Published in final edited form as:

Neuromuscul Disord. 2013 May ; 23(5): 432–436. doi:10.1016/j.nmd.2013.02.009.

A novel mutation expands the genetic and clinical spectrum of *MYH7*-related myopathies

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Abstract

MYH7 mutations are an established cause of Laing distal myopathy, myosin storage myopathy, and cardiomyopathy, as well as additional myopathy subtypes. We report a novel *MYH7* mutation (p.Leu1597Arg) that arose *de novo* in two unrelated probands. Proband 1 has a myopathy characterized by distal weakness and prominent contractures and histopathology typical of multi-minicore disease. Proband 2 has an axial myopathy and histopathology consistent with congenital fiber type disproportion. These cases highlight the broad spectrum of clinical and histological patterns associated with *MYH7* mutations, and provide further evidence that *MYH7* is likely responsible for a greater proportion of congenital myopathies than currently appreciated.

Keywords

Congenital myopathies; *MYH7*; Laing distal myopathy; Axial myopathy

Introduction

MYH7 encodes slow/ β -cardiac myosin heavy chain, a class II myosin found in cardiac and type I skeletal myofibers [1]. It is a critical component of the force generation apparatus in both heart and skeletal muscle. Mutations in *MYH7* are an established cause of cardiomyopathy [2] and of an expanding range of skeletal myopathies that includes Laing distal myopathy [3,4], myosin storage myopathy [5–8], congenital fiber type disproportion (CFTD) [9,10], myopathy with serpiginous cytoplasmic bodies and myofibrillar changes [11], and core myopathy (including multi-minicore disease) [12,13]. Mostly these disorders follow autosomal dominant inheritance although a family with autosomal recessive myosin storage has been reported [14]. Mutations for the different disorders cluster in different parts of the protein with some overlap. For example, most cardiomyopathy mutations are located in the myosin head and neck domains [15] while skeletal myopathy mutations are usually in the distal regions of the rod domain [16].

Until recently, *MYH7* has been an uncommon cause of skeletal myopathy, associated with a narrow range of clinical and histological phenotypes. Recent case reports link *MYH7* mutations to several new histological and clinical patterns of disease [9–11,17,18], and it is possible that mutations in *MYH7* may be responsible for a significant proportion of a wide range of skeletal myopathies. We present two new cases that support this hypothesis. These two unrelated patients have a previously unreported *MYH7* mutation (p.Leu1597Arg) and have strikingly different clinical and histological presentations. These cases thus broaden the known spectrum of *MYH7* myopathy and also show that the same mutation can cause highly variable clinical and histological phenotypes that include axial myopathy and multiminicore disease.

Case report

Case 1

This female patient (currently age 32 years old) has prominent and multiple joint contractures and generalized weakness that is most notable in the distal musculature. She presented with toe walking at age 2 years and required multiple Achilles tendon lengthening surgeries between ages 11–14 years. From age 19 years she developed progressive weakness and contractures. At age 32 years, she could walk only short distances and had prominent contractures of the finger flexors (Fig 1A), neck flexors, and tendo-Achilles. There was marked weakness of neck flexion, shoulder abduction, hip flexion and ankle dorsiflexion and moderate weakness of wrist/hand flexors and mild weakness of knee flexion/extension. Facial and ocular muscle function was normal.

Electromyography (EMG) showed myopathic features and serum CK was mildly elevated. Cardiac evaluation (via EKG and echocardiogram) was unremarkable. At age 32 years, based on formal pulmonary function testing, she exhibited moderate restrictive lung disease (forced vital capacity [FVC] 63% of predicted). Muscle MRI showed severe fatty replacement in quadriceps and soleus muscles with sparing of biceps femoris and medial gastrocnemius (Fig 1C). A quadriceps muscle biopsy performed at age 11 years showed non-specific myopathic changes while a gastrocnemius biopsy performed at age 32 years

showed prominent mini-cores, increased internalized nuclei (~40% of fibers), type I fiber predominance, mildly increased endomysial fibrosis and focal fatty replacement (Fig 2). Sanger sequencing was normal for *RYR1* (full exonic sequencing), *SEPNI*, *LMNA*, and *COL6A1/2/3*. A heterozygous *MYH7* p.Leu1597Arg (c.4790T>G) missense change was detected in the patient and not found in either parent. This change was absent from the NCBI dbSNP database, from the 1000 genomes database (<http://www.1000genomes.org/>), and from the Exome Variant Server, (NHLBI Exome Sequencing Project (ESP), Seattle, WA (<http://evs.gs.washington.edu/EVS/>)).

Case 2

This female patient (last assessed at age 16 years) has a predominantly axial myopathy phenotype. She presented with toe-walking at age 5 years and required bilateral tendo-Achilles releases at ages 7 and 13 years. A progressive scoliosis required surgical stabilization at age 12 years. At age 13 years neck movements were markedly restricted in all directions except extension, and there were mild flexion contractures at the hips, knees and ankles. There was marked neck flexion weakness, moderate weakness of hip extension and ankle dorsiflexion, and mild weakness of shoulder abduction, hip flexion and knee flexion/extension. While walking her upper body was angled forward, there was external rotation of the feet and mild foot-drop. Of note, the axial involvement in this case largely spares the lumbar musculature and is restricted to the upper thoracic and neck regions.

In terms of diagnostic studies, serum creatine kinase was 308 iu/l (24–215). There was moderate restrictive lung disease (as determined by formal pulmonary function testing) at age 12 years (FVC 55% of predicted). Electromyography, sural nerve biopsy and cardiac investigations (EKG and echocardiogram) were normal. A quadriceps muscle biopsy taken at age 13 years demonstrated congenital fiber type disproportion. There was type 1 fiber predominance (82%), marked type 1 hypotrophy and type 2 fiber hypertrophy (Fig 3A–C). Muscle MRI scan at age 12 years showed selective fatty infiltration of spinalis muscles in the upper thoracic and cervical regions (Fig 3D–I). A heterozygous *MYH7* p.Leu1597Arg (c.4790T>G) missense change was found by whole exome sequencing studies, and confirmed by Sanger sequencing. This change was absent in parental DNA samples. Unreported heterozygous variants in *RYR1* (p.Asn4200Ser), *COL6A3* (p.Ser2829Pro) and *TTN* (p.Gly4604Glu) were also detected, but were all present in a healthy parent. In addition, Sanger sequencing was normal for *ACTA1*, *SEPNI*, *LMNA*, *TPM3*, *TPM2*, *TNNT1* and *MYOZ2*.

Discussion

We present strong evidence that a heterozygous p.Leu1597Arg *MYH7* change is the cause of myopathy in two unrelated probands with distinct clinical and histopathological presentations. This evidence includes the fact that the variant is not present in large control datasets and that it arose *de novo* in both individuals in association with a congenital myopathy phenotype, which is very unlikely to occur by chance. This missense change is located within the light meromyosin (LMM) region, similar to other skeletal myopathy

MYH7 mutations [16]. The LMM has been implicated as a mediator of protein–protein interactions between myosin and other known myosin-binding proteins.

The most significant observation to emerge from these cases is the divergent clinical course and histopathological pattern between two unrelated individuals with the same mutation. The most prominent clinical features of Case 1 are progressive joint contractures in the distal upper and lower extremities as well as prominent neck flexor contractures, though with MRI and biopsy features (as well as some clinical features) distinct from either Ullrich CMD or Bethlem myopathy [19,20]. Histopathology showed multi-minicore myopathy. The most striking clinical feature in Case 2 was her axial muscle involvement, and her biopsy revealed congenital fiber type disproportion. Clinical heterogeneity associated with a single mutation has been reported previously for a familial case of myosin storage myopathy due to a pLeu1793Pro mutation, though in this case there was a more extreme difference in clinical severity [18]. Phenotypic variability has also been demonstrated for *MYH7* associated cardiomyopathy [21]. One potential theory to explain variable presentation in *MYH7* myopathies is that differing phenotypes and severities result from differences in the ratio of mutant to wild type protein. Previous experimentation has documented variable levels of mutant protein in different muscles in an *MYH7* patient [22], and this concept has support from studies of *ACTA1* mutations [23,24]. Additional future studies are, of course, necessary to support this hypothesis.

In addition to expanding the spectrum of known disease-associated *MYH7* mutations, these cases demonstrate that independent clinical and histological features can result from the same mutation. This fact complicates the identification of *MYH7* myopathy patients based solely on clinical or histological features. The shared features between the two cases (early onset ankle dorsiflexion and neck flexion weakness) are common in Laing distal myopathy and myosin storage myopathy, and may represent the most consistent clinical indicators of a *MYH7* myopathy. Of note, the two histopathologic patterns observed (minicore myopathy and CFTD) in our cases have historically not been commonly associated with *MYH7* mutations, though recent case studies suggests that these are likely to be common histopathologic subtypes of *MYH7*-related myopathies [10,12].

These reports raise the possibility that *MYH7* may be an important cause of a wide range of congenital myopathies. Cohort studies are needed required to confirm the full range of clinical and histological patterns and to better establish the overall burden of disease associated with *MYH7*. However, a high index of suspicion for *MYH7* mutations appears warranted in a wide range of clinical and histopathologic contexts in genetically unsolved congenital myopathies.

Acknowledgments

This research has been supported by Australian National Health and Medical Research Council grants 1022707 and 1031893 (KN & NC), and 1035828 (NC). It was additionally supported in part through the Taubman Medical Institute and the Department of Pediatrics at the University of Michigan. Partial support was also derived from NIH K08AR054835 (JJD) and MDA186999 (JJD).

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Fig. 1.

Clinical and MRI features of Case 1. (A) Prayer sign, illustrating long finger flexor contractures. (B) Muscle MRI of the thigh (top panel) reveals involvement of many muscles including sartorius, quadriceps, and adductors, with relative sparing of biceps femoris. Muscle MRI of the distal lower extremity shows fatty infiltration in the soleus and lateral gastrocnemius with relative sparing of the medial gastrocnemius.

Fig. 2. Muscle biopsy features of Case 1. (A) Hematoxylin and eosin staining showing increased internalized nuclei, variation in fiber size, and focal fatty replacement. (B) ATPase pH 4.2 staining showing type 1 predominance. (C–D) SDH (C), and COX (D) staining show central clearing and absence of staining suggestive of core-like areas. (E–F) Electron micrographs reveal myofibrillar disarray of the sarcomeres with exclusion of mitochondria, ranging from only 4 microns to more than 20 microns in diameter, consistent with the presence of minicores.

Fig. 3.

Muscle biopsy and muscle MRI images from Case 2. Haematoxylin & eosin stain shows marked fiber size variability with occasional internalized nuclei (A), ATPase (pH 4.2) stain shows typical features of congenital fiber type disproportion (B). Mean diameter of type 1 fibers (dark) was 24.0 μm (normal $\sim 50 \mu\text{m}$) and of type 2 fibers (pale) was 83.3 μm (normal $\sim 50 \mu\text{m}$). NADH stain shows an absence of cores (C). Muscle MRI shows marked selective fatty infiltration (arrows) of the spinalis muscles of the upper thoracic (H) and cervical (I) spine with only minor fatty marbling of other muscles of the spine in lumbar (F) and lower thoracic (G) regions, pelvis (D) and thighs (E).