

BRIEF COMMUNICATION

Laing distal myopathy pathologically resembling inclusion body myositisRicardo H. Roda^{1,2}, Alice B. Schindler³, Craig Blackstone², Andrew L. Mammen^{4,5,6}, Andrea M. Corse⁴ & Thomas E. Lloyd^{4,7}¹Neuromuscular Disorders and Neurogenetics Divisions, Department of Neurology, New York University Langone Medical Center, New York, New York²Cell Biology Section, Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland³Hereditary Neurological Diseases Section, Neurogenetics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland⁴Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland⁵Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland⁶Muscle Disease Unit, Laboratory of Muscle Stem Cells and Gene Regulation, National Institutes of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland⁷Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland**Correspondence**

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Introduction

The inherited distal myopathies are a group of genetically heterogeneous muscle disorders characterized by weakness of the distal muscles of the arms and legs. They are caused by defects in several genes including *TTN*, *DYSF*, *GNE*, *LDB3*, and *MYH7*.¹ *MYH7* (slow/ β -cardiac myosin heavy chain 7) is expressed in both skeletal muscle and

Abstract

Mutations in *MYH7* cause autosomal dominant Laing distal myopathy. We present a family with a previously reported deletion (c.5186_5188delAGA, p.K1729del). Muscle pathology in one family member was characterized by an inflammatory myopathy with rimmed vacuoles, increased MHC Class I expression, and perivascular and endomysial muscle inflammation comprising CD3⁺, CD4⁺, CD8⁺, and CD68⁺ inflammatory cells. Interestingly, this biopsy specimen contained TDP-43, p62, and SMI-31-positive protein aggregates typical of inclusion body myositis. These findings should alert physicians to the possibility that patients with *MYH7* mutations may have muscle biopsies showing pathologic findings similar to inclusion body myositis.

cardiac muscle,² and mutations can give rise to a familial hypertrophic or dilated cardiomyopathy³ as well as several skeletal muscle disorders: Laing distal myopathy (MPD1; MIM# 160500), scapuloperoneal myopathy (MIM# 181430), and myosin storage myopathy (MSM)/hyaline body myopathy (MIM# 608358).

Laing distal myopathy^{4–7} presents clinically with weakness and atrophy of the forearm finger extensors and the

anterior compartment muscles of the legs.¹ Only within the last decade, *MYH7* has been identified as a gene causing distal skeletal myopathy.⁶ Although clinical findings have been fairly uniform, biopsy findings have proven to be more varied. Observed features include type 1 fiber atrophy, myofiber degeneration with regeneration, endomysial fibrosis, and fatty replacement. In addition, findings suggestive of mitochondrial dysfunction such as ragged red fibers have also been noted. Rimmed vacuoles, similar to those seen in inclusion body myositis, are observed rarely.^{5,8} We present a patient with Laing distal myopathy with endomysial invasion by inflammatory cells on muscle biopsy and positive staining for markers associated with inclusion body myositis.

Case Report

We examined five members of this family (Fig. 1A), four from generation III (III.7, III.9, III.13, III.15) and one from generation IV (IV.15). All subjects provided informed consent to participate in this study under a clinical research protocol approved by the NIH Combined Neuroscience Institutional Review Board.

The family traces their roots to German immigrants to the United States. The proband, III.15, is a 52-year-old male who first noted difficulty running as a teenager. This progressed in his early twenties, at which point he could not rise from a squat. In his early thirties he noticed atrophy of his quadriceps, and in his late forties he required a cane to ambulate. He came to our attention at the age of 51 years. On neurological examination, he showed weakness in his arms on wrist flexion and extension as well as finger flexion and extension, while in the lower extremities he exhibited hip flexion, knee extension, and severe ankle dorsiflexion and large toe extensor weakness. He had atrophy of the quadriceps and anterior compartment of the leg. His quadriceps atrophy and wrist and finger flexion weakness were reminiscent of sporadic IBM (sIBM). Muscle MRI of the lower extremities showed asymmetric atrophy and fatty replacement of the vastus intermedius and vastus medialis (Fig. 1B). This type of asymmetry is typical of sIBM.⁹ Particularly worrisome to the patient was that his rate of worsening had significantly increased over the past several years, and he had new onset of hand weakness over the past few years. Interestingly, his family tree (Fig. 1A) suggested that other family members might also be affected with muscle disease.

To further characterize the phenotype in this family, additional family members underwent neurological examination at our institution (Fig. 1C) (summarized in Table 1). Subject III.9 is a 62-year-old man who first developed difficulty walking at the age of 10 years. He was able to play baseball in high school but was not a fast

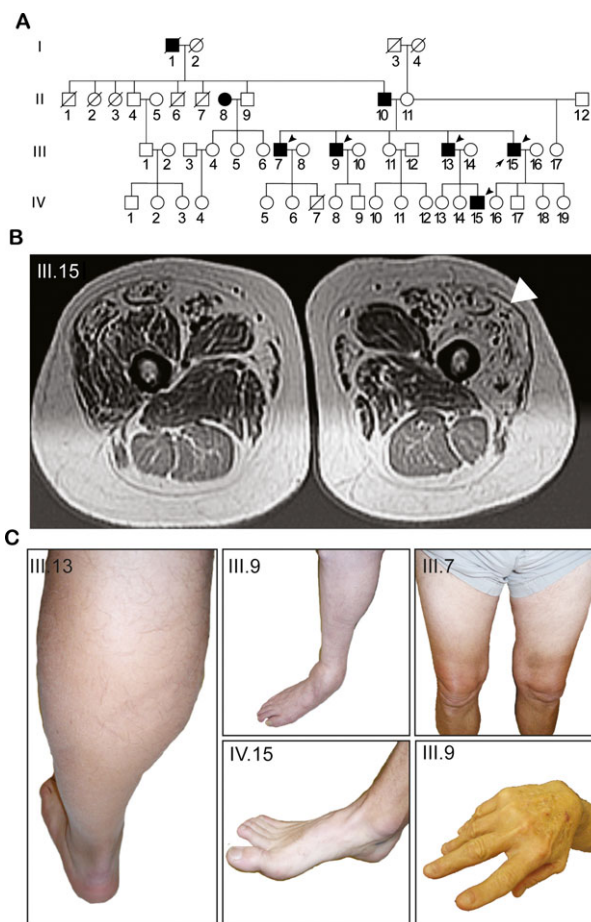


Figure 1. Identification of *MYH7* mutation and clinical characteristics. (A) Pedigree of the reported family. The proband (III.15), indicated by the arrow, carries the c.5186_5188delAGA (p.K1729del) mutation. Subjects III.7, III.9, III.13, and IV.15 all tested positive for the mutation. Filled symbols indicate affected members of the family, arrowheads point to those tested for the mutation. (B) T1-weighted MRI of the upper thighs of index patient III.15 shows atrophy and fatty replacement of quadriceps and rectus femoris with sparing of the abductors, hamstring, and right vastus intermedius and vastus medialis. An arrow points to an area of atrophy and fatty replacement. (C) Selected physical findings from subjects with *MYH7* mutation. Clockwise from top left: III.13 has significant calf hypertrophy; III.9 displays anterior compartment atrophy; quadriceps atrophy is also observed in III.7; III.9 showing limited wrist extension due to weakness of the extensor compartment of the arm. The “hanging big toe sign” was observed in all patients; in this image, the foot of IV.15 is shown.

runner. He noted in his early thirties that his gait was stable when wearing boots that provided ankle support. Exam showed wrist drop and finger extension weakness (Fig. 1C). He had a left gastrocnemius muscle biopsy, for which we only have a report, which notes that there was a small number of necrotic but no regenerating fibers. There was no inflammation and no vacuoles.

Table 1. Clinical features.

	III.7	III.9	III.13	III.15*	IV.15
Age at examination	63	62	54	51	28
Age of onset of symptoms	Early teens	Early teens	Late thirties	Mid teens	None yet
Flat smile	Yes	No	Yes	No	No
"Hanging Big Toe" sign	Yes	Yes	Yes	Yes	Yes
Quadriceps atrophy	+++	+++	+	+++	None
Tibialis anterior atrophy	++	+	+	++	+
Able to stand on heels	No	No	No	No	No
Calf Hypertrophy	Yes, asymm	Yes	Yes, asymm	Yes	No
Weakness of wrist and finger extensors	Yes, asymm	Yes	Yes, asymm	Yes	No
Weakness of wrist and finger flexors	No	Yes	Yes	Yes	No
Scapular winging	Yes	No	No	No	No
High arched palate	No	No	No	No	No
CK, U/L (nl 52–386)	96	166	161	172	57
Sensory exam	Reduced vibration	Normal	Normal	Normal	Normal
Cardiac evaluation					
EKG	Normal	Normal	Normal	ND	ND
Echocardiogram	ND	ND	EF 50%	ND	ND

Atrophy was rated as mild (+), moderate (++) and severe (+++). Asymm, asymmetric; ND, not done.

*Index case.

Subject III.13 is a 54-year-old man who initially noted frequent falls while playing sports in his late thirties. His exam showed quadriceps and tibialis anterior atrophy, toe dorsiflexion weakness, and calf hypertrophy (Fig. 1C).

IV.15 is a 28-year-old man who was asymptomatic but noted to have mild weakness of toe dorsiflexion on exam (Fig. 1C).

III.7 is a 63-year-old man who developed difficulty walking in his early teenage years. Gait instability slowly progressed until he started to fall frequently in his fifties. On exam he had mild facial weakness, mild-to-moderate proximal lower extremity weakness and atrophy, (Fig. 1C) and weakness of ankle dorsiflexion and toe extension. All family members with the exception of IV.15 had involvement of the distal upper limb (Table 1).

Given the mixed clinical features at presentation of our index patient, we decided to proceed with muscle tissue evaluation before genetic testing. A first biopsy of the right thigh of the index patient done several years before was only moderately useful, showing extensive fatty replacement, endomysial fibrosis, fiber size variation, and endomysial perivascular inflammation with rare vacuolated fibers (Fig. 2A–C). We performed an additional muscle biopsy of the left biceps and performed immunostaining for inflammatory cells and proteinaceous aggregates (Figs. 2, 3).

On frozen H&E stains, there was fiber size variability with rounded and polygonal myofiber atrophy, rare hypertrophied fibers, and occasional angular atrophic fibers (Fig. 2D). Most importantly, there were also many areas of primary endomysial inflammation (Fig. 2D–F

and Fig. S1A–C), with chronic mononuclear inflammatory cells surrounding and invading nonnecrotic fibers as well as perivascular chronic inflammation seen on frozen (Fig. 2H and Fig. S1B) and paraffin sections. Many fibers contained small to medium-sized vacuoles, both subsarcolemmal and sarcoplasmic in location (Fig. 2G and Fig. S1E and F). These vacuoles were blue-rimmed on H&E staining and red rimmed on Gomori trichrome staining. Many of the vacuoles were also acid phosphatase positive.

In addition, we noted myofiber degeneration and necrosis with occasional regeneration. There were many fibers undergoing myophagocytosis, and acid phosphatase staining was increased in degenerating and necrotic fibers and in the areas of myophagocytosis (Fig. 2I). There were many COX-negative fibers, some of which were SDH dark (Fig. 2J). Ragged red fibers were also seen. Many fibers also showed increased subsarcolemmal NADH staining (not shown).

Immunostaining demonstrated markedly increased MHC Class I staining in nonnecrotic myofibers (Fig. 3A), and also in perimysial regions (Fig. 3E). There were many scattered CD4⁺ (Fig. 3C), CD8⁺ (Fig. 3D), and CD68⁺ cells (Fig. 3F) in the endomysium and invading degenerating fibers as well as in the perivascular infiltrates. CD20⁺ cells were rare.

Significantly, many muscle fibers were positive for proteinaceous inclusions commonly seen in sporadic inclusion body myositis (s-IBM): TDP-43, p62, and SMI-31 (Fig. 3G–I). We are not aware of cases in which these antibodies have been tested in cases of Laing distal myopathy. Testing of the proband revealed a c.5186_5188delAGA

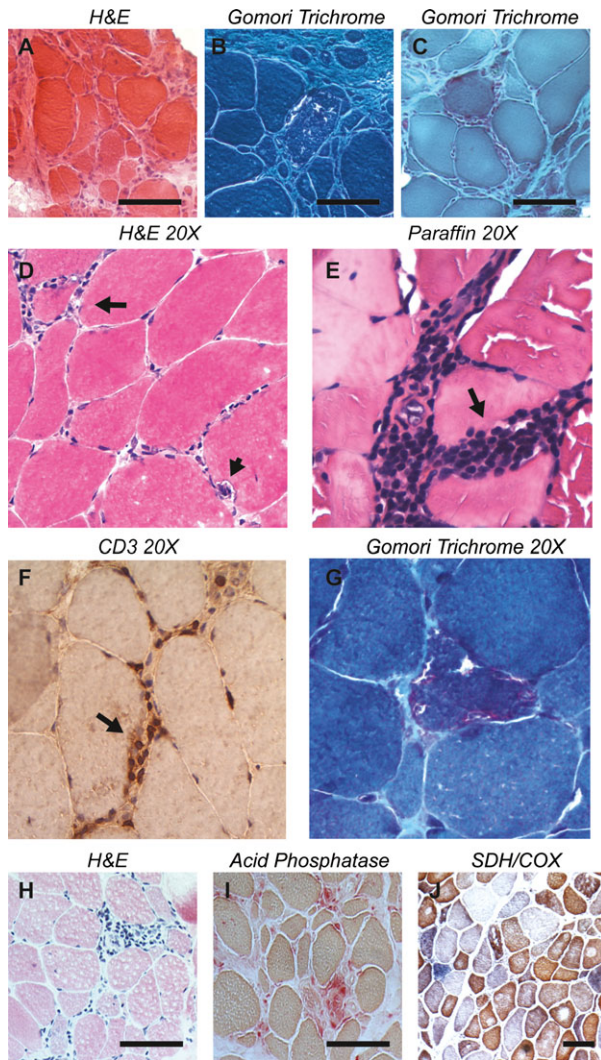


Figure 2. Histological and immunological analysis of muscle specimens. (A) Frozen H&E and (B and C) Gomori trichrome stains from the initial biopsy of index case. Follow-up biopsy years later. (D and E) H&E staining of frozen and paraffin sections and (F) CD3 stain show normal fibers undergoing invasion by mononuclear cells. (G) Vacuoles which are blue-rimmed on H&E and red-rimmed on Gomori trichrome are also seen. (H) H&E stain of frozen sections shows an area of perivascular inflammation, and (I) acid phosphatase staining is increased in fibers undergoing myophagocytosis. (J) Several blue COX-negative fibers are visualized. Scale bar, 100 μ m, otherwise magnification is shown on the image label.

(p.K1729del) deletion in exon 36 of *MYH7*. Additional affected family members also tested positive for the same mutation.

Discussion

Mutations in *MYH7* cause Laing distal myopathy (MPD1), myosin storage/hyaline body myopathy,

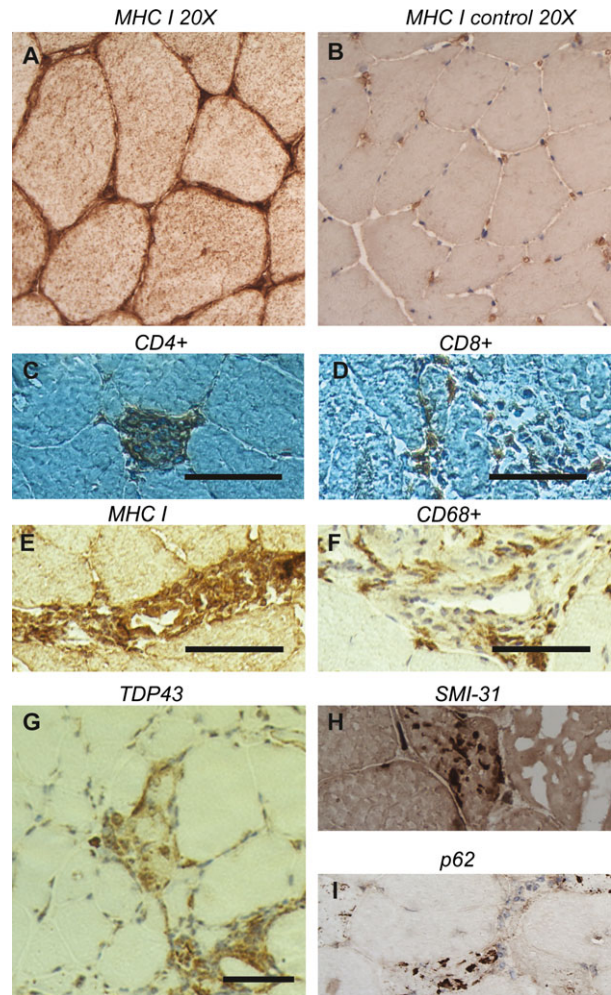


Figure 3. Immunohistochemical analysis of the specimen. (A) Increased MHC-I expression, compare to (B) control, and T-cell predominant lymphocytic infiltrates (C) CD4⁺ and (D) CD8⁺. Perivascular infiltrates are also seen, which stain with the markers (E) MHC-I and (F) CD68⁺. Immunostaining indicates the presence of markers for IBM including (G) TDP43, (H) SMI-31, and (I) p62. Scale bar, 100 μ m; otherwise, magnification is shown on image labels.

scapuloperoneal myopathy, and familial hypertrophic or dilated cardiomyopathy. In this report, we present a family of German ancestry with a c.5186_5188delAGA (p.K1729del) deletion in exon 36 of *MYH7*. A similar mutation resulting in the same amino acid deletion is also associated with a skeletal myopathy reported previously in an American family of Italian descent and in a family from Spain.^{6,10–12}

Onset of symptoms in our kindred was in the teenage years (Table 1), with two exceptions. Subject III.9 developed symptoms in his thirties, and IV.15 denied symptoms despite having toe extensor weakness on exam. The distribution of weakness in the patients we examined was

in toe and ankle dorsiflexion initially, then progressed to involve finger extensors, in agreement with other reports typical of patients with Laing distal myopathy. Our index patient, however, had distinct finger flexor weakness.

The biopsy findings in Laing early onset distal myopathy are pleiotropic. Both Muelas et al. and Lamont et al. have summarized many of the reported findings.^{10,13} Myofiber size variability, degenerating and regenerating fibers, endomysial fibrosis with fatty replacement, type 1 fiber atrophy, ragged red fibers, and sarcoplasmic inclusions have all been observed. Cores and minicores have been reported as well in patients with mutations in *MYH7*.^{10,13}

Inflammation is seen in other muscular dystrophies including the dystrophinopathies, dysferlinopathies, and facioscapulohumeral muscular dystrophy among others. A single report has shown rare inflammation mostly surrounding and within degenerating fibers in a patient with a *MYH7* mutation.¹⁴ The nature of the infiltrate was noted to be mostly CD4 and CD68 positive, with only faint expression of MHC-I. In the case presented here, the presence of primary inflammation in combination with red-rimmed vacuoles and positive staining for proteinaceous aggregates has not been reported in Laing myopathy patients.

The presence of primary inflammation and red-rimmed vacuoles is a hallmark of inclusion body myositis. In the index patient, we have demonstrated T-cell predominant inflammatory infiltrates surrounding and invading nonnecrotic fibers and increased MHC-I staining. We have also observed red-rimmed vacuoles and positive staining for TDP-43, p62, and phospho-Tau (SMI-31)-positive protein aggregates. A recent study by Brady et al. found that in biopsies in which vacuoles were present, the combination of a specific pattern of p62 staining, and increased MHC-I staining yielded a sensitivity of 93% and specificity of 100% for IBM, demonstrating the utility of this particular stain as a diagnostic marker.¹⁵ This case, though, demonstrates that some inherited myopathies may also yield similar findings on muscle biopsy and emphasizes the importance of the clinical exam.

Genetic testing provided the definitive diagnosis, confirming the pathogenic mutation in *MYH7*. The mixed clinical presentation as well as the pathology findings raises the remote possibility that the index case suffers from both Laing distal myopathy and sporadic IBM. The co-occurrence of an inflammatory myopathy with an inherited myopathy has been previously reported¹⁶ and we have seen other sporadic IBM patients with inherited neuromuscular diseases, including FSHD (pers. comm.). In order to determine whether our patient had IBM in addition to Laing distal myopathy, further investigations to identify protein aggregates labeled for SMI 31 and p62

in this and other distal myopathies with rimmed vacuoles would be helpful. These issues notwithstanding, this case report highlights the need to consider genetic muscle disease in patients with an atypical IBM history and phenotype (in our case, positive family history, weakness onset before the age of 45, and wrist/finger extensor weakness greater than flexor weakness) even in the context of classic IBM pathology.

Acknowledgments

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Conflict of Interest

None declared.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. (A and B) H&E at two magnifications showing endomysial inflammation. (C) Congo red stain demonstrates primary inflammation. (D) ATPase pH 9.4. (E) Gomori trichrome and (F) H&E show additional vacuoles; insert shows a vacuolated fiber from 10× image (white dashed lines).