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Report

A Mutation in the Dimerization Domain of Filamin C Causes a Novel Type of Autosomal Dominant Myofibrillar Myopathy

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Myofibrillar myopathy (MFM) is a human disease that is characterized by focal myofibrillar destruction and pathological cytoplasmic protein aggregations. In an extended German pedigree with a novel form of MFM characterized by clinical features of a limb-girdle myopathy and morphological features of MFM, we identified a cosegregating, heterozygous nonsense mutation (8130G→A; W2710X) in the filamin c gene (*FLNC*) on chromosome 7q32.1. The mutation is the first found in *FLNC* and is localized in the dimerization domain of filamin c. Functional studies showed that, in the truncated mutant protein, this domain has a disturbed secondary structure that leads to the inability to dimerize properly. As a consequence of this malfunction, the muscle fibers of our patients display massive cytoplasmic aggregates containing filamin c and several Z-disk–associated and sarcolemmal proteins.

Myofibrillar myopathy (MFM) is a neuromuscular disorder, usually with adult onset and an autosomal dominant inheritance pattern, that results in slowly progressive weakening of limb muscles. MFM may lead to multisystem involvement (eye, peripheral nerve, and heart), and progressive cardiorespiratory complications are potentially lethal (Goldfarb et al. 1998, 2004; Selcen and Engel 2003; Bär et al. 2005). Typically, skeletal-muscle fibers of patients with MFM show Z-disk pathologies in association with cytoplasmic accumulation of several Z-disk and cytoplasmic proteins (Selcen and Engel 2004*b*). MFM is genetically heterogeneous. Thus far, four genes have been associated with MFM: the genes encoding desmin (*DES* [MIM 125660]) (Goldfarb et al. 1998), myotilin (*TTID* [MIM 604103]) (Hauser et al. 2000; Selcen and Engel 2004*a*), Z-band alternatively spliced PDZ motif-containing protein (*LDB3* [MIM 605906]) (Selcen and Engel 2005), and αB-crystallin (*CRYAB* [MIM 123590]) (Vicart et al. 1998). However, in the majority of patients with MFM, the presence of mutations in these genes was excluded (Selcen and Engel 2005), indicating that mutations in other genes are also causative of this disease.

In the present study, we have identified an extended family of German origin with MFM, and we have excluded the involvement of the *DES, TTID,* and *CRYAB* genes by haplotype analysis (data not shown). Informed consent was obtained from all subjects (with approval of the ethics committee of Ruhr-University Bochum [#2221]). A total of 17 individuals (12 females and 5 males) were clinically affected. All patients presented with slowly progressive skeletal-muscle weakness, beginning in the lower extremities, which is compatible with the clinical signs of limb-girdle muscular dystrophy (LGMD). Eight of these patients (five females and three males) had been examined clinically (table 1). Their weakness started between the ages of 37 years and 57 years and was more prominent proximally in seven patients, whereas one patient (IV:16) had distal weakness of the calf muscles only. Serum creatine kinase levels were moderately elevated, up to 8-fold higher than the normal upper limit. Four of the patients had respiratory symp-

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toms, and, in two of them (III:14 and III:16), nocturnal ventilation was required. One affected individual (IV:3) revealed findings compatible with cardiac involvement; three of the eight patients had evidence of an additional peripheral neuropathy (table 1). Individual IV:18 carries the *FLNC* mutation but appears to be presymptomatic as a result of his young age (28 years).

In patients III:18 and IV:3, the histological findings of muscle biopsies from a clinically affected muscle were typical of MFM. Many fibers showed structural changes harboring amorphous, granular, or hyaline deposits best recognized in trichrome-stained frozen sections (fig. 1*A*), whereas some fibers showed vacuoles. Oxidative enzyme activities (nicotinamide adenine dinucleotide dehydrogenase, succinic dehydrogenase, and cytochrome oxidase) were sharply reduced in these abnormal fiber regions. In each biopsy, increased internal nuclei, fiber splitting, and isolated necrotic fibers were present. Serial transverse cryostat sections (4 μm) of skeletal-muscle biopsies from these patients were studied by immunofluorescence assays with the use of monoclonal antibodies against filamin c (clone RR90; dilution 1:2) (van der Ven et al. 2000*a*), desmin (D33; 1:500 [DAKO]), myotilin (RSO34; 1:20), dystrophin (Dy8/6C5; 1:20), α-, β-, γ-, and δ-sarcoglycan (Ad1/20A6, βSarc/SB1, 35DAG/21B5, δ-Sarc3/12C1; 1:100 [Novocastra]), and isotype-specific secondary antibodies conjugated with fluorescein isothiocyanate or Cy2 (Southern Biotech). In each patient, many abnormal fibers revealed a marked accumulation of desmin, the histopathological hallmark of MFM, as well as filamin c in massive aggregates. These aggregates also showed strong immunoreactivity for the filamin c–binding Z-disk protein myotilin, for the sarcolemma-associated protein dystrophin, and for all sarcoglycans (fig. 1*A*). Ultrastructural analysis of skeletal muscle from patient IV:3 showed myofibrillar changes, including Z-disk streaming and extensive nemaline-rod formation (data not shown). As in MFMs that are due to heterozygous desmin mutations (Schröder et al. 2003; Goldfarb et al. 2004; Selcen and Engel 2004*b*; Bär et al. 2005), multiple fibers displayed intermyofibrillar and subsarcolemmal granulofilamentous protein aggregates (fig. 1*B*).

The dramatic mislocalization of filamin c in the muscle fibers of our patients prompted us to perform haplotype analysis, by use of microsatellite markers of the *FLNC* gene region, and subsequently to screen the family with MFM for mutations within the *FLNC* gene (MIM 102565). For haplotype and mutational analyses, genomic DNA was isolated from peripheral blood lymphocytes in accordance with standard procedures. Haplotype analysis of the candidate *FLNC* gene on chromosome 7q32.1 was performed with markers included in the deCODE genetic map. Primer pairs were designed with the OLIGO software (primer sequences are available on request). The primers were labeled with one of four fluorophores: FAM, VIC, PET, or NED. PCR amplifications were performed in a T3 thermal cycler (Biometra), and amplicons were separated on an ABI 3100 Genetic Analyzer (Applied Biosystems). The pedigree was drawn with Cyrillic software, version 2.1 (Cherwell Scientific Publishing), and haplotype analysis was performed manually. Two-point LOD score calculations were

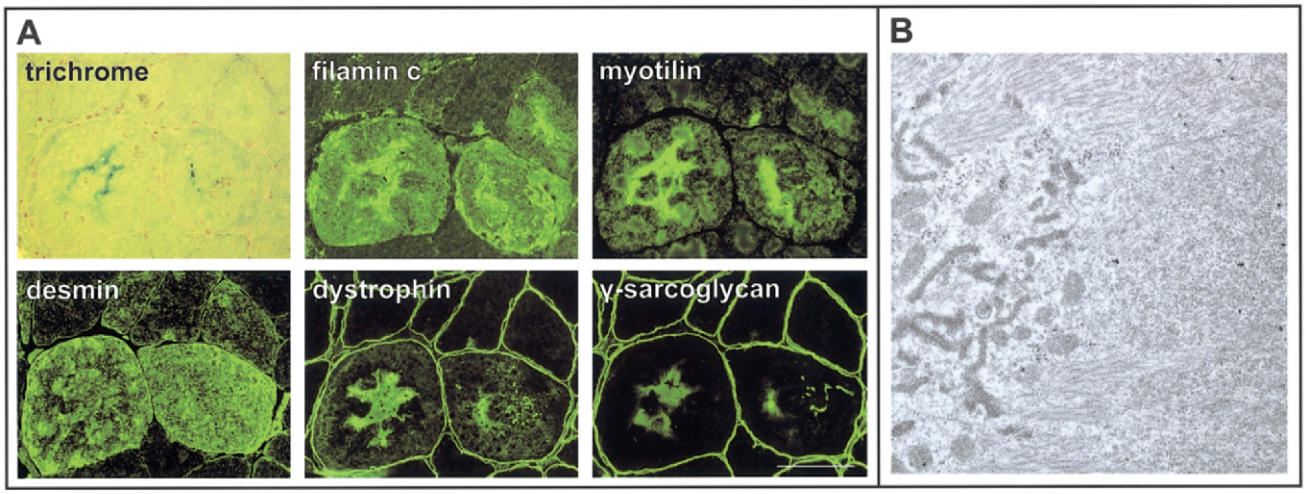

Figure 1 Immunohistochemical and ultrastructural analysis of aggregates in patient IV:3 from the pedigree with MFM. *A*, Several muscle fibers with structural changes in the trichrome-stained sections, showing intracytoplasmic accumulation of the Z-disk–associated proteins filamin c, myotilin, and desmin. Aggregates also show strong immunoreactivity for dystrophin and the sarcoglycans (as exemplified by γ-sarcoglycan), which are main components of the sarcolemmal dystrophin-glycoprotein complex (bar = 100 μm). *B*, Ultrastructural analysis of skeletal muscle, showing multiple fibers displaying intermyofibrillar granulofilamentous protein aggregates (original magnification: × 20,000).

Table 1

Clinical Data of Eight Affected Individuals in a Pedigree with a Proven *FLNC* W2710X Mutation

Patient	Sex	Age at Onset of MFM (years)	Age at Examination (years)	Initial Symptoms	Distribution of Weakness and Muscle Atrophy	Evidence of Peripheral Nerve/Eye/Cardiac Involvement	Creatine Kinase Increase
III:14	F	37	64	Weakness when climbing stairs, back pain	Proximal > distal, lower > upper extremities; respiratory insufficiency	No	2-fold
III:16	M	45	62	Weakness when climbing stairs, lower back pain	Proximal > distal, lower > upper extremities; respiratory insufficiency	No	6-fold
III:18	M	45	58	Waddling gait, chronic lumbar back pain	Proximal > distal, lower > upper extremities; respiratory insufficiency	No	8-fold
III:19	F	49	54	Waddling gait, lower back pain	Proximal in lower extremities	Peripheral nerve	3-fold
III:20	F	44	48	Weakness in legs, lower back pain	Proximal in upper extremities; proximal > distal in lower extremities	No	2-fold
IV:3	M	57	60	Weakness when climbing stairs or walking uphill	Proximal > distal, lower > upper extremities; respiratory insufficiency	Peripheral nerve/incomplete right bundle branch block, ejection fraction 66%	2-fold
IV:16	F	43	50	Unsteady gait	Distal in lower extremities	No	4-fold
IV:17	F	46	48	Waddling gait, weakness when climbing stairs, lower back pain	Proximal-dorsal and distal-anterior in lower extremities	Peripheral nerve	2-fold

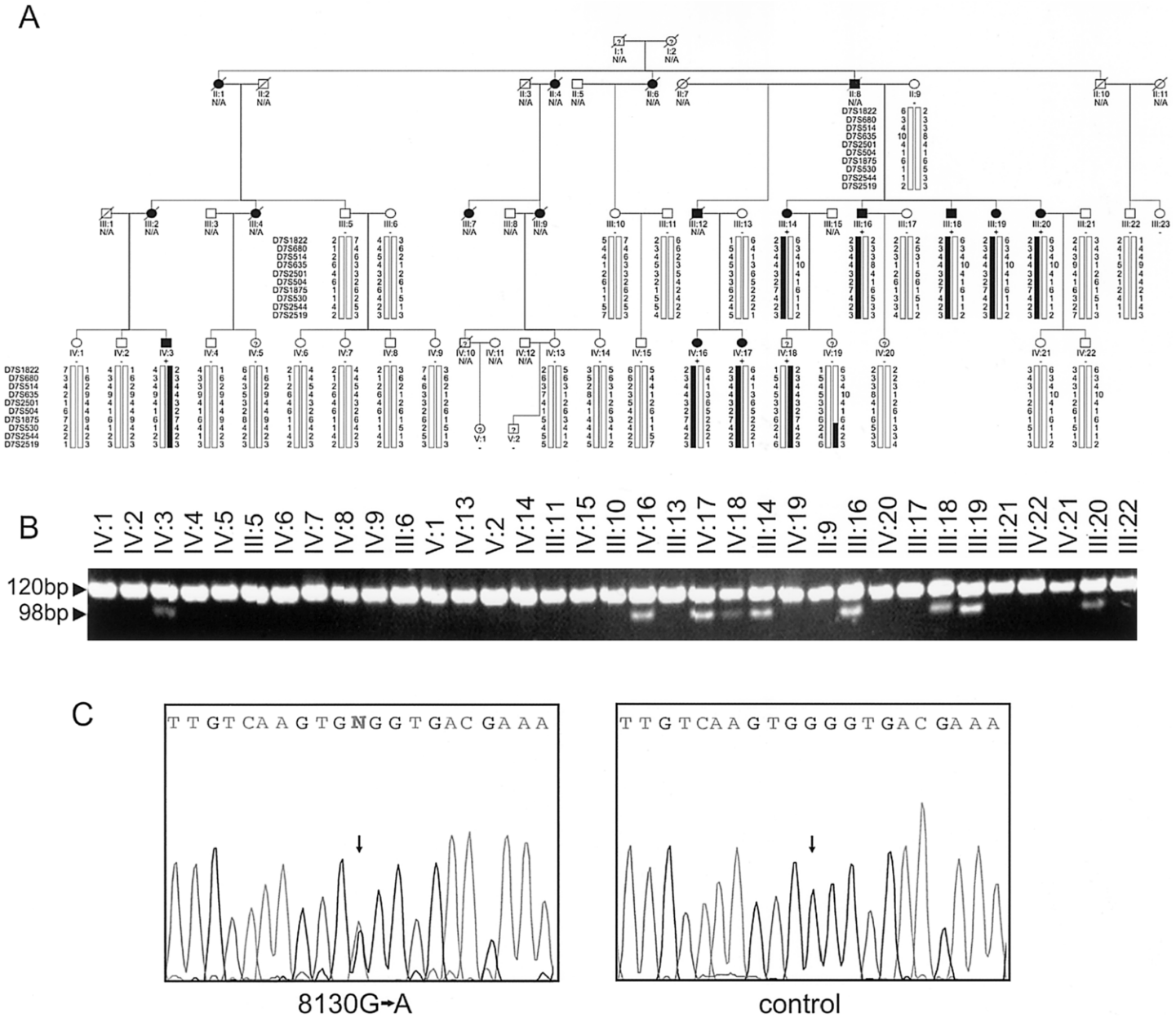
A
B
C
120bp
98bp
IV:1 IV:2 IV:3 IV:4 IV:5 III:5 IV:6 IV:7 IV:8 IV:9 III:6 V:1 IV:13 V:2 IV:14 III:11 IV:15 III:10 IV:16 III:13 IV:17 IV:18 III:14 IV:19 II:9 III:16 IV:20 III:17 III:18 III:19 III:21 IV:22 IV:21 III:20 III:22
T T GT CA A GT GNG G T GAC GA A A
8130G→A
T T GT CAA GT GGGGT GAC GA A A
control

Table 2

Two-Point LOD Scores between Chromosome 7 Markers and the *FLNC* Locus

	LOD AT θ =								
MARKER	.000	.001	.010	.050	.100	.150	.200	.300	.400
D7S487	2.458	2.453	2.407	2.207	1.964	1.727	1.492	1.014	.509
D7S2527	.299	.306	.355	.490	.546	.533	.479	.307	.124
D7S1873	2.310	2.306	2.274	2.117	1.894	1.655	1.410	.931	.470
D7S1822	2.417	2.415	2.393	2.262	2.050	1.807	1.548	1.020	.505
D7S680	2.871	2.865	2.808	2.549	2.218	1.885	1.553	.914	.360
D7S514	2.501	2.495	2.444	2.213	1.922	1.629	1.340	.787	.317
D7S635	4.879	4.870	4.786	4.408	3.920	3.416	2.897	1.827	.767
D7S2501	2.798	2.793	2.750	2.549	2.274	1.983	1.682	1.075	.499
D7S504	3.022	3.015	2.954	2.682	2.343	2.007	1.678	1.050	.483
D7S1875	4.286	4.278	4.203	3.865	3.434	2.994	2.547	1.640	.741
D7S530	1.822	1.817	1.771	1.575	1.352	1.143	.941	.550	.219
D7S2544	2.902	2.894	2.829	2.549	2.220	1.907	1.604	1.003	.419
D7S2519	1.460	1.458	1.437	1.338	1.202	1.057	.906	.597	.294
D7S2531	.294	.296	.312	.359	.375	.358	.315	.186	.056
D7S640	−2.090	1.047	1.988	2.417	2.366	2.178	1.926	1.317	.639

performed using the LINKAGE program package, with the help of the LINKRUN program (T. F. Wienker, personal communication), under the assumption of autosomal dominant inheritance, equal male and female recombination rates, full penetrance, and a disease-allele frequency of 0.0001. The National Center for Biotechnology Information (NCBI) Map Viewer and Ensembl Genome Browser databases were used for localization of the microsatellite marker loci and identification of transcripts in the candidate region. The GDB Human Genome Database was used for information about microsatellite markers and their primer sequences. Indeed, haplotype analyses established linkage of the disease to the *FLNC* locus (fig. 2*A*), with a maximum LOD score of 4.879 ($\theta = 0$) at marker *D7S635* (table 2).

Sequence analysis of *FLNC* included all 48 exons and was performed on genomic DNA from individuals IV:3 and IV:16 of the present family, as well as on DNA from four sporadic cases with similar clinical and morphological features pointing to LGMD or MFM. Sequencing was performed with an ABI 3100 Genetic Analyzer (Applied Biosystems) by use of the BigDye Terminator v 1.1 Cycle Sequencing kit (Applied Biosystems). Although no *FLNC* mutations were found in the sporadic cases, a single heterozygous nucleotide substitution (8130G→A), resulting in a substitution of tryptophan at position 2710 by a stop codon (W2710X) (human *FLNC* [GenBank accession number AF252549], human chromosome 7 clones containing *FLNC* [GenBank accession numbers AC025594 and AC024952], and FLNC [accession number Q14315]), was identified in exon 48 in patients IV:3 and IV:16 from the present family (fig. 2*C*).

To confirm cosegregation of the mutation with the MFM disease phenotype, all available family members and 110 control individuals were investigated for the 8130G→A mutation by RFLP analysis and/or direct sequencing. Since the mutation did not delete or introduce a restriction site, a new *Alu*I restriction site was created in the mutant PCR product by use of a lower primer with a single-nucleotide mismatch at the penultimate 3′ position (primer sequences are available on request). For restriction-enzyme digestion, the PCR product was incubated with *Alu*I, and the cleaved fragments were separated on a 2% agarose gel and were visualized by ethidium bromide staining (for details, see the legend to fig. 2*B*). The 8130G→A mutation was detected in all affected family members and was confirmed by direct sequencing (fig. 2*B*). It was not observed in 220 control chromosomes.

Recently, a large five-generation Spanish family with LGMD, with clinical features similar to those seen in the German family, was described (Gamez et al. 2001), and,

Figure 2 *A,* Pedigree and genotypic analysis of the German family with autosomal dominant MFM segregating with *FLNC*. Marker haplotypes on chromosome 7q31.33-7q32.3 that are linked to MFM are indicated by blackened bars. Blackened and unblackened symbols represent clinically affected individuals and unaffected individuals, respectively; unblackened symbols with question marks represent individuals of undetermined disease status. Presence (+) or absence (−) of the *FLNC* mutation in those individuals available for mutation analysis is indicated. N/A = not available for genetic diagnosis. *B,* RFLP analysis of the 8130G→A mutation, by digestion of a PCR product with *Alu*I. Undigested PCR product (120 bp) corresponds to the G allele, and digested PCR product (98 bp + unverifiable 22 bp) corresponds to the A allele. *C,* Sequence chromatograms demonstrating the heterozygous mutation (8130G→A; W2710X) found in affected family members (*left*) and the corresponding normal sequence (*right*).

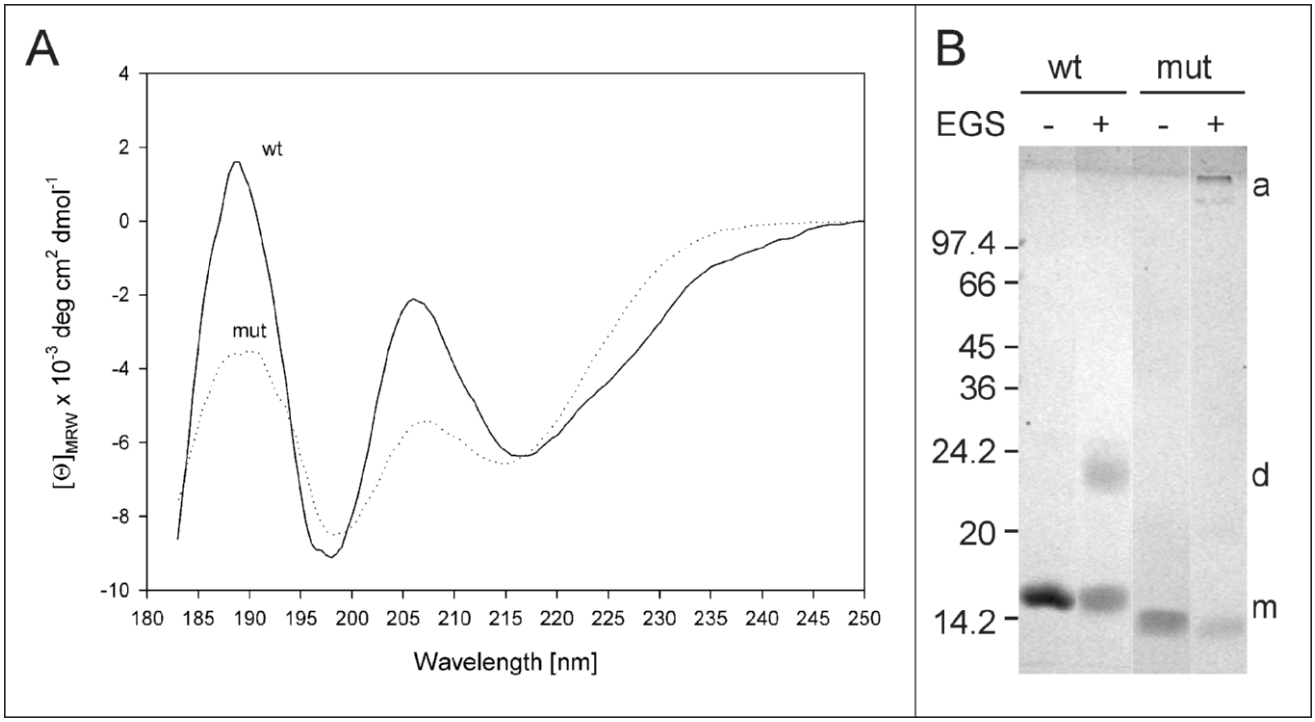

Figure 3 Functional studies of the *FLNC* W2710X mutation. *A,* Circular dichroism spectrometry of filamin c domain 24 in the far UV range, performed with purified, bacterially expressed proteins. Note that the wild-type protein (wt) shows the typical β-sheet secondary structure, whereas the mutant-protein (mut) spectrum has lower amplitudes, indicating improper folding. deg = degrees; $[\Theta]_{MRW}$ = mean residue weight ellipticity. *B,* The same recombinant polypeptides as above were cross-linked using ethylene glycol bis(succinimidylsuccinate) (EGS). Proteins were separated by SDS-PAGE, and the gel was stained with Coomassie Brilliant Blue. Without cross-linking (−), only monomers (m) of the wild type and the truncated mutant polypeptide are visible. Note that, on cross-linking (+), the wild-type protein yields dimers (d), whereas the mutant protein yields aggregates (a) of higher molecular mass.

subsequently, the disorder was referred to as "LGMD1F" (MIM 608423) and was mapped to chromosome 7q32, which includes the *FLNC* locus. However, in this family, *FLNC* was excluded as a candidate gene (Palenzuela et al. 2003). In the Spanish family, skeletal-muscle weakness, predominantly involving the pelvic and shoulder girdle, started between the ages of 1 year and 58 years, whereas, in the German family, no patient with a juvenile-onset form was observed. In the Spanish family, the histochemical and immunohistochemical findings were compatible with LGMD; desmin immunostaining was not reported. In contrast, the massive protein aggregates in the German family clearly indicated MFM. Despite substantial overlap in the clinical phenotype, patients in the German family are distinct—not only genetically but also morphologically—from patients with LGMD1F. Because of the protein defect, we suggest classification of the disease found in the German family as "autosomal dominant filaminopathy," a novel form of MFM.

Filamins are a family of actin-binding proteins involved in reshaping the actin cytoskeleton and its associated structures (Stossel et al. 2001; van der Flier and Sonnenberg 2001). Actin binding is conferred by a pair of amino-terminal CH domains. For their actin filament–bundling and cross-linking activities, the filamins depend on their C-terminal region—more specifically, the immunoglobulin-like domain 24, which is responsible for dimer formation (Himmel et al. 2003). Furthermore, filamins interact with a plethora of cellular proteins of great functional diversity, indicating that they are multifunctional signaling adapter proteins (van der Flier and Sonnenberg 2001). Although mutations in the ubiquitously expressed genes encoding filamin a (Fox et al. 1998; Robertson et al. 2003) and filamin b (Krakow et al. 2004) are causative for a strikingly wide range of human diseases (Feng and Walsh 2004), up to the present, no disease-causing mutations had been found in *FLNC,* the gene encoding the muscle-specific filamin isoform. Its up-regulation during initial stages of myocyte differentiation, its localization predominantly at the periphery of Z-disks (van der Ven et al. 2000*a*), and its direct interaction with myotilin (van der Ven et al. 2000*b*) imply an important role for this filamin isoform during myofibrillogenesis. Since filamin c also binds γ- and δ-sarcoglycan at the sarcolemma (Thompson et al. 2000), it was hypothesized that filamin c is involved in

signaling pathways from the sarcolemma to the myofibril (Thompson et al. 2000; van der Ven et al. 2000*b*).

The W2710X mutation in the reported family with MFM leads to a truncation of the filamin c immunoglobulin domain that is responsible for dimerization (Himmel et al. 2003). To assess the pathogenic potential of the mutation, we examined its effects on the secondary structure of the mutant domain 24 and on its ability to dimerize. cDNA fragments encoding the wild-type and mutant domain 24 were cloned in pET23-T7 (Obermann et al. 1998), and recombinant proteins were expressed in and purified from *Escherichia coli* BL21-CodonPlus-RP cells by use of standard procedures (Himmel et al. 2003). Circular dichroism spectra were recorded from both proteins on a Jasco J-715 spectropolarimeter. Whereas analysis of the wild-type domain resulted in the typical β-sheet secondary structure that was previously reported for this domain (Himmel et al. 2003; Pudas et al. 2005), analysis of the truncated, mutated domain resulted in significantly lower signals, suggesting improper folding (fig. 3*A*).

We next examined dimerization of mutant filamin c by chemical cross-linking experiments, essentially using previously established conditions for the wild-type protein (Himmel et al. 2003), except that PBS was used instead of cross-linking buffer. Whereas the dimerization of the wild-type variant was reproduced under these conditions, cross-linking of the truncated domain 24 did not result in the detection of dimers. Instead, high–molecular mass aggregates of the mutated filamin fragment were observed on the SDS-polyacrylamide gel (fig. 3*B*) and on immunoblots (not shown). Although the precise structural changes that occur in the mutated filamin c are currently unknown, the formation of aggregates in the cross-linking assay and the tendency to precipitate in solution (not shown) imply a weaker stability of mutated filamin c in comparison with the wild-type protein and indicate a strong tendency for uncontrolled aggregation rather than defined dimerization.

We have provided evidence of an altered distribution of myotilin and the dystrophin-sarcoglycan complex in affected individuals. We hypothesize that the fine balance of filamin c and its binding partners in both the Z-disk and the cell membrane may be disturbed. Therefore, defects in this protein may weaken myofibrils and, at the same time, destabilize the muscle cell membrane. This may ultimately result in clinical and molecular features resembling both MFM and LGMD.

In summary, we describe here the first disease-related mutation within the *FLNC* gene and also the first mutation in a dimerization domain in the filamin family. The mutation results in the inability of the mutant protein to dimerize and leads to the generation of large filamin c–containing aggregates within the skeletal-muscle fibers. Biochemical experiments provide an explanation for this observation and show that dimer formation is essential for the biological function of filamin.

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Web Resources

Accession numbers and URLs for data presented herein are as follows:

Ensembl Genome Browser, http://www.ensembl.org/
GDB Human Genome Database, http://www.gdb.org/
GenBank, http://www.ncbi.nih.gov/Genbank/ (for human *FLNC* [accession number AF252549], human chromosome 7 clones containing *FLNC* [accession numbers AC025594 and AC024952], and FLNC [accession number Q14315])
NCBI Map Viewer, http://www.ncbi.nlm.nih.gov/mapview/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/entrez/Omim/ (for *DES, TTID, LDB3, CRYAB, FLNC,* and LGMD1F)

References

Bär H, Fischer D, Goudeau B, Kley RA, Clemen CS, Vicart P, Herrmann H, Vorgerd M, Schröder R (2005) Pathogenic effects of a novel heterozygous R350P desmin mutation on the assembly of desmin intermediate filaments in vivo and in vitro. Hum Mol Genet 14:1251–1260

Feng Y, Walsh CA (2004) The many faces of filamin: a versatile molecular scaffold for cell motility and signalling. Nat Cell Biol 6:1034–1038

Fox JW, Lamperti ED, Eksioglu YZ, Hong SE, Feng Y, Graham DA, Scheffer IE, Dobyns WB, Hirsch BA, Radtke RA, Berkovic SF, Huttenlocher PR, Walsh CA (1998) Mutations in filamin 1 prevent migration of cerebral cortical neurons in human periventricular heterotopia. Neuron 21:1315–1325

Gamez J, Navarro C, Andreu AL, Fernandez JM, Palenzuela L, Tejeira S, Fernandez-Hojas R, Schwartz S, Karadimas C, DiMauro S, Hirano M, Cervera C (2001) Autosomal dominant limb-girdle muscular dystrophy: a large kindred with evidence for anticipation. Neurology 56:450–454

Goldfarb LG, Park KY, Cervenakova L, Gorokhova S, Lee HS, Vasconcelos O, Nagle JW, Semino-Mora C, Sivakumar K, Dalakas MC (1998) Missense mutations in desmin associated with familial cardiac and skeletal myopathy. Nat Genet 19:402–403

Goldfarb LG, Vicart P, Goebel HH, Dalakas MC (2004) Desmin myopathy. Brain 127:723–734

Hauser MA, Horrigan SK, Salmikangas P, Torian UM, Viles KD, Dancel R, Tim RW, Taivainen A, Bartoloni L, Gilchrist JM, Stajich JM, Gaskell PC, Gilbert JR, Vance JM, Pericak-Vance MA, Carpen O, Westbrook CA, Speer MC (2000) Myotilin is mutated in limb girdle muscular dystrophy 1A. Hum Mol Genet 9:2141–2147

Himmel M, van der Ven PFM, Stöcklein W, Fürst DO (2003) The limits of promiscuity: isoform-specific dimerization of filamins. Biochemistry 42:430–439

Krakow D, Robertson SP, King LM, Morgan T, Sebald ET, Bertolotto C, Wachsmann-Hogiu S, Acuna D, Shapiro SS, Takafuta T, Aftimos S, Kim CA, Firth H, Steiner CE, Cormier-Daire V, Superti-Furga A, Bonafe L, Graham JM Jr, Grix A, Bacino CA, Allanson J, Bialer MG, Lachman RS, Rimoin DL, Cohn DH (2004) Mutations in the gene encoding filamin B disrupt vertebral segmentation, joint formation and skeletogenesis. Nat Genet 36:405–410

Obermann WMJ, van der Ven PFM, Steiner F, Weber K, Fürst DO (1998) Mapping of a myosin-binding domain and a regulatory phosphorylation site in M-protein, a structural protein of the sarcomeric M band. Mol Biol Cell 9:829–840

Palenzuela L, Andreu AL, Gamez J, Vila MR, Kunimatsu T, Meseguer A, Cervera C, Fernandez Cadenas I, van der Ven PFM, Nygaard TG, Bonilla E, Hirano M (2003) A novel autosomal dominant limb-girdle muscular dystrophy (LGMD 1F) maps to 7q32.1-32.2. Neurology 61:404–406

Pudas R, Kiema TR, Butler PJ, Stewart M, Ylanne J (2005) Structural basis for vertebrate filamin dimerization. Structure 13:111–119

Robertson SP, Twigg SR, Sutherland-Smith AJ, Biancalana V, Gorlin RJ, Horn D, Kenwrick SJ, Kim CA, Morava E, Newbury-Ecob R, Orstavik KH, Quarrell OW, Schwartz CE, Shears DJ, Suri M, Kendrick-Jones J, Wilkie AO (2003) Localized mutations in the gene encoding the cytoskeletal protein filamin A cause diverse malformations in humans. Nat Genet 33:487–491

Schröder R, Goudeau B, Casteras Simon M, Fischer D, Eggermann T, Clemen CS, Li Z, Reimann J, Xue Z, Rudnik-Schöneborn S, Zerres K, van der Ven PFM, Fürst DO, Kunz WS, Vicart P (2003) On noxious desmin: functional effects of a novel desmin insertion mutation on the extrasarcomeric desmin cytoskeleton and mitochondria. Hum Mol Genet 12: 657–669

Selcen D, Engel AG (2003) Myofibrillar myopathy caused by novel dominant negative α-B-crystallin mutations. Ann Neurol 54:804–810

——— (2004*a*) Mutations in myotilin cause myofibrillar myopathy. Neurology 62:1363–1371

——— (2004*b*) Myofibrillar myopathy. In: Engel AG, Franzini-Armstrong C (eds) Myology. McGraw-Hill, New York, pp 1187–1202

——— (2005) Mutations in ZASP define a novel form of muscular dystrophy in humans. Ann Neurol 57:269–276

Stossel TP, Condeelis J, Cooley L, Hartwig JH, Noegel A, Schleicher M, Shapiro SS (2001) Filamins as integrators of cell mechanics and signalling. Nat Rev Mol Cell Biol 2:138–145

Thompson TG, Chan YM, Hack AA, Brosius M, Rajala M, Lidov HG, McNally EM, Watkins S, Kunkel LM (2000) Filamin 2 (FLN2): a muscle-specific sarcoglycan interacting protein. J Cell Biol 148:115–126

van der Flier A, Sonnenberg A (2001) Structural and functional aspects of filamins. Biochim Biophys Acta 1538:99–117

van der Ven PFM, Obermann WMJ, Lemke B, Gautel M, Weber K, Fürst DO (2000*a*) Characterization of muscle filamin isoforms suggests a possible role of γ-filamin/ABP-L in sarcomeric Z-disc formation. Cell Motil Cytoskeleton 45: 149–162

van der Ven PFM, Wiesner S, Salmikangas P, Auerbach D, Himmel M, Kempa S, Hayess K, Pacholsky D, Taivainen A, Schröder R, Carpén O, Fürst DO (2000*b*) Indications for a novel muscular dystrophy pathway: γ-filamin, the muscle-specific filamin isoform, interacts with myotilin. J Cell Biol 151:235–248

Vicart P, Caron A, Guicheney P, Li Z, Prevost MC, Faure A, Chateau D, Chapon F, Tome F, Dupret JM, Paulin D, Fardeau M (1998) A missense mutation in the αB-crystallin chaperone gene causes a desmin-related myopathy. Nat Genet 20:92–95