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Novel *FLNC* mutation in a patient with myofibrillar myopathy in combination with late-onset cerebellar ataxia

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Abstract

Introduction—Mutations in the gene that encodes filamin C, *FLNC*, represent a rare cause of a distinct type of myofibrillar myopathy (MFM).

Methods—We investigated an Italian patient by means of muscle biopsy, muscle and brain imaging and molecular analysis of MFM genes.

Results—The patient harbored a novel 7256C>T, p.Thr2419Met mutation in exon 44 of *FLNC*. Clinical, pathological and muscle MRI findings were similar to the previously described filaminopathy cases. This patient had, in addition, cerebellar ataxia with atrophy of cerebellum and vermis evident on brain MRI scan. Extensive screening failed to establish a cause of cerebellar atrophy.

Discussion—We report an Italian filaminopathy patient, with a novel mutation in a highly conserved region. This case raises the possibility that the disease spectrum caused by *FLNC* may include cerebellar dysfunction.

Keywords

filaminopathy; *FLNC*; myofibrillar myopathy; cerebellar ataxia; muscle MRI

1. Introduction

Myofibrillar myopathies (MFM) are a group of muscle diseases defined by the presence of distinctive muscle biopsy findings that include focal areas of myofibrillar disorganization, accumulation of myofibrillar degradation products, and ectopic expression of several proteins inside the muscle fibers¹. Although the histological findings in MFM are by definition rather homogenous, the genetic causes as well as the phenotype are heterogeneous. At present, mutations in six genes that encode Z-disk associated proteins

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(desmin, alpha-B crystallin, myotilin, ZASP, filamin C, and Bag-3) are known to account for less than one-half of the MFM cases². Some authors broaden the genetic spectrum of MFM to include myopathies caused by mutations in *FHL1*, *PLEC* and *SEPNI*, although specific clinical and histological features often distinguish these diseases. From a clinical point of view, MFMs can show predominantly distal or proximal muscle involvement, or mixed patterns. Sometimes associated findings include cardiac involvement or extramuscular manifestations such as peripheral neuropathy. Filamin-C mutations cause an MFM that typically manifests with late onset proximal weakness^{3, 4}. In the majority of known cases of filaminopathy the onset of illness was in the early 40s (range 24 to 60)^{3, 5}.

Filamins are a family of proteins that crosslink actin filaments into networks and anchor membrane proteins to the cytoskeleton. Three isoforms are encoded by the human genome: filamin A, B and C. Filamin C (or gamma-filamin) is a Z-disk protein whose expression is largely restricted to skeletal and cardiac muscle⁶. Only three mutations in the gene encoding filamin C, *FLNC*, associated with autosomal dominantly inherited MFM have been described so far. The first mutation, p.W2710X (c.8130G>A), was identified in the last *FLNC* exon⁷ in four German families who likely share a common founder³, and subsequently in three other MFM families at the Mayo Clinic⁸. Two other mutations have been reported in the seventh immunoglobulin-like repeat of the *FLNC* gene, a p.Val903_Thr933del (c.2997_3008del) and a p.Val899_Cys900ins/del in a German and a Chinese family, respectively^{5, 9}. Recently two additional mutations have been described in the actin binding domain of *FLNC* in the N-terminal region of the protein, which are associated with a different phenotype, i.e. distal myopathy without MFM features¹⁰. While this manuscript was under review a frameshift deletion (c.5160delC) was reported to cause a distal myopathy with upper limb predominance and minor myofibrillar changes on muscle biopsy¹¹.

Here we describe clinical, histological and muscle MRI data in an Italian patient with a complex phenotype characterized by pathologically confirmed MFM and concomitant ataxia with cerebellar atrophy. The molecular culprit in this case was a novel 7256C>T, p.Thr2419Met *FLNC* mutation.

2. Materials and methods

2.1. The affected family

A 70-year-old man was admitted to the Neurology Department of the Catholic University in Rome for investigations of slowly progressive walking difficulties that began 10 years previously. His parents were first cousins and were reported to be unaffected (they died at ages 95 and 92 years). His sister who died at age 78 did not show symptoms of a neuromuscular or cerebellar disorder. His 44-year-old son, who suffered from idiopathic epilepsy with generalized seizures, and his 75-year-old brother were examined and found not to show any of the signs and symptoms detected in the index case.

2.2. Muscle biopsy

10-μm thick cryostat sections were stained by routine histochemical techniques: hematoxylineosin, nicotinamide adenine dinucleotide dehydrogenase tetrazolium reductase (NADH-TR), succinate dehydrogenase, cytochrome-C oxidase, modified Gomori trichrome, alkaline phosphatase, periodic acid-Schiff, Congo red and ATPase pH 4.3, 4.6 and 9.4. Immunohistochemistry was performed on 6-μm thick sections using FITC-conjugated phalloidin (Sigma, St. Louis, MO, USA) and the following primary antibodies: monoclonal anti desmin (Chemicon, Temecula, CA, USA) diluted 1/100, monoclonal anti myotilin (Novocastra, Newcastle, UK) diluted 1/20, anti alpha-dystroglycan clone I1H6C4 (Upstate,

Lake Placid, NY, USA) diluted 1/100, and monoclonal anti slow- and fast-myosin (Novocastra, Newcastle, UK) diluted 1/20. For electron microscopy, a specimen was fixed in 2.5% glutaraldehyde and processed by standard methods. Ultrathin skeletal muscle sections were analyzed using a Zeiss Libra 120 electron microscope.

2.3. Mutation detection

The strategy of genetic analysis in this family was based on direct sequencing of candidate genes selected with consideration of the complicated phenotype that included muscle pathology reminiscent of MFM and cerebellar dysfunction. The following myopathy-associated genes were analyzed: *LMNA* (lamin A/C), the (CCTG)_n expansion in *ZNF9* (zinc finger protein 9), *DES* (desmin), *CRYAB* (alpha-B crystallin), *TTID* (myotilin), *LDB3* (ZASP), *BAG3* (BCL2-associated athanogene 3), *FLNC*, *ACTA1* (actin alpha 1), *TPM2* and *TPM3* (two tropomyosin genes), and *MYH7* (myosin heavy chain 7, exons 30 to 40). In addition, a series of tests was performed to investigate the possible cause of cerebellar disease including analysis of the genes for spinocerebellar ataxia types 1, 2, 6, 7 and 17, *POLG* (mitochondrial polymerase gamma), and the CGG expansion in *FMR-1* (FXTAS). Genomic DNA was extracted from anticoagulated blood of the index patient, his brother and his son and used for amplification of each coding exon with intronic primers constructed to amplify the exons and intron-exon boundaries of the listed genes (primer sequences are available on request). Resulting fragments were purified by MinElute™ 96 UF PCR purification kit (Qiagen Sciences, Gaithersburg, MD, USA) and sequenced in both directions using DyeTerminator™ Sequencing Protocol on an ABI 3100 Prism Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). Mutation detection was accomplished by aligning results with the database sequences utilizing the Mutation Surveyor Software (SoftGenetics, State College, PA, USA). Negative controls were included as part of each run. Total mRNA was extracted from muscle biopsy tissue of the index patient using Trizol® Reagent (Gibco BRL, Grand Island, NY) and DNA contaminants were removed using Turbo DNA-free™ (Ambion, Austin, TX, USA). 0.5 microgram of total RNA was used for reverse transcription (RT) with SuperScript™ First-Strand Synthesis system (Invitrogen, Carlsbad, CA). The exon 44 region of *FLNC* was amplified with primers 44Rf (TCCAGCTCAGAGACGTAGCA) and 44Rr (ATTCACCACAAAGGGGCTCT) and sequenced.

Genetic studies were approved by the institutional review boards of each collaborating institution and were performed in accordance with the Declaration of Helsinki. All subjects gave written informed consent prior to participation.

3. Results

3.1. Clinical manifestations

At age 70 years, the patient was able to walk only with support and for short distances. His difficulties were due to both muscle weakness and trunk and gait ataxia. He could rise from a chair only with assistance. He had lumbar hyperlordosis, mild pes cavus and moderate calf hypertrophy. Examination also disclosed limb dysmetria and slightly dysarthric and hypernasal speech. The Romberg maneuver was negative. There was mild facial weakness. Eye movements were normal. Manual muscle strength testing revealed weakness of neck flexors, biceps brachialis and triceps muscles (MRC 4). Axial weakness was also evident. Muscle stretch reflexes were absent, and plantar responses were normal.

The patient's serum CK level was normal. EMG examination disclosed myopathic abnormalities and spontaneous activity characterized by fibrillation potentials and rare myotonic discharges. Motor and sensory nerve conduction studies and motor and sensory

evoked potentials were normal. ECG disclosed a complete right bundle branch block, and echocardiogram documented mild left ventricle hypertrophy with normal ejection fraction that could be ascribed to hypertension. His forced vital capacity was 67% of the predicted value.

Lower limb muscle MRI showed marked involvement of paraspinal muscles (erector spinae in particular), vastus lateralis (with a thin peripheral rim of relative sparing), followed by less severe involvement of vastus intermedius and medialis (Figure 1 A–C). In the anterior compartment of the thigh, rectus femoris, sartorius and gracilis were relatively spared. In the posterior compartment, semimembranosus was more involved than semitendinosus, and biceps femoris short head was relatively spared. At calf level, soleus and gastrocnemius medialis were severely involved. Brain and spine MRI were performed and showed bilateral cerebellar hemisphere and vermis atrophy (Figure 1D).

There was no history of chronic alcohol use, exposure to toxic agents, celiac disease or autonomic failure. There were no vitamin deficiencies, and paraneoplastic onconeural antibodies (anti Hu, Yo, Ri, amphiphysin) were absent.

Clinical examination 3 years later showed deterioration of walking ability mainly due to worsening imbalance. Muscle weakness had extended to scapular and upper limb proximal (supra and infraspinatus MRC 3, deltoid MRC 4), and lower limb distal muscles (tibialis anterior and extensor hallucis longus MRC 4).

3.2. Muscle pathology

Biopsy of the deltoid muscle showed myopathic features with increased fiber size variation and internal nuclei. Infrequently, fibers contained a few rimmed vacuoles. Some fibers harbored small subsarcolemmal cytoplasmic bodies or small collections of rod bodies. On NADH-TR and oxidative enzyme staining, many fibers showed uneven staining. Rare COX-negative ragged red fibers and ring fibers were evident, and type 1 fibers were predominant. Immunoreaction with the anti alpha-dystroglycan antibody was normal. Abnormal accumulations of desmin and myotilin were present in many fibers; some of the inclusions displayed congophilia with a dotted pattern. In some cases, the desmin reaction was positive in a rim, surrounding subsarcolemmal, roughly triangular structures that could morphologically resemble caps. However, unlike cap structures, the subsarcolemmal areas which appeared hyaline-like on hematoxylin-eosin and blue with NADH-TR contained slow-myosin as judged by their positive staining with anti slow-myosin heavy chain antibody, but they lacked myosin-ATPase activity (Figure 2).

Electron microscopy (EM) on the available transverse sections (Figure 3) showed subsarcolemmal regions composed of dissolved myofilaments, including thick filaments and sarcomeric remnants, which likely correspond to the areas that were reactive for slow-myosin without ATPase activity. Subsarcolemmal accumulations of mitochondria, Z-disk streaming (that in some regions constituted true minicores) and focal accumulations of dense and filamentous material were present as well. One nucleus displayed a deposit of thin filaments and Z-disk density material (Figure 3F).

3.3. Analysis of gene sequences and mutation screening

Analysis of DNA sequences of coding exons in studied genes resulted in the identification of a heterozygous C>T substitution at the c.7256 position within exon 44 of *FLNC* corresponding to a predicted p.Thr2419Met mutation (Figure 4). No other known or unknown variations in genes associated with myopathy or cerebellar dysfunction were encountered. The mutation was found in the genomic DNA of the patient and his unaffected son, but not the unaffected brother. Sequencing of the patient's RT-PCR fragment of exon 44

that was amplified from mRNA extracted from a biopsied muscle confirmed the presence of the c.7256 C>T mutation at the RNA level. No sequence irregularities in *FLNC* exon 44 were identified in 232 control individuals of the same ethnic background and 100 additional controls from other European countries (664 chromosomes). In addition, this change was not observed in the latest 1000 genome data release which contains data from 629 control individuals¹². The Thr2419 residue is located within the *FLNC* immunoglobulin-like repeat 22 that is highly conserved in evolution (Figure 4). The variant is located outside the region of homology of the transcribed *FLNC* with the recently identified *FLNC*-like pseudogene¹³.

4. Discussion

This patient who harbors the novel *FLNC* mutation presented with a late onset slowly progressive axial and proximal myopathy, mild nasal speech, mild restrictive respiratory insufficiency, arrhythmogenic heart disease with a right bundle branch block and ataxia. Muscle biopsy findings were suggestive of MFM, with evidence of abnormal protein aggregation detectable with histochemical and immunohistochemical stainings, and myofibrillar disorganization observed in many areas on EM. Typical granulofilamentous material was not detected on EM, however, its absence could be due to the availability of only a small muscle fragment for EM analysis. Unusually for an MFM, along with the classical intracellular inclusions, some areas of myofibrillar degradation assumed a subsarcolemmal, triangular “cap-like” appearance. Unlike caps, these areas also displayed slow-myosin immunoreactivity, which has been reported in hyaline bodies. All of the genes known to be associated with cap myopathy (*TPM2*, *TPM3*, *ACTA1*)^{14–16} and hyaline body myopathy (*MYH7*)¹⁷ have been screened with negative results in our patient. Another interesting feature is the peculiar intranuclear accumulation of filamentous and Z-disk density material. Whereas the presence of filamentous or tubulofilamentous material inside the nuclei has been described in various diseases (such as inclusion body myositis, oculopharyngeal muscular dystrophy¹⁸ and myotilinopathy¹⁹), the occurrence of intranuclear Z-disk derived material (in the shape of rods) is generally considered a distinctive feature of nemaline myopathies with *ACTA1* mutations²⁰. Interestingly however, small intranuclear rods can be found occasionally in MFMs¹⁹, thus giving rise to interesting theories concerning their origin. While intranuclear rods associated with *ACTA1* mutations are known to originate from abnormal aggregation of nuclear actin²⁰, the detected accumulation in our case could derive from the cytoplasm through a nuclear membrane rupture (or a physiological opening). This perturbation in the nuclear structure and eventual function may represent a mechanism that contributes to muscle damage.

MFM is known to be associated with mutations in one of six genes: *DES*, *MYOT*, *ZASP*, *CRYAB*, *BAG3*, or *FLNC*¹. The overall phenotypic profile of a late-onset myopathy involving predominantly proximal muscles, the suggestive muscle imaging pattern and the identification of a non-synonymous mutation in the highly conserved through evolution rod domain of the patient's *FLNC* gene at the genomic and RNA levels, together with the absence of this mutation in healthy unrelated controls, strongly indicates that the patient is affected with filaminopathy. Filaminopathy is a rare subtype of MFM worldwide, although the disease frequency is likely to be higher in Germany due to a founder effect³. The distribution of muscle weakness in the filaminopathy cases published so far is strikingly homogenous as compared with the other MFMs. There is early involvement of proximal lower and upper limb muscles, followed by distal lower limb muscles, and there is often associated axial and abdominal weakness^{3, 5, 9}. Our patient showed a typical limb-girdle phenotype and a consistent muscle imaging pattern of involvement that perfectly matches the previously described filaminopathy characteristics²¹. In the lower limbs, muscle weakness was not very pronounced, although the involvement was clearly seen on muscle imaging. Muscle imaging findings are very homogeneous in the reported filaminopathy

cases, and the pattern of fatty replacement helps to distinguish filaminopathy from other MFMs²². At variance with other MFMs, peripheral neuropathy is uncommon, while myotonic discharges on EMG and cardiomyopathy, both arrhythmogenic and dilated, are frequent features³. The patient's son harbors the same mutation, but he belongs to an age group below the maximal age of disease onset. Periodic follow-up may reveal emergence of the disease.

Almost concomitantly with the skeletal and cardiac muscle condition, the patient developed progressive gait and trunk ataxia with a brain MRI scan indicating cerebellar atrophy, which is not explained by the investigated acquired or genetic etiologies. Cerebellar atrophy is a finding that has never been reported to accompany filaminopathy or other subtypes of MFM. The possibility that the patient is affected by some other myopathy known to be associated with central nervous system involvement, such as mitochondrial myopathies or alpha-dystroglycanopathies, has been ruled out by histopathological analysis. In addition, our patient was screened and found to be negative for the most prevalent spinocerebellar ataxias in the Italian population, Fragile X-associated Tremor/Ataxia Syndrome, and ataxia due to mitochondrial polymerase gamma mutations. Other causes of late-onset ataxia including alcoholism, vitamin deficiencies, celiac disease and paraneoplastic syndromes have been excluded as well. We could not exclude that our patient is affected by an autosomal recessive cerebellar ataxia (ARCA), which can be a possibility considering that the patient's parents were reported to be first cousins. ARCA is a genetically heterogeneous group of rare disorders that generally present with a complicated phenotype and an earlier onset than occurred in our patient²³. However, some of them can have onset in the early forties, and a relatively pure phenotype has been described recently for ARCA1 due to mutations in the giant nuclear gene SYNE1²⁴ in only Quebec families to date.

On the other hand, one should consider the intriguing perspective that the *FLNC* mutation is responsible for both muscle and cerebellar diseases. Mutations in *FLNA*, another filamin gene, are associated with periventricular heterotopia, a disorder of cerebral cortex neuron migration²⁵, and the possibility that C-filaminopathy represents a multisystem disorder involving tissues other than skeletal and cardiac muscle is also suggested by the presence of chronic diarrhea in the Chinese patients⁹. However, although *FLNC* transcript has been demonstrated in the fetal brain in one study²⁶, this remains a very controversial finding^{27, 28}, and it is generally accepted that filamin C expression is limited to striated muscle⁶.

In conclusion, we report a novel *FLNC* mutation causing proximal MFM, the fourth described to date and the first in a non-German European patient. Our report confirms previous findings that the muscle phenotype associated with *FLNC* mutations is consistent, and we describe the coexistence of filaminopathy-associated muscle disease with adult-onset cerebellar ataxia of unknown etiology. The possible association between these two diseases deserves further study.

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ABBREVIATIONS

EM	electron microscopy
MFM	myofibrillar myopathy

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Figure 1.

T1-weighted MRI images of pelvic and lower limb muscles (A–C) and sagittal T1-weighted brain MRI image (D). Note the prominent involvement of erector spinae at the pelvic level (A), vastus lateralis and intermedius, semimembranosus and biceps femoris long head at the thigh level (B), gastrocnemius medialis and soleus at the calf level (C), and the evident cerebellar atrophy (D).

Figure 2.

Light microscopy of a muscle biopsy sample from the index patient. (A) Hyaline-like peripheral inclusion with a basophilic rim (asterisk); (B) Arrows indicate small pleomorphic aggregates that stain dark green with Gomori Trichrome; (C) NADH-TR showing fibers with unevenness of stain; (D) Desmin immunoreactivity in central regions of some fibers, often with a serpiginous appearance (arrows); some subsarcolemmal structures are diffusely stained (asterisk), and some appear as surrounded by a positive rim (“cap-like” appearance - arrowhead); (E) The same structures are visible with double immunolabeling for desmin (red) and phalloidin (green); (F) Myotilin accumulations are present in a number of fibers; (G) ATPase pH 4.3 showing type 1 fiber predominance and focal absence of the reaction in some subsarcolemmal regions, corresponding to areas that still maintain immunoreactivity with the anti slow-myosin heavy chain antibody (H, arrowhead); (I) Congo red under Texas Red optics showing a round inclusion with dotted congophilia.

Figure 3.

Ultrastructural findings of a muscle biopsy sample from the index patient. (A) A subsarcolemmal triangular area of dissolved myofilaments; some sarcomeric remnants are still visible at a higher magnification in the insert; (B) Focal sarcomeric disruption and deposits of dense and filamentous material; (C) Small focus of Z-line streaming; (D) Myeloid structures among apparently intact myofibers; (E) Nuclear accumulation of filamentous and Z-disk density material (higher magnification in E), possibly deriving from the sarcoplasm through nuclear membrane leakage (arrowhead).

Figure 4.

Sequence analysis of the *FLNC* gene fragments. (A) Chromatogram of a nucleotide sequence demonstrating the c.7256 C>T missense mutation in exon 44 of the *FLNC* gene. (B) Amino acid sequence alignment of a fragment of filamin C 22nd Ig-like repeat showing that the threonine (highlighted) is conserved through evolution from *Xenopus* to humans.