ACTA MYOLOGICA 2020; XXXIX: p. 24-28
doi: 10.36185/2532-1900-004

Laing early-onset distal myopathy with subsarcolemmal hyaline bodies caused by a novel variant in the *MYH7* gene

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Myopathies caused by *MYH7* gene mutations are clinically and pathologically heterogeneous and, until recently, difficult to diagnose. The availability of NGS panels for hereditary neuromuscular diseases changed our insight regarding their frequency and allowed a better perception of the different phenotypes and morphological abnormalities associated.
We present a male Portuguese patient with the classical phenotype of Laing early-onset distal myopathy (MPD1) beginning at 6 years of age, very slowly progressive, and with a mild to moderate impact on daily life by the age of 56. Muscle biopsy showed a myopathic pattern with hyaline bodies and cores. The NGS panel for structural myopathies identified a novel missense heterozygous variant, c.T4652C (p.Leu1551Pro), in the exon 34 of the *MYH7* gene.

Key words: *MYH7* gene variant, laing early-onset distal myopathy, subsarcolemmal hyaline bodies

Received: November 25, 2019
Accepted: March 20, 2020

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Conflict of interest
The Authors declare no conflict of interest

Funding
None

How to cite this article: Luís Negrão L, Machado R, Lourenço M, et al. Laing early-onset distal myopathy with subsarcolemmal hyaline bodies caused by a novel variant in the *MYH7* gene. Acta Myol 2020;39:24-8. https://doi/org/10.36185/2532-1900-004

Introduction

The *MYH7* gene, located at chromosome 14, encodes the slow/b-cardiac myosin heavy chain (MyHC I), a class II myosin expressed in cardiomyocytes and type 1 striated muscle fibers [1]. Cardiac and skeletal muscle diseases can be caused by *MYH7* gene mutations, the former being much more common [1]. Most of the *MYH7* gene mutations responsible for cardiomyopathies are located in the globular head domain of the protein, while mutations causing myopathies tend to be localized in the distal region of the rod domain [2-4]. Almost all reported *MYH7* gene mutations are dominant [1,2], with very few cases reported of autosomal recessive inheritance [5].

MYH7-related myopathies are less rare than once expected [6]. Based on clinical and morphological data, they are classified as myosin storage myopathy (MSM) and Laing early-onset distal myopathy (MPD1), the latter much more common [6,7]. While MPD1 is characterized by very distal lower limb muscle weakness [8] and variable morphological data, MSM is defined by specific subsarcolemmal accumulation of hyaline bodies (HB), with a predominant limb-girdle clinical phenotype [9].

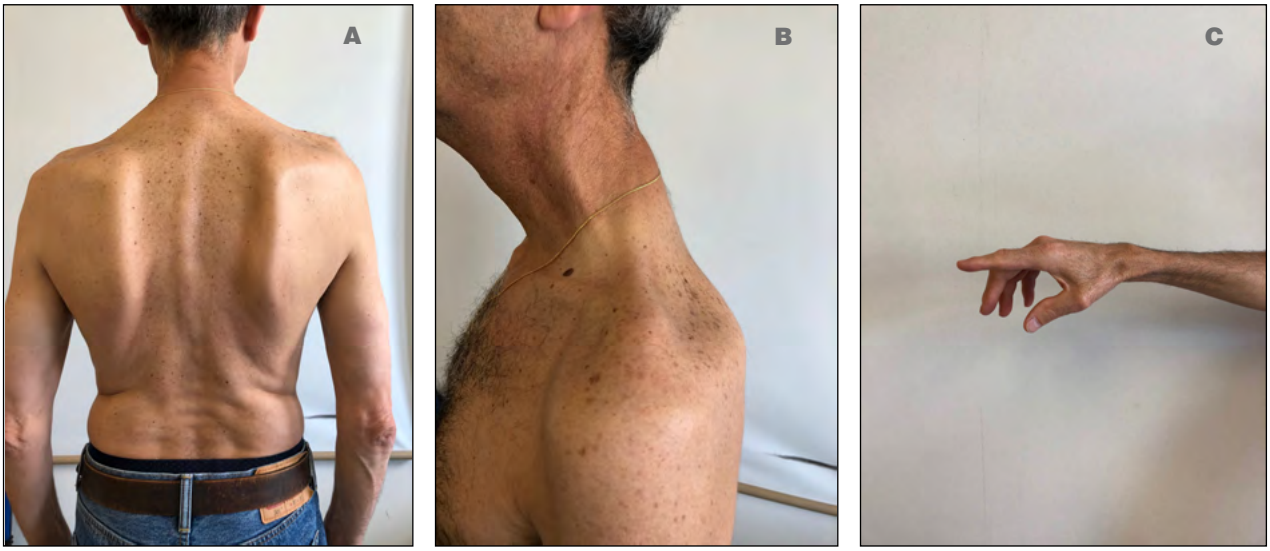

Figure 1. Muscle atrophy of the shoulder girdle muscles (trapezius, supraspinatus and infraspinatus) (A, B). Finger-drop with preserved extension of the second finger (C).

Herein, we present a male Portuguese patient with a *MYH7*-related myopathy caused by a novel missense heterozygous variant, c. 4652T > C (p. Leu1551Pro), in the exon 34 of *MYH7* gene.

Clinical case

The patient is a 56-year-old man, the single offspring of a non-consanguineous Azorean couple. His father and brother were suspected of having a similar muscular condition, but were not available to examination.

At the age of 6 years, he reported walking difficulties, probably with minor impact on daily life in the following years, since he was admitted to the military service by the age of 18. At 30 years of age, he reported difficulty in raising both arms and, at the age of 40 years, he developed weakness of the extensor muscles of the fingers.

Neurological examination at 52 years of age revealed muscle atrophy of the shoulder girdle muscles (Figs. 1A-B), particularly of the trapezius, supraspinatus and infraspinatus, and of the posterior muscles of the forearm and of the tibial anterior muscles, bilaterally. There was no calf hypertrophy. At rest, the scapula was displaced posteriorly and, with arm abduction, it moved laterally and inferiorly. There was bilateral foot-drop with "big-toe dropping", Achilles tendon retraction and bilateral finger-drop with preserved extension of the second finger (Fig. 1C). The patient walked with a steppage gait and walking on tip-toes was possible. Gowers maneuver was negative. Muscle strength evaluation of the upper limbs revealed severe symmetrical weakness of the long extensor muscles of the thumb and of the 3rd to 5th fingers (0/5 MRC), and weakness of the long extensor muscle of the 2nd finger, abductor pollicis brevis, abductors muscles of the arm and of the infraspinatus muscle (4-/5 MRC). In the lower limbs, there was bilateral severe weakness of the tibial anterior muscle and of the long extensor muscle of the hallux (0/5 MRC) and weakness of the extensor muscles of the 2nd to 4th toes (3/5 MRC). Cervical flexion was weak (4-/5 MRC). Myotatic reflexes were abolished throughout. Sensory examination and cranial nerves evaluation were normal.

Complementary exams

Laboratory workout was repeatedly performed and revealed normal CK values. Cardiac evaluation via echocardiogram and evaluation of respiratory function were unremarkable. Electrophysiologic studies showed normal peroneal (recording from the EDB muscle) and sural nerve conduction velocities and amplitudes. Muscle needle examination showed the presence of repetitive complex discharges on the tibial anterior muscles with sparse fibrillations potentials and positive waves. No motor unit potentials could be activated. Motor unit potentials of short amplitude and duration, and polyphasic, were observed on the right vastus medialis and extensor indicis muscles.

Muscle biopsy

Deltoid muscle biopsy revealed a myopathic pattern with variation in fiber size with marked atrophy and hypertrophy, increased internalized nuclei and mild interstitial fibrosis (Fig. 2A). Some muscle fibers had hyaline

material, mildly eosinophilic with the hematoxylin and eosin stain (Fig. 2B) and pale-green with the Gomori thricrome, without reactivity for oxidative enzymes, suggestive of hyaline bodies. Multiple fibers presented irregularity of the intermyofibrillar reticulum and occasional core formation (Fig. 2C). Pronounced type 1 predominance with very rare type 2 fibers was observed (Fig. 2D). Subsarcolemmal hyaline material lacked immunoreactivity for desmin (Fig. 2E).

Molecular study

The next generation sequencing (NGS) panel for structural myopathies was performed through a custom targeted NGS panel. Enrichment was performed by in-solution hybridization and, after library preparation, the DNA library was subjected to NGS.

Variants that passed the quality control step were prioritized according to their minor allele frequencies (MAF < 0.01) in the following databases: 1000G, Exome Aggregation Consortium (ExAC), Exome Variant Server (EVS), Genome Aggregation Database (gnomAD), and our in-house population database (IberDB). Possible pathogenicity of the missense variants detected was assessed using the in silico tools CONDEL[3] researchers have developed various methods and their related computational tools to classify these missense SNVs as probably deleterious or probably neutral polymorphisms. The outputs produced by each of these computational tools are of different natures and thus difficult to compare and integrate. Taking advantage of the possible complementarity between different tools might allow more accurate classifications. Here we propose an effective approach to integrating the output of some of these tools into a unified classification; this approach is based on a weighted average of the normalized scores of the individual methods (WAS, GERP++[4] (4)such as protein-coding exons, noncoding RNAs, and regulatory sequences that control the transcription of genes. However, these functional sequences are embedded in a background of DNA that

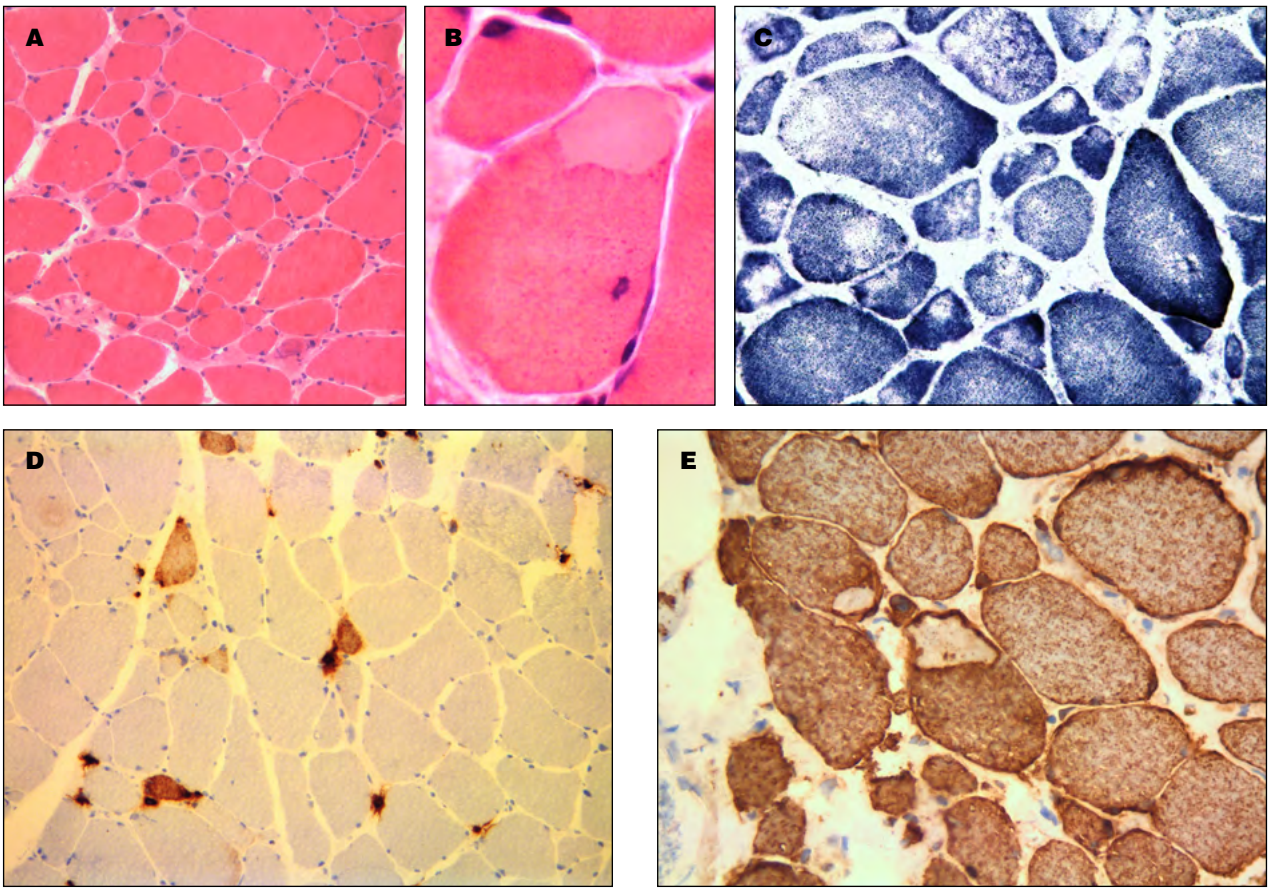

Figure 2. Deltoid muscle biopsy. Muscle fiber size variability with marked atrophy and hypertrophy and fibers (H&E – 100x) (A); with subsarcolemmal hyaline material (*) (H&E – 400x) (B); rare core lesions (*) (SDH – 200x) (C); pronounced type 1 fiber predominance with only few scattered type 2 fibers (fast myosin immune – 100x) (D); subsarcolemmal material without immunoreactivity for desmin (*) (400x) (E).

serves no discernible function. Thus, a major challenge in the field of genomics is the accurate identification of functional sequences in the human genome. One approach to identify functional sequences is to align the genome sequences of many divergent species and search for sequences whose similarity has been maintained during evolution. We have developed GERP++, a software tool that utilizes this "comparative genomics" approach to identify putatively functional sequences. Given a multiple sequence alignment, GERP++ identifies sites under evolutionary constraint, i.e., sites that show fewer substitutions than would be expected to occur during neutral evolution. GERP++ then aggregates these sites into longer, potentially functional sequences called constrained elements. Using GERP++ results in improved resolution of functional sequence elements in the human genome and reveals that a higher proportion of the human genome is under evolutionary constraint (~7%, and CADD [5].

A missense heterozygous variant, c.4652T > C (p. Leu1551Pro), was detected in the exon 34 of *MYH7* gene (Fig. 3).

This *MYH7* gene sequence variant was not registered in the 1000G, Exome Aggregation Consortium (ExAC), Exome Variant Server (EVS), Genome Aggregation Database (gnomAD), our in-house population database (IberDB) or in ClinVar associated with disease. This residue is highly conserved (GERP score 4,55) and bioinformatic analysis with CONDEL (score: 0,75) and CADD (score 29,9) suggests that this variant is potentially deleterious.

Discussion

Classical phenotypes associated with *MYH7* gene mutations include the limb-girdle and distal myopathic phenotypes, firstly describe in 1971[9] and 1995[8], respectively. In the following years, different clinical presentations were identified and in 2016, there was a proposal to group them into 3 forms of *MYH7*-related myopathies: 1- early onset form of distal myopathy with cores; 2- late onset form of distal myopathy without cores and variable association with cardiomyopathy and/or fiber type disproportion and 3- limb-girdle involvement with myofibrillar damage resembling MSM [6].

The current perspective on *MYH7*-related myopathies is that there is a continuum in the clinical presentation of the different clinical phenotypes, in some way related to the age of onset of the disease [6].

The pathological findings followed a similar evolution in classification, firstly with a dichotomous division comprising the presence of subsarcolemmal hyaline bodies, characteristic of MSM, or the presence of non-specific abnormalities with predominance of type I fibers, typical of

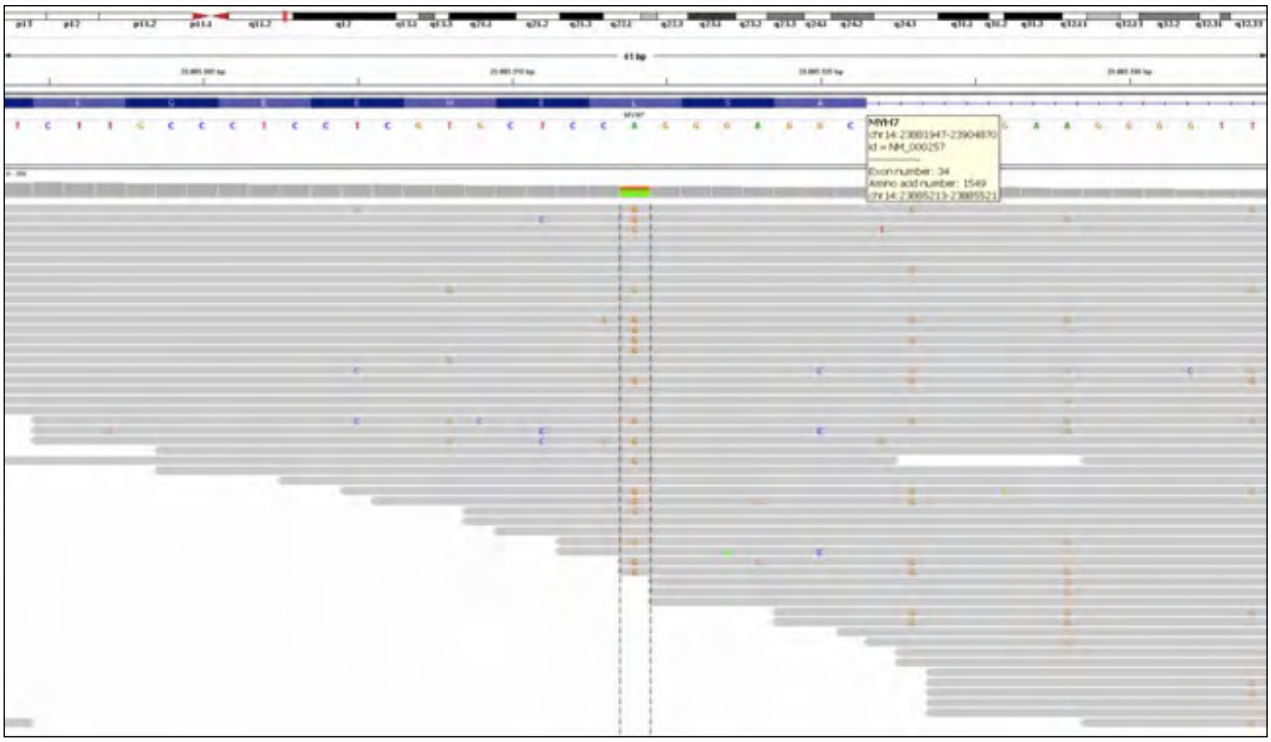

Figure 3. I.G.V. (integrative genomics viewer): the missense heterozygous variant, c.4652T > C (p. Leu1551Pro), in the exon 34 of *MYH7* gene, detected in the case report.

MPD1 [10]. Later on, other pathological patterns were consistently identified: congenital fiber-type disproportion and central core disease, most commonly seen in MPD1 [6,7,11].

In the first descriptions of *MYH7*-related cardiomyopathies and myopathies, there were no reports on the simultaneous occurrence of both diseases in the same patient. At that time, this was explained by the different locations of the *MYH7* gene mutations causing cardiac or skeletal diseases: mutations in the NH globular head were associated with cardiomyopathy, whereas mutations in the COOH tail domain were more prone to cause myopathy. However, more recently, it became clear that mutations in either location could cause either disease, and both could coexist in the same patient [12].

This clinical case has the classical MPD1 phenotype, namely: 1) clinical onset in the distal muscles of the lower limbs, followed by involvement of the shoulder girdle muscles and later, weakness of the long extensor muscles of the fingers; 2) very slowly disease progression; 3) muscle weakness compatible with an ambulant and active life, fifty years after the first symptoms, at a time when cardiac involvement is still absent. Furthermore, the location of the *MYH7* gene variant in exon 34 is characteristically associated to MPD1.

The pathological findings, namely the presence of hyaline bodies, which are atypical or absent in MPD1 cases, together with the novel *MYH7* gene variant here reported, grant uncommon and interesting features to this clinical case.

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