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Case report

Novel mutation in *TCAP* manifesting with asymmetric calves and early-onset joint retractions

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Abstract

A 29-year-old man, born from consanguineous parents, started with toe walking and frequent falls during his second year of life. He developed weakness in lower limbs during the first decade that subsequently extended to upper limbs. On examination, the patient had weakness in proximal muscles of all four limbs and in the tibialis anterior muscle. In addition, he had bilateral Achilles and patellar contractures, bilateral scapular winging, asymmetric calves and a positive Beevor sign, an upward movement of the umbilicus on contraction of rectus femoris due to weakness in the lower part. The muscle biopsy showed dystrophic changes and lobulated fibers. Genetic analysis through a next-generation sequencing panel of genes related to neuromuscular disorders revealed a novel homozygous nonsense mutation (p.Tyr85*) in the *TCAP* gene. Subsequent western blot assay showed a complete telethonin deficiency. Our observation expands the phenotypic spectrum of *TCAP* mutations and indicates that telethonin deficiency should be considered in the differential diagnosis of patients presenting with asymmetric calves and early joint retractions.

Keywords: Telethonin deficiency; LGMD2G; *TCAP*; Muscular dystrophy

1. Introduction

Mutations in the *TCAP* gene may cause autosomal recessive limb-girdle muscular dystrophy type 2G (LGMD2G) [1], congenital muscular dystrophy (CMD) [2], hypertrophic and dilated cardiomyopathy [3] and intestinal pseudo-obstruction [4].

TCAP, located on chromosome 17q12, has two exons and encodes the sarcomeric protein telethonin, also called titin cap. Telethonin is a 167 aminoacid protein of 19 kDa localized to the Z-disc of adult striated and cardiac muscles, where it interacts with titin and other sarcomeric proteins, playing an important role in sarcomeric assembly [5–7]. It has also been found in the human gastrointestinal smooth muscle, co-localized with $Na_V1.5$ [4]. It received its name after its identification in a research that was supported by the Italian Telethon ("tele" from "television" and "thon" from "marathon") [5,8].

Telethoninopathy was originally described in Brazilian patients of Italian ancestry, but in recent years additional patients from diverse geographical origin have been reported [1,2,8–21], indicating that the disease probably exists worldwide.

2. Case report

The patient is a 29-year-old man born from consanguineous parents originating from Asturias, in northern Spain. There is no family history of muscle disease. He had no delay of gross motor milestones and started to walk independently at age 12

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months. During his second year of life, the patient's parents noted a tendency to toe walking, mainly with the right foot, and frequent falls. When he was 4 years old, he stood up from the floor with a conspicuous Gowers' maneuver. The patient had asymmetric Achilles contractures and he underwent bilateral Achilles elongation at age 7 years and right Achilles tenotomy at age 14 years. During the first decade of life, he developed a slowly progressive proximal and distal muscle weakness in lower limbs. In the second decade, he began noticing weakness in upper limbs.

On examination, the patient had preserved cognitive functions. He had asymmetric Achilles contractures, with the right Achilles tendon more shortened than the left one, so that he stood up on his tiptoes with the right foot, but not with the left one. He also had patellar contractures, bilateral scapular winging and severe wasting of thighs muscles and of the tibialis anterior muscles. There were asymmetric calves, with left calf hypertrophy and right calf atrophy (Fig. 1A–D). Muscle strength testing revealed weakness involving iliopsoas (4/5 on the Medical Research Council scale), hip adductors (2/5), quadriceps (3/5), ischiotibialis (3/5) and tibialis anterior muscles (0/5). Proximal and distal muscles in upper limbs were also impaired (pectoralis scored 0/5; deltoids, biceps brachii, triceps brachii, wrist flexors, wrist extensors, finger flexors and finger extensors scored between 4/5 and 4 + /5). The patient had a symmetric abdominal weakness and a positive Beevor sign (an upward migration of the umbilicus in the act of sitting up from supine position due to weakness of the lower half of the

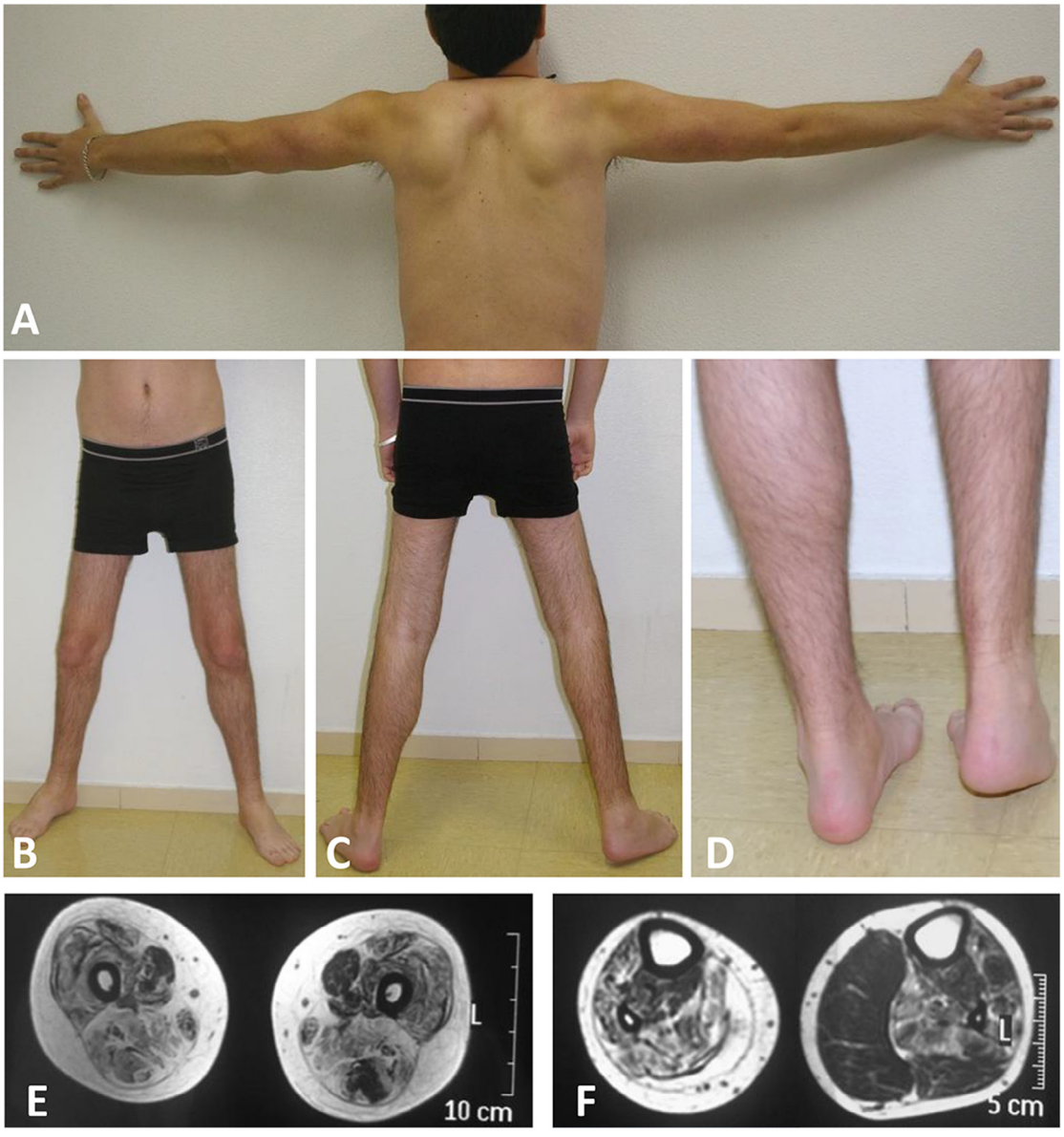

Fig. 1. A–D: clinical phenotype of the patient. A: bilateral scapular winging. B–D: atrophy of the anterior and posterior thigh muscles and anterior tibialis. Asymmetric calves. Shorten of the right Achilles tendon. E–F: T-1 weighted MRI. E: Thighs. Note the severe fatty infiltration of almost every muscle. Left biceps femoris and right sartorius are less affected. Left sartorius is spared and hypertrophic. F: Legs. Tibialis anterior, soleus, peroneus longus and right gastrocnemii show a severe fatty infiltration. Left medial gastrocnemius is markedly hypertrophic.