Phenotypic Variability and Disease Progression in FLNC p.Ala193Thr-Associated Myopathy: A Family-Based Study with Longitudinal Follow-Up

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INTRODUCTION

Filamin C (FLNC)-related myopathies are autosomal dominant muscle disorders caused by mutations in the FLNC gene. Two main phenotypes have been described: a proximal myopathy associated with rod domain mutations, with myofibrillar myopathy (MFM) features; and a distal phenotype, caused by frameshift mutations causing haploinsufficiency or by actin-binding domain (ABD) missense mutations, showing distal weakness, moderate or absent MFM features. The c.577G>;A (p.Ala193Thr) mutation has been associated with a prominent distal muscle involvement in a limited number of patients, and no longitudinal follow-up has been reported so far.

MATERIALS AND METHODS

We report clinical and muscle magnetic resonance imaging (MRI) data of a family harbouring the FLNC p.Ala193Thr mutation. Two family members (III-1, III-6) underwent muscle biopsy, too. At the first evaluation in our center, four patients (III-1, III-6, III-7, IV-7) showed both proximal and distal lower limb involvement, while one patient had only calf atrophy (IV-2). MRI revealed fatty replacement of the gastrocnemius (medial and lateral) and soleus muscles in all patients, with quadriceps and hamstring involvement in the four patients with proximal lower limb weakness. Muscle biopsies from the two patients studied showed myopathic changes with moderate MFM histological features. Longitudinal clinical and imaging follow-up performed in the patient with calf atrophy at onset demonstrated the progression of the disease toward proximal lower limb muscle involvement.

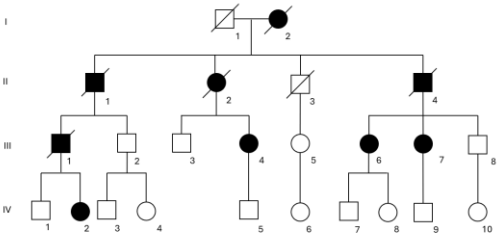

Figure 1

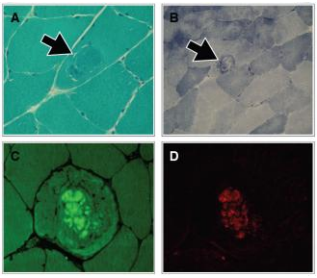

Figure 3

Figure 1. Family-tree of the family we report in this study.

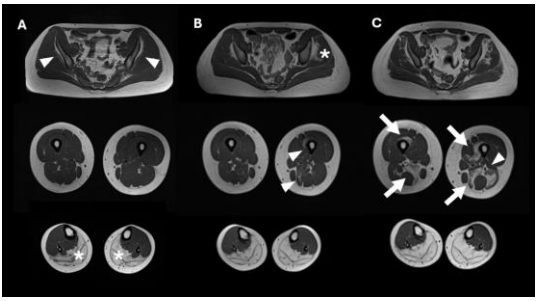

Figure 2

Figure 2. Patient IV-2: **A)** Baseline muscle MRI (T1-weighted) showing bilateral involvement of the gluteus minimus (arrowheads), soleus, medial and lateral gastrocnemius (asterisks), replaced by fatty tissue. **B)** Muscle MRI at 5-year follow-up (T1-weighted) showing bilateral involvement of the gluteus medius (asterisk), with early changes in the left adductor magnus and vastus intermedius (arrowheads) **C)** Muscle MRI at 10-year follow-up (T1-weighted) showing bilateral involvement of the vastus intermedius, adductor magnus (arrows), and the long head of the left biceps femoris (arrowhead).

Figure 3 Pt. III-4 muscle biopsy: Minor myofibrillar changes are evident (arrows) on modified Gomori trichrome stain (A, 40x) and NADHTR (B, 20x). Aggregates are reactive with phalloidin (C, 40x) and anti-myotilin (D, 40x) antibodies.

CONLUSIONS

This study provides a characterization of the phenotypic spectrum associated with the p.Ala193Thr mutation and describes the longitudinal progression of the disease. The findings support the concept of FLNC-related myopathies as a clinical spectrum and highlight the importance of ongoing follow-up to understand disease course.

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