

A Window Into the Myofibrillar Myopathy Proteome

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Myofibrillar myopathy is a pathologically diagnosed myopathy encompassing a clinically and genetically heterogeneous group of myopathies that share common histopathologic features of dissolution of myofibrils, accumulation of myofibrillar degradation products, and ectopic expression of multiple proteins.¹ Patients with myofibrillar myopathy present with progressive proximal or distal predominant weakness at a variable age at onset, ranging from childhood to late adulthood. Cardiomyopathy and peripheral neuropathy are frequent extramuscular manifestations. To date, mutations in more than 10 genes underlie myopathies with myofibrillar pathology, most of which encodes Z disc-associated proteins or proteins involving in chaperon-assisted selective autophagy.¹

Filamin C is a muscle-specific actin-cross-linking protein localizing to Z discs, sarcolemma, myotendinous junctions, and intercalated discs. It consists of an N-terminal actin binding domain (ABD) and 24 immunoglobulin (Ig)-like domains. The Ig-like domains 1–15 and 16–23 form ROD1 and ROD2 domains, respectively, whereas the C-terminal Ig-like domain 24 is critical for its dimerization.² Dominant mutations in filamin C (*FLNC*) gene give rise to 3 distinct clinical phenotypes: proximal myopathy, distal myopathy, and isolated dilated or hypertrophic cardiomyopathy.² Patients with *FLNC* proximal myopathy typically develop limb-girdle weakness with frequent axial muscle involvement during their fourth to sixth decade, followed by respiratory muscle involvement in the advanced stage of the disease, and the muscle biopsy displays characteristic myofibrillar pathology (*FLNC* myofibrillar myopathy).³ Patients with *FLNC* distal myopathy typically have an earlier age at onset in their third to fourth decade, with hand muscles being the most severely affected muscle, and the muscle biopsy does not portray the classic myofibrillar pathology.³ It was initially thought that the mutations affecting the ABD are specific for *FLNC* distal myopathy, whereas the mutations in the Ig-like domains cause *FLNC* proximal myopathy.³ Subsequent studies showed that mutations in the ABD can also cause proximal weakness⁴ and the mutations in the Ig-like domains can also manifest with distal predominant weakness.⁵ Recently, a novel mutation in the ABD was reported to cause distal nemaline myopathy without myofibrillar pathology.⁶ In *FLNC* cardiomyopathy, the mutations spread throughout the entire gene.²

In this issue of *Neurology*[®] *Genetics*, Kley et al.⁷ report a 3-generation German kindred with autosomal dominant myopathy due to a novel c.8025_8030delCAAGACinsA (p.K2676Pfs*3) mutation in the Ig-like domain 24 of *FLNC*. The clinical and histopathologic findings are typical of *FLNC* myofibrillar myopathy. The authors showed that the mutant mRNA was not degraded via nonsense-mediated decay and the mutant protein impaired the dimer formation.

Laser capture microdissection is a method to isolate cells of interest under the microscope using the laser beam. Combined with mass spectrometry, it allows a study of the proteome of the target cells, which has advantages over a proteomic study of the whole tissue. The laser capture microdissection coupled with mass spectrometry has been used successfully to identify the causative genes in other myopathies featuring protein aggregates, including reducing body myopathy⁸ and

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myopathies with myofibrillar pathology due to mutations in genes coding for desmin (*DES*)⁹ and myotilin (*MYOT*).¹⁰ Kley et al.⁷ elegantly applied this technique to their cohort of *FLNC* myofibrillar myopathy and identified 88 proteins that were significantly overrepresented in the sarcoplasmic aggregates compared with the myofibers obtained from the same biopsy but without aggregates. Among these proteins, filamin C was the major constituent of the aggregates. The authors also extended their proteomic analysis to other patients with myofibrillar myopathy with or without *FLNC* mutations. The ratio of filamin C in aggregate-containing myofibers to filamin C in myofibers without aggregates above 5 appears to be highly sensitive (100%) and specific (99%) for *FLNC* myofibrillar myopathy regardless of the individual *FLNC* mutations. This cutoff value of filamin C ratio could be very helpful in verifying the pathogenicity of variants of unknown significance in *FLNC* in the presence of sarcoplasmic aggregates.

Future studies looking into the proteomic profile of each myofibrillar myopathy genotype are crucial to identify the cutoff ratio of mutant protein in aggregates compared with nonaggregates. These data will allow us to implement this proteomic technique into our everyday clinical practice when encounter patients with myofibrillar myopathy. The same technique could also be used as a research tool to identify the candidate genes in genetically uncharacterized patients with myofibrillar myopathy. As laser capture microdissection and mass spectrometry are now the gold standard for amyloid subtyping in patients with amyloid neuropathy,¹¹ this combined proteomic technique could also revolutionize the

aggregate subtyping in patients with myofibrillar myopathy or other protein aggregate myopathies.

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Disclosure

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