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Case report

Autosomal dominant distal myopathy with nemaline rods due to p.Glu197Asp mutation in *ACTA1*

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Abstract

In a previous report of a new phenotype with predominant scapulo-humeral-peroneal-distal myopathy associated with the Glu197Asp mutation in *ACTA1*, muscle biopsies did not show nemaline rods, nor could nemaline rods formation be demonstrated in an exhaustive functional *in vivo* or *in vitro* study. However, muscle biopsy in members of our family, carrying a similar clinical phenotype of some members of the original family and the same *ACTA1* mutation, revealed the presence of numerous nemaline rods, suggesting that there must be other factors that explain the absence of nemaline rods.

Keywords: ACTA1; Congenital myopathy; Nemaline rod; Distal.

Mutations in *ACTA1* comprise a heterogeneous clinical and histological spectrum. In a large family with predominant scapulo-humeral-peroneal-distal myopathy associated with the Glu197Asp mutation in *ACTA1*, muscle biopsies did not show nemaline rods, nor could they be demonstrated after a thorough functional study in vivo or in vitro. Here, we report a family that share the same clinical phenotype of some members of the original family and the same mutation in *ACTA1*, but in which nemaline rods were broadly present in muscle biopsies.

Mutations in *ACTA1* cover a heterogeneous clinical and histological spectrum [1–3]. A new phenotype associated with *ACTA1* mutation (Glu197Asp) has recently been published [4]. In this large multi-generation family, with predominant scapulo-humeral-peroneal-distal myopathy, but significant intrafamilial phenotypical variability, the mutation did not lead to rod formation in vitro or in vivo. Herein, we report a family that share the same clinical manifestations of some family members and the same mutation in *ACTA1* as the original publication, but in which nemaline rods were broadly present in muscle biopsies.

The proband is a 42-year-old Spanish woman who was referred to our hospital due to slowly progressive distal muscle weakness, predominantly in the upper limbs, beginning in the second decade of her life.

Her neurological exam revealed mild bilateral ptosis associated with facial, cervical and all four-limb weakness. The weakness was predominantly distal and in the upper limbs, especially in the flexors and extensors of the finger in the hands (MRC scale 2/5).

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CPK levels were repetitively normal. EMG exhibited myopathic changes. MRI of lower limbs showed atrophy and fatty replacement of the hamstring, vastus intermedius and rectus femoris on the thighs and incipient signs of fatty infiltration in the tibialis anterior and peroneal muscles in the lower legs (Fig. 1(A) and (B)).

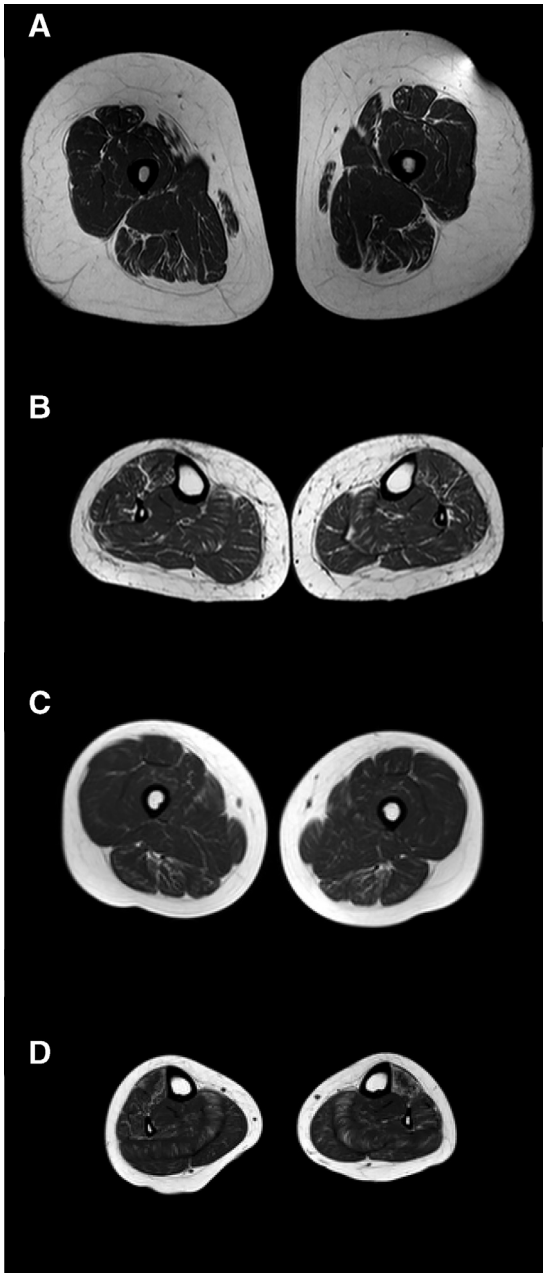

Figure 1. MRI of the mother shows atrophy and fatty replacement of the hamstring, vastus intermedius and rectus femoris on the thigh (A) and incipient signs of fatty infiltration in the tibialis anterior and peroneal muscles in the lower legs (B).
MRI of the son shows atrophy and fatty replacement of the semimembranosus, biceps on the thigh (C) and tibialis anterior and extensor digitorum longus in the lower legs (D).

A biceps brachii muscle biopsy showed variability in fiber size with predominance and hypotrophy of type I fibers. Type I fibers accounted for 59% of the total and the average diameter of type I fibers was 40% smaller than type II. The most striking finding was the presence of numerous sarcoplasmic nemaline rods that were more abundant in the subsarcolemal locations. They were more evident with the modified Gomori-trichrome stain and in the ultrastructural study. No intranuclear nemaline rods were detected. With NADH and SDH oxidative techniques some non-specific irregularities were present (Fig. 2(A)–(D)).

The second of her three sons, aged 9, presented a delay in the acquisition of motor milestones, not sitting until 10–11 months of life and unable to walk until 23 months. He presented early-onset distal weakness in both arms and legs, with bilateral foot drop since early childhood. He also had mild facial and severe flexor cervical weakness. He had no scapular winging nor contractures.

MRI showed atrophy and fatty replacement of the semimembranosus, biceps, tibialis anterior and extensor digitorum longus (Fig. 1(C) and (D)).

A muscle biopsy of the biceps brachii showed no predominance or asymmetry in fiber size between the two types of fibers. No rods were detected with H&E and other routine histological stains, including modified Gomori tricrome, but they were frequently detected in the ultrastructural study. All the nemaline rods had sarcoplasmic localization, no intranuclear nemaline rods were identified.

NADH, SDH and COX stains showed frequent single or multiple irregularities, some relatively well demarcated. No cores or minicores were detected with electron microscopy. (Fig. 2(E)–(H)).

Molecular diagnosis was achieved by next generation sequencing (NGS) of a targeted panel of 59 genes related to progressive myopathies that revealed a missense heterozygous mutation (c.591G>C, p.Glu197Asp) in exon 4 of *ACTA1* gene (NM_001100.3). Sanger sequencing was performed in order to confirm this variant in both patients.

In the previous report of a large family of multiple generations with the same mutation in *ACTA1*, muscle biopsies did not show nemaline rods [4]. In addition, the presence or formation of nemalin rods could not be demonstrated in an exhaustive in vivo or in vitro functional study, suggesting a molecular mechanism different from that of other *ACTA1* mutations.

In the family that was previously published by Zukosky et al., the core clinical phenotype was "scapulo-humeral-peroneal-distal", with significant phenotypical variability among family members. Distal involvement was present in almost all the members of the family. Some of the patients were significantly more affected in the upper limbs and some of them did not have scapular winging. Therefore, we consider that our family and the family previously published share a similar clinical phenotype. Recently, another family with a

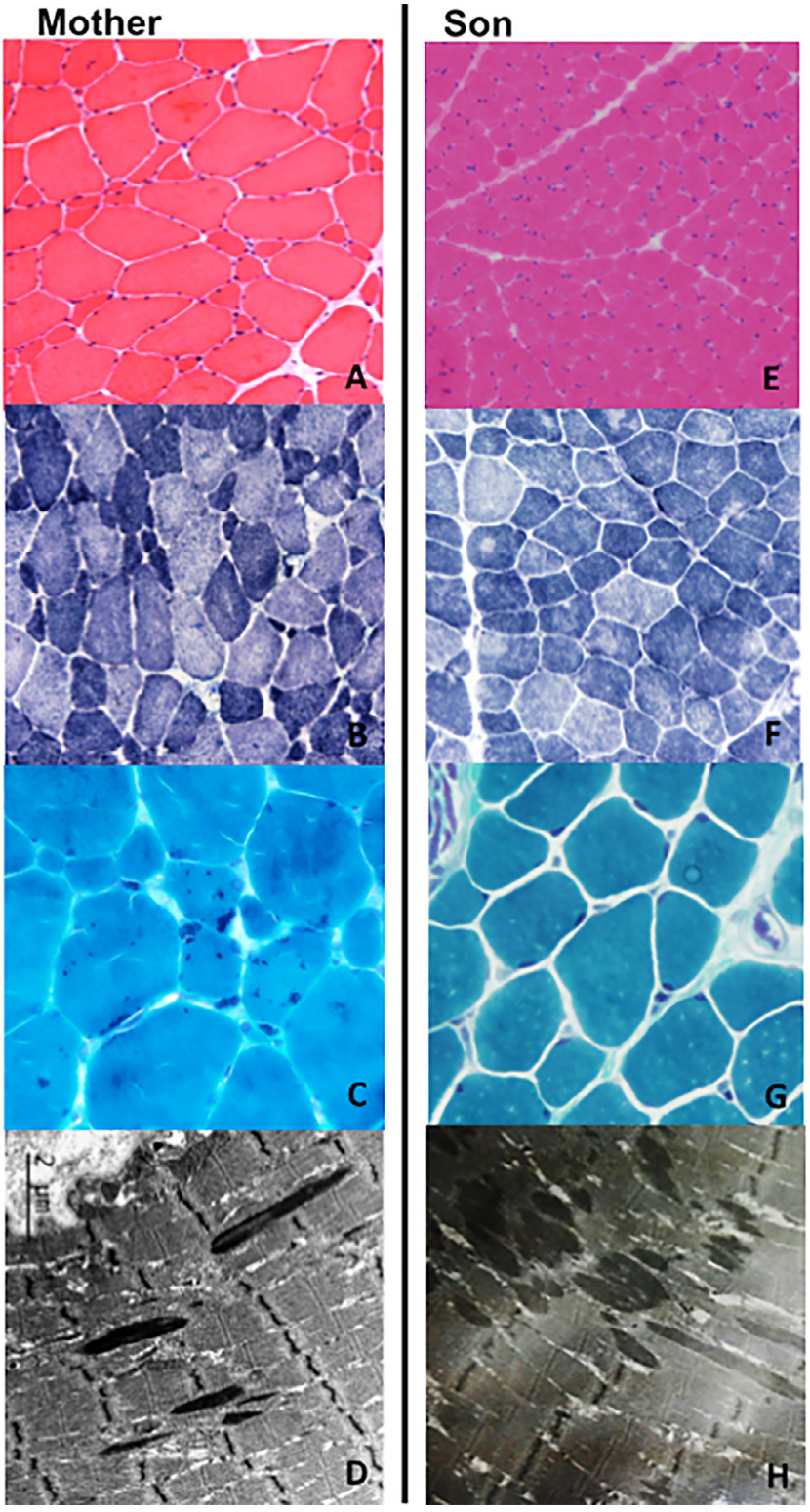

Figure 2. A biceps brachii muscle biopsy of the mother shows variability in fiber size (A) (hematoxylin-eosin stain; original magnification, x200). NADH shows some non-specific irregularities (B) (x200). Modified Gomori-trichrome stain numerous sarcoplasmic nemaline rods (C) (x400) which are also very evident and numerous in the ultrastructural study (D).
A muscle biopsy of the biceps brachii of the son does not show significant fiber size variability (E) (hematoxylin-eosin stain; original magnification, x100). NADH shows frequent single or multiple irregularities, some relatively well demarcated (F) (x200). No rods are detected with modified Gomori-trichrome stain (G) but they are frequent in the ultrastructural study (H).

similar distal phenotype was described, in which the presence of nemaline rods was also detected, but it was related to a different *ACTA1* mutation (p.Gly253Arg) [5].

There may be variability in the detection of nemaline rods in muscle biopsies, which includes the processing technique, the age of the patient and the possible variability between individuals, between different muscle groups and even within the same muscle [6–8].

In conclusion, muscle biopsy in both members of our family, that share the same clinical manifestations of some members of the previously published family and the same p.Glu197Asp mutation in *ACTA1,* evidenced the presence of numerous nemaline rods, suggesting that there must be other factors that explain the absence of nemaline rods.

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