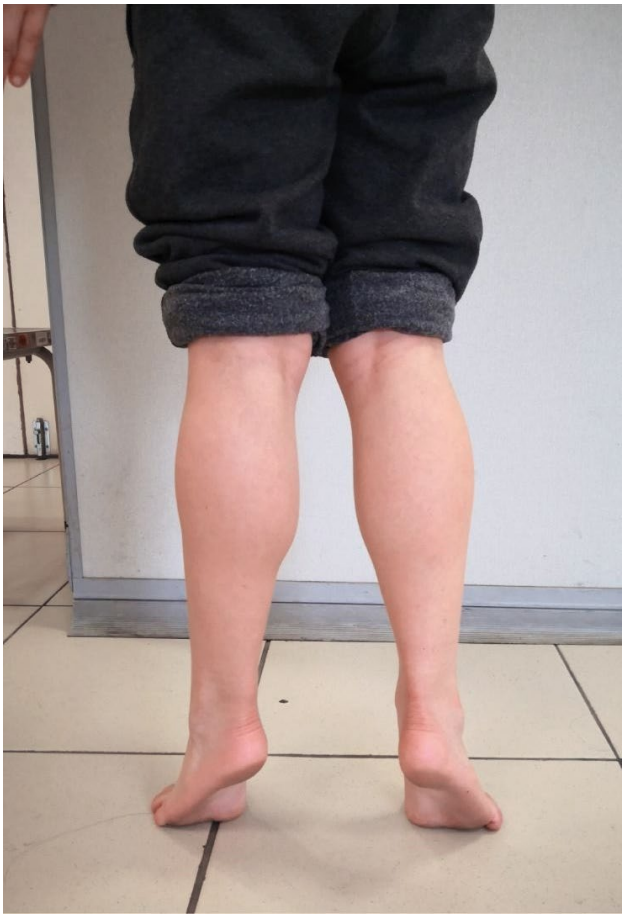


Figure 1. Calf hypertrophy and Achilles tendon contracture in the child

The distribution of affected individuals in the family was consistent with an autosomal dominant inheritance pattern (4). Initially, a diagnosis of non-dystrophic myotonia was proposed due to the presence of muscle hypertrophy, painful stiffness in the lower limbs, and a possible warm-up phenomenon. However, clinical and electromyographic evaluation of the mother did not demonstrate a myotonic phenomenon.

Analysis of the genes *CLCN1* and *SCN4A* was performed using a saliva sample from the patient to rule out this hypothesis. No variants were identified in either of the analyzed genes. The combination of rippling, stiffness, calf hypertrophy, toe walking, and persistent hyperCKemia ultimately suggested a primary caveolinopathy as an alternative diagnosis. Next-generation sequencing with a 148-gene neuromuscular panel identified a previously reported heterozygous pathogenic variant in *CAV3*: c.99C>G (p.Asn33Lys).

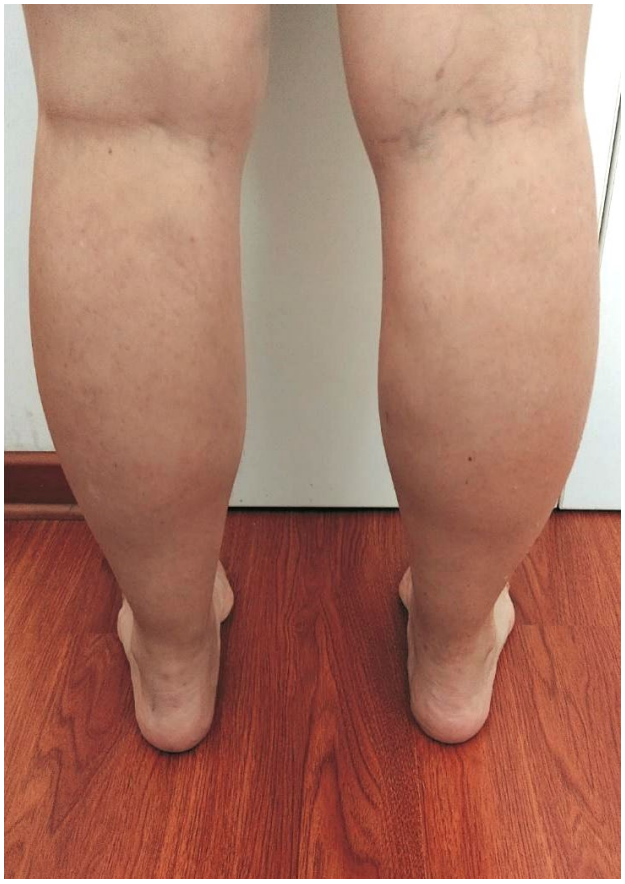
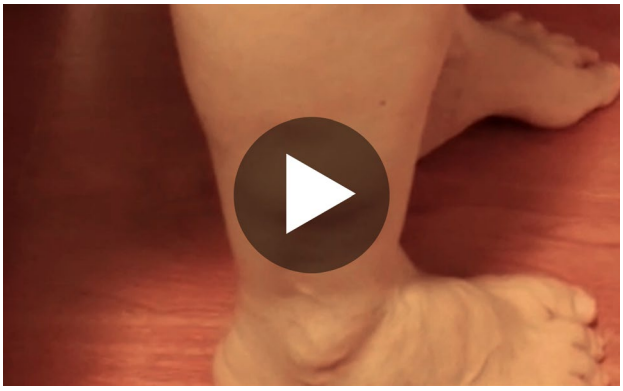
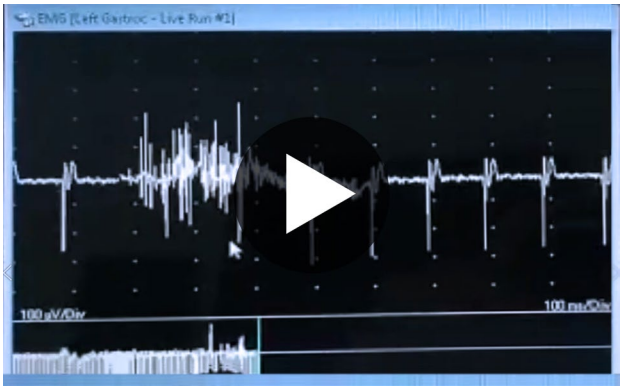


Figure 2. Calf hypertrophy in the child's mother



Video 1. Rippling in the mother



Video 2. Electromyography in the mother

Segregation studies confirmed the presence of this variant in the affected mother and maternal grandfather, as well as in the twin siblings (Figure 3). Up to 3 years of age, neither twin had presented symptoms or rippling; the male twin showed only mild calf hypertrophy on physical examination (Figure 4). CK levels were not measured in them. Two maternal aunts have calf hypertrophy, and to date, no genetic study has been performed. It is noteworthy that none of the patients underwent a muscle biopsy due to financial and logistical limitations.

DISCUSSION

Caveolinopathies caused by variants in the gene *CAV3* are rare entities. In a series of 663 cases of unclassified muscular dystrophies, only 1% presented variants in the gene *CAV3* (5). In this context, the present case provides additional evidence on a rare condition and contributes to expanding the description of the clinical expression of caveolinopathies in the pediatric population.

From a genetic perspective, multiple pathogenic variants have been described in exons 1 and 2 of the gene *CAV3*, associated with different phenotypes within the spectrum of caveolinopathies (5,6). The variant c.99C>G (p.Asn33Lys) identified in the patient has been previously reported in clinical databases and is classified as pathogenic (7), with an autosomal dominant inheritance pattern, as observed in this case.

In previously published series of patients carrying variants in the gene *CAV3*, variable clinical manifestations have been described, including predominantly proximal or distal muscle weakness, hyperCKemia, calf hypertrophy, myalgia, cramps, and stiffness after exercise, as well as signs of muscle hyperirritability, including percussion-induced rapid contraction (PIRC) and percussion-induced muscle mounding (PIMM) (4–6,8–11).

Rippling muscle disease is characterized by signs of increased muscle irritability, manifested by PIRC, PIMM, and/or electrically silent muscle contractions (rippling) (4,5,8). In agreement with this description, the patient presented stiffness and myalgia, calf hypertrophy, toe walking, and hyperCKemia, and the mother presented toe walking in childhood, calf hypertrophy, and rippling upon awakening, findings consistent with two phenotypes related to *CAV3*: rippling muscle disease and hyperCKemia. From a pathophysiological perspective, a possible interaction between CAV-3 and sarcolemmal neuronal nitric oxide synthase (nNOS) has been proposed, whose alteration could contribute to the muscle dysfunction observed in caveolinopathies and represent a potential molecular target in patients with caveolin-related muscle atrophy and weakness (12). Likewise, experimental studies

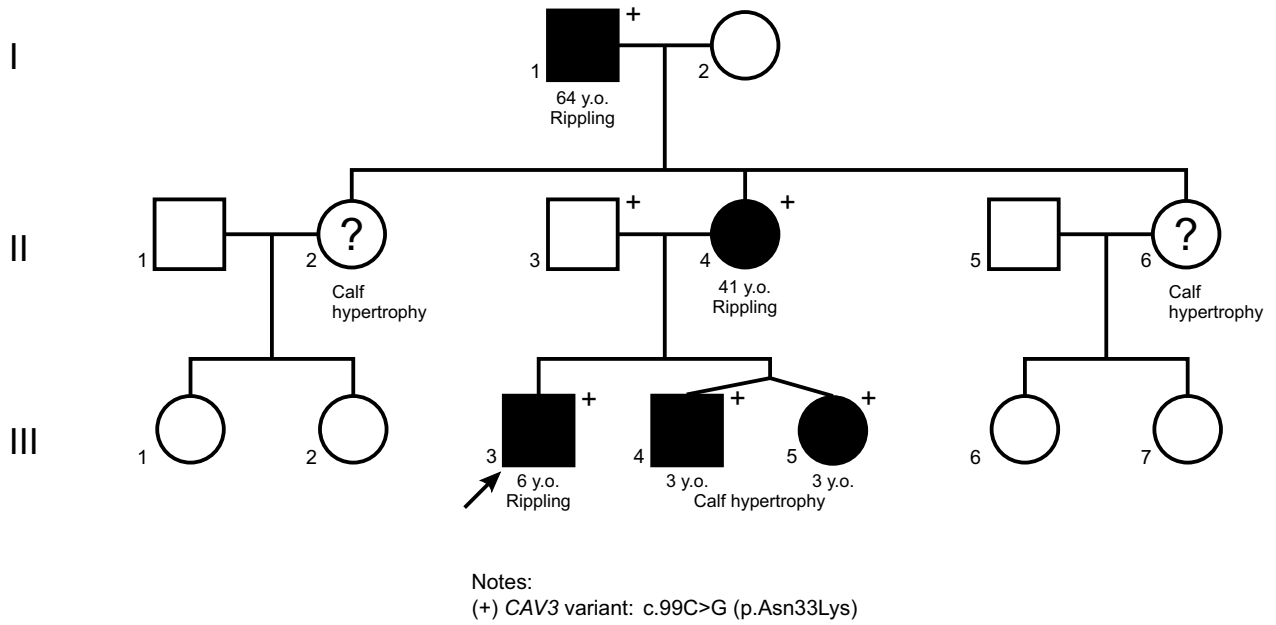


Figure 3. Pedigree

Black symbols indicate individuals affected with the rippling phenomenon, and gray symbols indicate individuals with calf hypertrophy. The square represents male and the circle female. The arrow indicates the index case. The (+) sign indicates carriers of the *CAV3* variant c.99C>G (p.Asn33Lys).

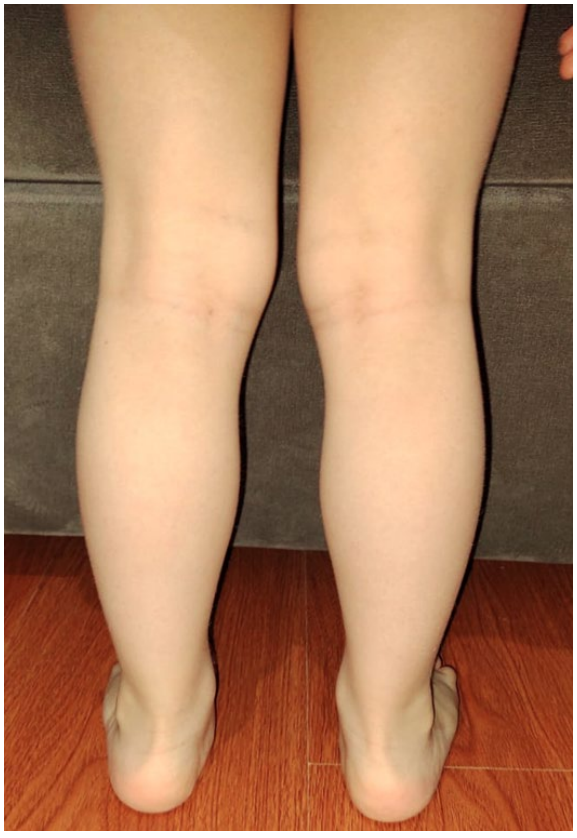


Figure 4. Calf hypertrophy in the child's sibling

in murine models have also demonstrated that deficiency of CAV-3 is associated with alterations in energy metabolism, which could guide the development of future therapeutic strategies (13).

The initial differential diagnosis included dystrophin-related dystrophies, limb-girdle muscular dystrophies, and myotonic disorders. In a child with calf hypertrophy and toe walking, the first diagnostic possibility to consider is a dystrophin-related dystrophy. Manifestations such as hypotonia, delayed motor milestones, weakness, clumsiness, Gowers' sign, difficulty climbing stairs, toe walking, and markedly elevated CK levels may be suggestive of this group of diseases (14). In this case, Duchenne muscular dystrophy was considered unlikely because CK levels remained only moderately elevated, in contrast to the typically marked elevations observed in this entity.

Currently, there is no specific treatment for caveolinopathies. Management is mainly supportive and aimed at preserving muscle function, maximizing functional capacity, and preventing complications through early physiotherapy and psychosocial support (4). Prognosis is generally favorable, and most patients maintain their daily activities without significant limitations. The clinical course observed in this family, characterized by mild symptoms beginning in childhood and absence of functional limitations in adulthood, is consistent with what has been previously described in patients with caveolinopathies related to variants in the gene *CAV3* (5).

Among the strengths of this report are the detailed clinical description performed by specialists and the segregation analysis in several family members; however, limitations include the absence of muscle biopsy and muscle magnetic resonance imaging, as well as the lack of follow-up in the years after diagnosis. These aspects highlight the need for adequate logistical, human, and financial resources to enable the full spectrum of complementary tests required in patients with myopathy, including muscle biopsies.

CONCLUSION

In conclusion, caveolinopathies related to variants in the gene *CAV3* are rare entities within neuromuscular diseases. They should be considered in the presence of rippling, myalgia, and stiffness associated with calf hypertrophy, toe walking, and hyperCKemia, particularly in the context of an autosomal dominant inheritance pattern. Genotype–phenotype correlations are not yet fully understood, and the same mutation may give rise to heterogeneous clinical phenotypes, making it essential to complete family studies to establish the diagnosis and provide appropriate genetic counseling.

Author contributions

PCME: Conceptualization, Investigation, Writing – original draft.

MSR: Formal analysis, Investigation, Methodology, Writing – original draft.

EM: Formal analysis, Methodology, Writing – review and editing.

JAU: Formal analysis, Methodology, Writing – review and editing.

Conflicts of interest

The authors declare no relevant financial or non-financial conflicts of interest.

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Data availability

The data supporting the findings of this report are available upon request from the corresponding author.

Ethical aspects

The report has informed consent granted by the patient's mother for the publication of the clinical, laboratory, and imaging findings in a scientific journal.

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