Clinical Neurology and Neurosurgery 176 (2019) 30–33

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Case Report

Expanding the phenotype of filamin-C-related myofibrillar myopathy

Josefine de Stricker Borch*,[1], Anne-Sofie Vibæk Eisum[1], Thomas Krag, John Vissing

Copenhagen Neuromuscular Center, Department of Neurology, Rigshospitalet, University of Copenhagen, Denmark

ARTICLE INFO

Keywords:
Myofibrillar myopathy
Filamin C-related myopathy
Trismus
Axial myopathy
Protein aggregates

ABSTRACT

We report three patients with a rare filamin C myofibrillar myopathy. They present with atypical symptoms that expand the phenotype of filaminopathy. The new findings are progressive contractures of muscles surrounding the temporomandibular joint, detailed single myofiber histology findings and demonstration of severe affection of paraspinal muscles on MRI.

1. Introduction

Filamin C is localized to the Z-disc and cross-links with actin. It is involved in sarcomere structure maintenance and mediates cytoskeletal signaling. Mutations in the gene encoding filamin C (*FLNC*), lead to an autosomal dominantly inherited progressive myopathy.

Filamin C myopathy present in three clinical forms; one with mutations in the FLNC rod domain, including the dimerization domain, resulting in late-onset, progressive proximal muscular weakness and large sarcoplasmic inclusions; a second with a frameshift mutation in *FLNC* leading to haploinsufficiency and a distal myopathy without sarcoplasmatic inclusions, and a third type caused by missense mutations in the actin-binding domain, causing either a proximal or a distal myopathy with nonspecific histopathological changes [1].

In this case report, we describe a Danish three-generation family carrying a p.Trp2710Ter mutation in the dimerization domain of the *FLNC* gene. The mutation has previously been reported in eight families, six of them with German descent [1,2]. We here describe a number of new phenotypic features associated with the gene variant.

2. Case report

2.1. Patients

The patients are three women from three generations in a family. They all developed progressive proximal weakness of lower limb between ages 35–45. The proband, from generation two, progressed rapidly from age 51–63 years and at age 58, she lost ambulation. At age 70, she could not lift her arms. At age 50, her daughter only had proximal weakness in the lower extremities. MRI of the daughter revealed fat replacement in the axial muscles and the leg muscles. The proband and her mother developed respiratory insufficiency in their 50 s. The proband experienced progressive closure of her mouth limiting eating and dental hygiene. Her mother required a wheelchair for longer distances at age 50. She died at age 66 from an aspiration pneumonia.

2.2. Investigations

Blood samples were obtained to measure CK levels.

DNA extracted from blood samples from the proband and patient 2 was tested with a panel of 156 muscle genes (gene list available on request). No DNA was available from the diseased mother of the proband.

Muscle tissue was obtained from vastus medialis in the proband and her daughter. The tissue was processed according to standard procedures. For additional methodology see legends of Fig. 2.

A T1-weighted, whole-body MRI of muscles was performed in the daughter of the proband.

2.3. Results

DNA testing revealed a heterozygous 8130 G > A, (p.Trp2710Ter) mutation in the *FLNC* gene of the proband and daughter.

In all family members, muscle weakness started proximally and progressed distally. The proband progressed rapidly from age 51–63 years (MRC: shoulder abduction 5- to 2; hip flexion 4+ to 2; ankle dorsiflexion 4+ to 0). At age 50, her daughter had normal strength in

* Corresponding author at: Copenhagen Neuromuscular Center, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.
E-mail address: josefine.de.stricker.borch@regionh.dk (J.d.S. Borch).
[1] These authors contributed equally.

https://doi.org/10.1016/j.clineuro.2018.11.013
Received 12 September 2018; Received in revised form 1 November 2018; Accepted 17 November 2018
Available online 19 November 2018
0303-8467/

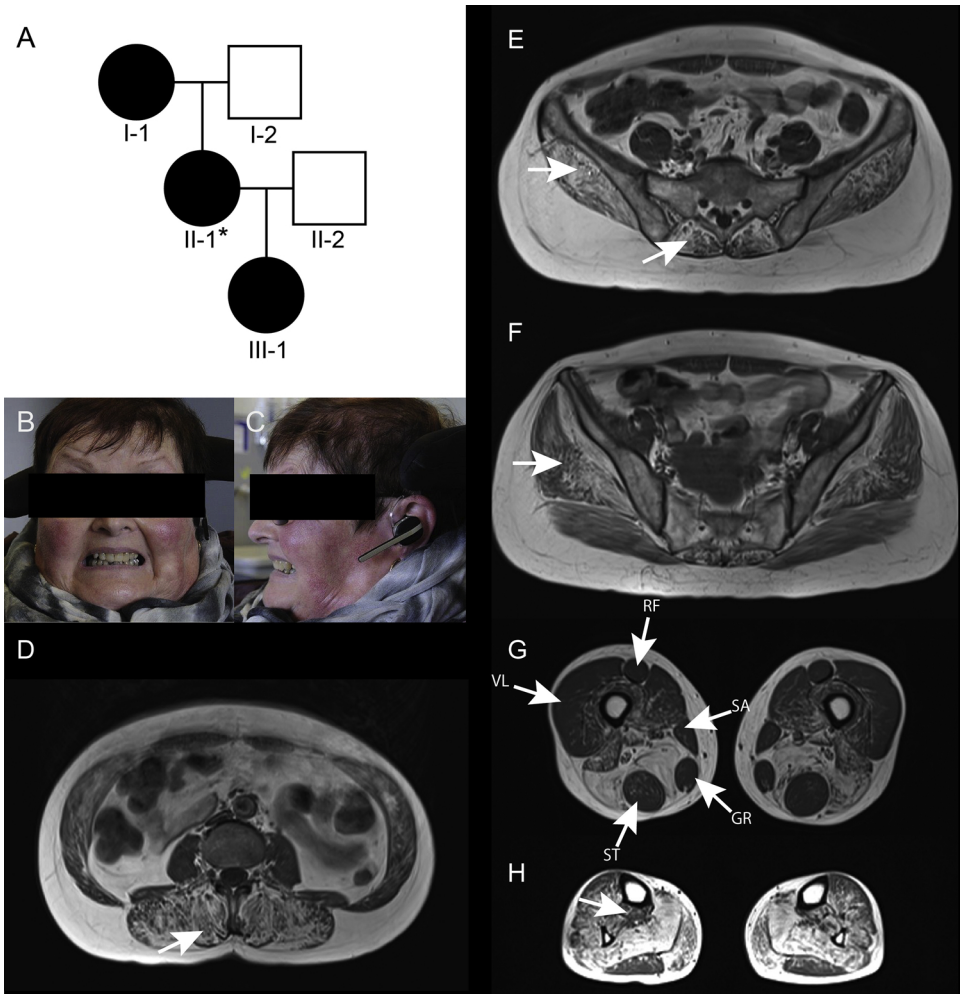


Fig. 1. Pedigree, clinical photograph of masseter/temporal muscle contractures and MRI revealing a distinct pattern of muscular affection. A is a pedigree of affected and unaffected individuals of the family. B–C is a photo of the proband's maximal ability to open her mouth. The restricted mouth opening is due to contractures in the muscles surrounding the temporomandibular joint. D–F, T1- weighed MRI, using a 1.5 T MR unit, in the daughter of the proband reveals extensive replacement of muscle by fat in erector spinal and medial gluteal muscles (arrows). G, at thigh level, there is a relative preservation of rectus femoris (RF), vastus lateralis (VL), sartorius (SA), gracilis (GR) and semitendinosus muscles (ST), which in some cases are hypertrophied. Adductors, vastus intermedius, biceps femoris and semimembranosus are heavily replaced by fat. H, there is extensive affection of the muscles at calf level with only moderate sparing of the lateral part of the gastrocnemius muscle, and disproportionate affection of the deep posterior compartment (arrow), which is atypical for most muscle diseases.

upper extremities, but muscle weakness proximally in legs (MRC 4−/4+). The proband has suffered progressive contractures of the temporal- and masseter muscles since her 20 s leading to inability to open her mouth at age 70 (Fig. 1B–C).

CK levels were mildly elevated in the proband (range; 122–497 units/L) and her daughter (range; 222–605 units/L, normal < 200).

MRI of the proband's daughter revealed extensive fat replacement of axial and leg muscles (Fig. 1D–H)

Electrocardiography, echocardiography and 24h-Holter-monitoring were normal in the proband and daughter. The proband and her diseased mother developed severe respiratory insufficiency. The proband required a tracheostomy at age 62 years. Respiratory function in the daughter was normal (FVC 3.4 L, FEV1 2.7L) at age 50 years.

Muscle biopsies of the proband and her daughter, and a post-mortem biopsy from the mother, showed myopathic patterns with variation in fiber size and internalized nuclei. Serial sections demonstrated substantial accumulation of subsarcolemmal and sarcoplasmic filamin C and other proteins involved in Z-disc attachment to surrounding myofibrils, organelles and sarcolemma. A significant presence of ubiquitin and plaque forming β-amyloid can be seen in these fibers as well. The protein aggregates are seen as diffuse as well as spheroid and appears to displace sarcomeres at the subsarcolemmal space (Fig. 2).

3. Discussion

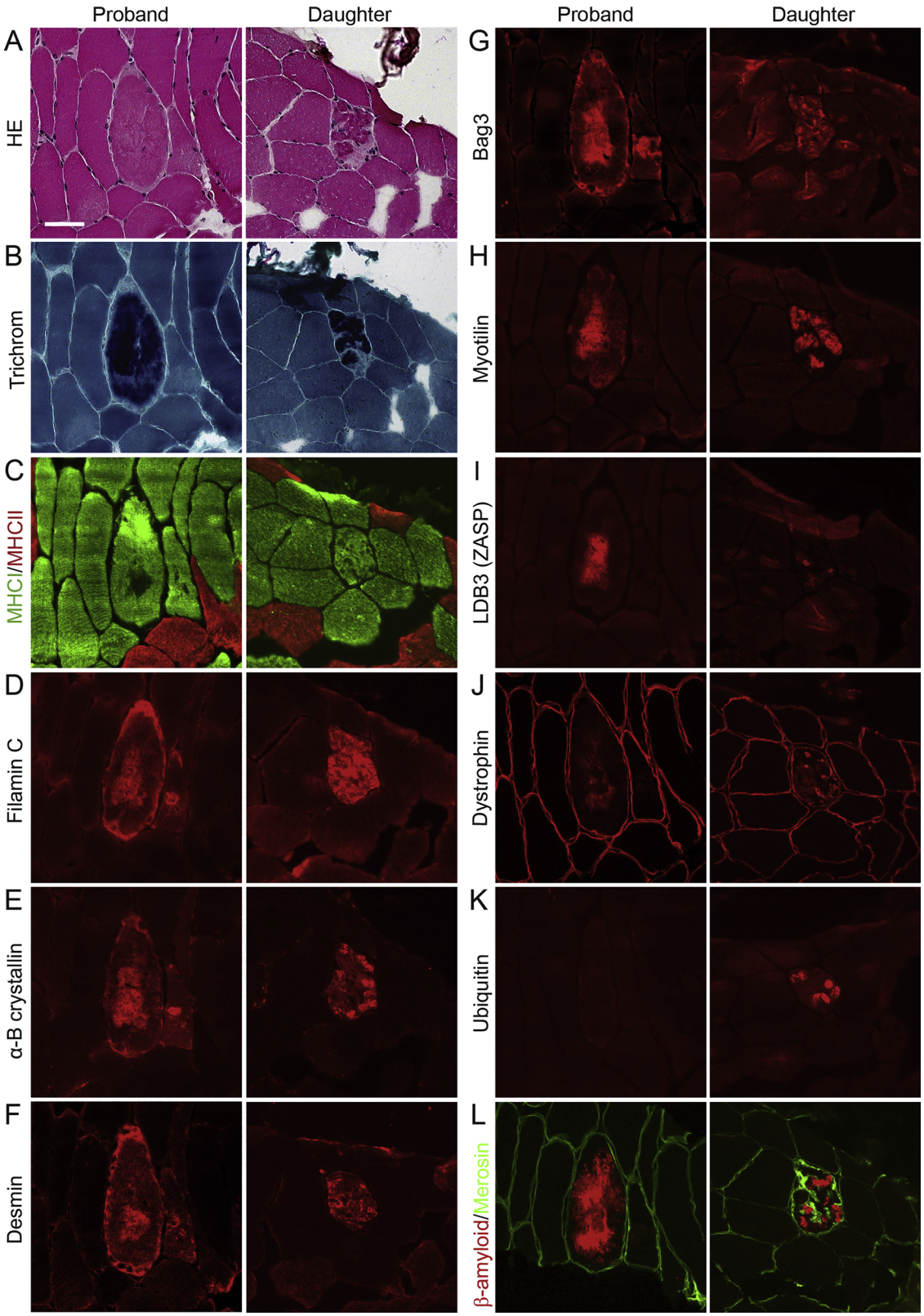
We present a 3-generation family with some atypical symptoms that expand the phenotype of filamin C myopathy. The p.Trp2710Ter mutation has been reported in eight families, six with German descent [1,2].

The new findings related to this mutation are progressive contractures of muscles surrounding the temporomandibular joint, detailed single cell histology findings and demonstration of severe affection of paraspinal muscles.

Progressive restricted mouth opening due to contractures of masseter and/or temporal muscles have been described for a number of congenital myopathies [3,4] and Bethlem myopathy, but never for filamin C myopathy patients. Interestingly, this was only present in the proband since her youth, but not in her affected family members. All three collagen VI genes were included in the gene panel and showed no pathogenic variants, which was also the case for genes involved in other dominantly inherited myopathies.

The histological hallmark of myofibrillar myopathy is the presence of protein aggregates in sarcoplasm [2]. In this report, we demonstrate a concurrent aggregation of sarcolemmal, subsarcolemmal and sarcoplasmic proteins in affected myocytes, accompanied by ubiquitin mediated protein degradation. Likely, an ensuing β-amyloid plaque formation as shown in this study, destroys contractile function in the affected myofibers, and is part of the disease process in filaminopathy.

MRI has been reported in a few patients with filamin C myopathy, and a common pattern of muscle affection seems to emerge, showing relative preservation of rectus femoris, superficial vastus, sartorius, gracilis and semitendinosus muscles, while adductors, vastus intermedius, biceps femoris and semimembranosus muscles are heavily replaced by fat [1,2]. At calf level, there is extensive affection of the muscles, which shows that filaminopathy, although preferentially proximal or distal at onset, converges to diffuse muscle affection. The



(caption on next page)

limb muscle affection found in our patient resembles previously reported cases.

A third of the patients with the p.Trp2710Ter mutation have cardiomyopathy, which was absent in our patients.

Respiratory insufficiency progressing to need for invasive ventilator assistance, as found in our family, has only been reported in very few filamin C myopathy patients before [5]. Most reported cases are described with primary proximal weakness, similar to our patients, but few patients presented with distal myopathy [2], which agrees with the more diffuse pattern of affected muscles found in MRI studies.

Fig. 2. Muscle histology of the proband and the proband's daughter demonstrates myofiber protein aggregates. A–L are serial sections of biopsies from the vastus lateralis muscle demonstrating protein accumulations. A, H&E-stain reveals a myopathic pattern with variation in fiber size, internalized nuclei and fibers with protein aggregation in both filaminopathy patients. B, Gomoris trichrome stain visualizes protein aggregates in both patients. C, myosin heavy chain (MHC) type I and II, demonstrate absence of subsarcolemmal and sarcoplasmic MHC I in the affected fibers. D-G, Filamin C, α-B-crystallin, desmin and BAG3, all involved in interconnecting the Z-disc to the surrounding environment and sarcolemma aggregate in the subsarcolemmal space and diffusely in the sarcoplasm. H-I, Myotilin and LDB3 (ZASP), Z-disc binding proteins, aggregate diffusely and in spheroids in the sarcoplasm, but not at the subsarcolemmal space. J, dystrophin is also seen aggregating diffusely in the sarcoplasm. K, ubiquitin co-localizes with the diffuse sarcoplasmic aggregates in the younger, but not in the older filaminopathy patient. L; β-amyloid is found in the severely affected fibers. Bar is 50 μm.
Immunohistochemical stains were applied using antibodies against myotillin, dystrophin (1:50, Dy8/6C5, Novocastra, Newcastle, UK), αB-crystallin (1:100, ab13496, Abcam, Cambridge, UK), desmin (1:50, DE-U-10, Sigma-Aldrich, St. Louis, MO), ubiquitin (1:250, ab7254, Abcam, Cambridge, UK), MHC fast (1:50, A4.74, DHSB, Iowa City, IA), MHC slow (1:40, B4-D5, DSHB, Iowa City, IA), filamin C (1:100, HPA006135, Sigma-Aldrich, St. Louis, MO), LDB3 (1:200, HPA048955, Sigma-Aldrich, St. Louis, MO), bag3 (1:100, Abcam, Cambridge, UK) and β-amyloid (1:250, aa1-42, Invitrogen, Carlsbad, CA.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest

Dr. Vissing has received research and travel support and speaker honoraria from Genzyme/Sanofi, Santhera Pharmaceuticals, Ultragenyx Pharmaceuticals and aTyr Pharmaceutical, and served as consultant on advisory boards for Genzyme/Sanofi, aTyr pharmaceuticals, Audentes Therapeutics, Inc., Ultragenyx Pharmaceuticals, Santhera Pharmaceuticals, Sarepta Therapeutics, NOVO Nordisk, Alexion Pharmaceuticals and Stealth BioTherapeutics within the last 3 years. All other authors report no disclosures

Acknowledgements

We thank Danuta Goralska-Olsen for laboratory assistance.

References

[1] R.A. Kley, P. Serdaroglu-Oflazer, Y. Leber, Z. Odgerel, V.D. Ven, M. Olivé, I. Ferrer, Pathophysiology of protein aggregation and extended phenotyping in filaminopathy, Brain 135 (9) (2012) 2642–2660 1. September.
[2] D.O. Fürst, L.G. Goldfarb, R.A. Kley, M. Vorgerd, M. Olivé, P.F.M. van der Ven, Filamin C-related myopathies: pathology and mechanisms, Acta Neuropathol. (Berl). 125 (1) (2013) 33–46 1. January.
[3] M. Catteruccia, F. Fattori, V. Codemo, L. Ruggiero, L. Maggi, G. Tasca, m.fl, Centronuclear myopathy related to dynamin 2 mutations: clinical, morphological, muscle imaging and genetic features of an Italian cohort, Neuromuscul. Disord. 23 (3) (2013) 229–238 March.
[4] M. Marttila, V.-L. Lehtokari, S. Marston, T.A. Nyman, C. Barnerias, A.H. Beggs, m.fl, Mutation update and genotype–Phenotype correlations of novel and previously described mutations in TPM2 and TPM3 causing congenital myopathies, Hum. Mutat. 35 (7) (2014) 779–790 July.
[5] R.A. Kley, Y. Hellenbroich, M.P.F. Ven VD, D.O. Fürst, A. Huebner, m.fl, Clinical and morphological phenotype of the filamin myopathy: a study of 31 German patients, Brain 130 (12) (2007) 3250–3264 1. December.