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ABSTRACT

Background Myosin heavy chain 7 (*MYH7*)-related myopathies (*MYH7*-RMs) are a group of muscle disorders linked to pathogenic variants in the *MYH7* gene, encoding the slow/beta-cardiac myosin heavy chain, which is highly expressed in skeletal muscle and heart. The phenotype is heterogeneous including distal, predominantly axial or scapuloperoneal myopathies with variable cardiac involvement.

Methods We retrospectively analysed the clinical, muscle MRI, genetic and myopathological features of 57 *MYH7* patients. Patients received a thorough neurological (n=57, 100%), cardiac (n=51, 89%) and respiratory (n=45, 79%) assessment. Muscle imaging findings and muscle biopsies were reappraised in 19 (33%) and 27 (47%) patients, respectively.

Results We identified three phenotypes with varying degrees of overlap: distal myopathy (70%), scapuloperoneal (23%) and axial with peculiar cervical spine rigidity called the 'sphinx' phenotype (7%). 14% of patients had either dilated cardiomyopathy, hypertrophic cardiomyopathy or left ventricular non-compaction cardiomyopathy. 31% of patients had prominent respiratory involvement, including all patients with the 'sphinx' phenotype. Muscle MRI showed involvement of tibialis anterior, followed by quadriceps, and erector spinae in patients with axial phenotype. Cores represented the most common myopathological lesion. We report 26 pathogenic variants of *MYH7* gene, 9 of which are novel.

Conclusions *MYH7*-RMs have a large phenotypic spectrum, including distal, scapuloperoneal or axial weakness, and variable cardiac and respiratory involvement. Tibialis anterior is constantly and precociously affected both clinically and on muscle imaging. Cores represent the most common myopathological lesion. Our detailed description of *MYH7*-RMs should improve their recognition and management.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ *MYH7*-related myopathies (*MYH7*-RMs) are a group of rare genetic muscle disorders presenting a wide clinical spectrum in form of different phenotypes and severity. Laing distal myopathy is the most common clinical presentation, but axial, limb-girdle and scapuloperoneal phenotypes are described. Cardiac involvement is usually associated with variants in the myosin globular head while a skeletal myopathy is often linked to variants in myosin tail domain. Muscle imaging reveals some particular findings such as the frequent and early involvement of tibialis anterior. Muscle biopsy shows heterogeneous myopathological lesions.

INTRODUCTION

Myosin is the major component of the thick filament of the sarcomere structure, playing a key role in cardiac and skeletal muscle contraction as an actin-dependent molecular motor.[1] The myosin heavy chain 7 gene (*MYH7*) is located on the long arm of chromosome 14 (14q11.2) and encodes the slow/beta-cardiac myosin heavy chain (MyHCI), a class II myosin expressed in type 1 skeletal muscle fibres and heart.[2] The protein is organised in three regions: the myosin motor domain (head), the S2 domain containing the flex neck and hinge and a coiled coil region (tail) allowing the dimerisation. Pathogenic variants in the head region of the *MYH7* gene were first associated with familial hypertrophic cardiomyopathy (HCM)[3] and successively with dilated or left ventricular non-compaction cardiomyopathies (LVNCs).[4]

MYH7-related myopathies (*MYH7*-RMs) are associated with a wide clinical spectrum, including scapuloperoneal (SP), distal or limb-girdle phenotypes, including the initially reported myosin

WHAT THIS STUDY ADDS

⇒ Our work enlarges the phenotypical spectrum of MYH7-RM, including the rare clinical axial phenotype linked to MYH7 variants presenting a severe scoliosis, a forward displacement of the trunk and a hyperextended neck leading the peculiar 'sphinx' posture. In our cohort, muscle-MRI also revealed a frequent and severe involvement of quadriceps with relative sparing of rectus femoris. We observed four variants leading to cardiac involvement localised in myosin tail domain. Nine novel variants are reported.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our work leads to a better knowledge of MYH7-RMs, expanding the clinical features with a deep characterisation of the 'sphinx' phenotype compared with other myopathies with early axial involvement. Muscle imaging revealed often a severe involvement of proximal muscle in lower limbs. All these features can help the clinicians and guide the diagnosis of this rare myopathy.

storage myopathy and Laing distal myopathy (LDM).[5–8] The severity is highly variable, ranging from absent or mild weakness to loss of ambulation and variable axial, cardiac and respiratory involvement. This heterogeneity can be partly explained by the localisation of the variants within the gene. Variants in the globular head and neck of myosin are usually associated with familial cardiomyopathy, while dominant mutations in the elongated C-rod domain of myosin are responsible for skeletal muscle disease.[2] Recessive inheritance is uncommon and has been reported in only two families.[9] Age at onset ranges from early childhood to later, adult-onset forms. Intrafamilial variability has also been reported. Myopathology of *MYH7*-RMs is also wide, ranging from protein aggregates in the form of tubulofilamentous hyaline inclusions (myosin storage), sometimes associated with rimmed vacuoles, cores, multiminicores and congenital fibre type disproportion, to poorly specific myopathic findings.[2 10]

Here, we describe the clinical, myopathological, imaging and genetic features of 57 patients with *MYH7*-RM, thus expanding the phenotypic and genetic spectrum of the disease.

MATERIALS AND METHODS

Patients

A multicentre retrospective study was conducted on 57 patients with genetically confirmed *MYH7*-RM, followed in 15 neuromuscular reference centres in France, belonging to the French neuromuscular network (FILNEMUS).

Patients with isolated *MYH7*-associated cardiomyopathy, asymptomatic carriers of *MYH7* gene variants and patients harbouring non-pathogenic *MYH7* gene variants were excluded. Data regarding family history and clinical features were retrieved from patients' medical records. Disease onset and progression, distribution of muscle weakness, clinical phenotype, gait disturbance, joint contractures and skeletal deformities were assessed. Concerning ancillary tests, serum creatine kinase (CK) levels, nerve conduction studies and electroneuromyography (ENMG), forced vital capacity (FVC) and cardiac evaluation, including standard ECG and echocardiography, were retrieved.

Table 1 Summarised features reported by clinicians

Patients (57) *	n (%)
Female/male	31 (54)/26 (46)
Age at onset of symptoms in years (years) (n=55) *	
<4 years	14 (24)
≥4–10 years	22 (40)
≥10–20 years	8 (14)
≥20 years	11 (20)
Family history (n=57) *	
AD	38 (67)
UD	19 (34)
First symptoms (n=57) *	
Motor disability (difficulty walking, running, reduced maximal walking distance, foot drops)	50 (88)
Respiratory symptoms (ie, dyspnoea)	2 (3)
Asymptomatic. Referred because of family history	5 (9)
At last neurological examination	
Muscle weakness distribution (n=57) *	
Upper limbs	
Normal strength	17 (30)
Isolated distal	24 (42)
Isolated proximal	5 (9)
Proximal and distal	11 (19)
Lower limbs	
Isolated distal	34 (60)
Isolated proximal	1 (2)
Proximal and distal	22 (38)
Facial weakness (n=57) *	13 (23)
Scapular winging (n=54) *	16 (30)
Axial weakness (n=54) *	34 (63)
Axial stiffness (n=47) *	10 (21)
Spine deformities and treatment (n=56) *	
Scoliosis, kyphosis, lumbar/cervical hyperlordosis (n=56) *	23 (41)
Arthrodesis (n=56) *	4 (7)
Brace (n=56) *	0
Total joint contractures (n=55) *	
Achilles' tendon contractures	36 (65)
Other joint contractures (elbow, knees, wrist flexor, fingers flexor)	13 (24)
Foot deformities (n=55) *	
Equinovarus	5 (9)
Pes cavus	7 (13)
Pes planus	8 (14)
Claw feet	2 (4)
Walking abilities (n=57) *	
Independent ambulation	33 (58)
Cane or ankle foot orthosis	13 (23)
Intermittent use of wheelchair	4 (7)
Wheelchair users	7 (12)

The denominator for percentage calculations was the number of cases with available data for each item (*). The inheritance of the MYH7 variant could not be determined as genetic tests were lacking for relatives.
AD, autosomal dominant; UD, undetermined.

Muscle imaging

An expert radiologist in neuromuscular disorders analysed all the available images: 16 muscle MRIs (whole body MRI n=10, 62%) and 3 lower limb muscle CT scans. The Mercuri score was used to assess the muscle fat replacement as a biomarker of muscle destruction.[11]

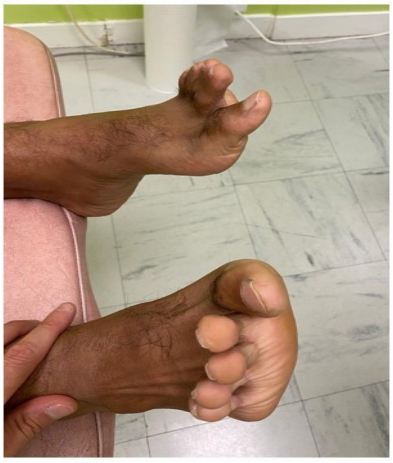

Figure 1 Distal involvement. Bilateral hanging big toe sign as peculiar feature in a patient with Laing distal phenotype.

Skeletal muscle biopsy

The histological slides or the reports of 27 muscle biopsies, including light and electron microscopy studies, were reviewed. All muscle biopsies were analysed using standard light and electron microscopy techniques as previously described.[12] The muscle biopsy site was known in 20 patients: deltoid (n=8; 40%), extensor carpi radialis brevis (n=3; 15%), quadriceps femoris (n=2; 10%), tibialis anterior (n=6; 30%) and gastrocnemius (n=1; 5%).

Genetic analysis

MYH7 gene was analysed on genomic DNA from peripheral blood using next-generation sequencing-based gene panels and Sanger sequencing. If an exome study identified an *MYH7* gene pathogenic variant, direct gene sequencing was performed subsequently to confirm the presence of the variant. Variants were interpreted and classified according to the 2015 American College of Medical Genetics Standards and Guidelines and only patients with pathogenic or likely pathogenic variants were considered as genetically confirmed.[13]

RESULTS

Clinical presentation

The main clinical features are summarised in table 1.

57 patients with *MYH7*-RM from 41 families (41 index cases and 16 relatives) were included. 31 patients (54%) were female. In 38 index patients (67%), there was a positive family history compatible with an autosomal dominant inheritance; for the other 19 patients (33%), the inheritance of the *MYH7* variant could not be determined, as genetic tests were lacking for relatives. 36 patients (65%) presented an early onset before the age of 10 years. 50 patients (88%) reported walking/running difficulties, frequent falls or foot drop as first symptoms. Two patients consulted for respiratory symptoms. Five patients were self-reported asymptomatic but when referred due to their family history, they had an abnormal clinical examination. Three main clinical patterns emerged, with a clear overlap in some patients: LDM in 40 patients (70%), SP myopathy in 13 patients (23%) and cervical rigid spine with huge trunk anteversion due to axial weakness, corresponding to the 'sphinx' phenotype, in four patients (7%). In the lower limbs, the most affected muscle was tibialis anterior, followed by toe extensor weakness. The

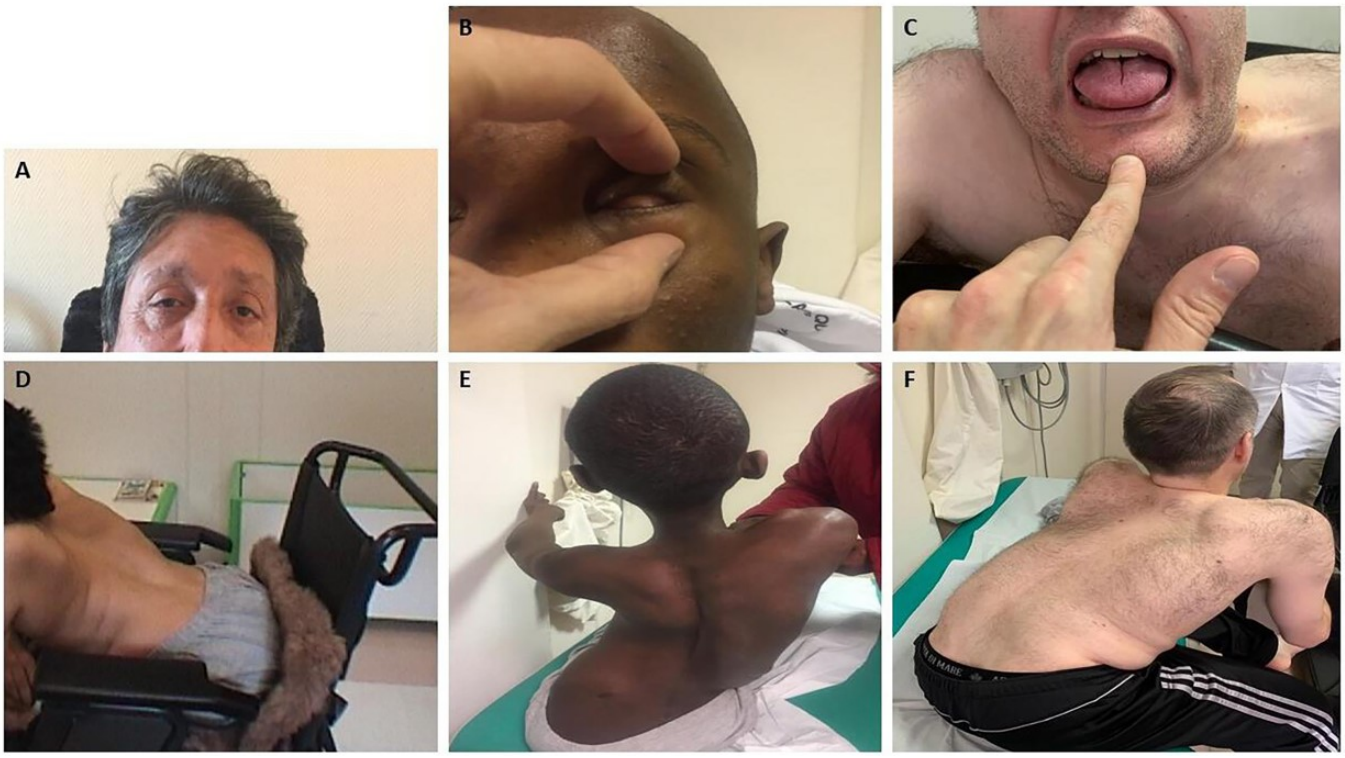

Figure 2 Sphinx phenotype: main clinical features. Bilateral ptosis (A). Weakness of orbicularis oculi (B). Masseter retraction (C). Forward displacement of the trunk due to extensor spinae global weakness (D–F). Severe scoliosis treated with arthrodesis (blue arrow) leading to an amelioration of the dorsal bending (E).

upper limbs were less severely and less often affected than the lower limbs. The most frequent weakness pattern was also distal with extensor digitorum communis involvement and especially toe extensor hallucis longus weakness leading to the peculiar 'hanging big toe' sign (figure 1). More rarely, patients had an early paravertebral or proximal muscle weakness. Other relevant findings were abolished Achilles' tendon reflexes and foot extensor weakness, leading to an initial clinical diagnosis of distal hereditary motor neuropathy (dHMN) in 21% (N=12) of patients.

The 'sphinx' phenotype was the rarest clinical presentation. It was characterised by an early involvement of the axial muscles with complete fibro-fatty replacement of the erector spinae at three levels: cervical, thoracic and lumbar. This led to severe scoliosis in all patients, requiring arthrodesis in half of them (n=2, 50%). In the sitting position, patients showed a forward displacement of the trunk with hyperextended neck keeping the peculiar 'sphinx' posture. Facial muscle weakness with ptosis, orbicularis oculi, orbicularis oris and limited buccal opening due to masseter retraction was found in three patients (n=3, 75%) (figure 2). Patients with 'sphinx' phenotype also presented scapular winging, large joint contracture and variable proximo-distal limb involvement (n=3, 75%).

Muscle weakness progressed during the disease course, affecting proximal lower limb muscles, proximal and distal upper limb muscles and paravertebral muscles, especially the erector spinae. Concerning the upper limbs, only five patients had isolated proximal weakness. Other interesting features were the spinal deformities, pes planus, pes cavus and equinovarus feet.

Despite an early presentation, 33 patients (58%) remained ambulant, and 13 patients (23%) needed canes or ankle foot orthosis. The remaining patients used a wheelchair intermittently (n=4, 7%) or permanently (n=7, 12%). Although representing only 7% of our population, patients with the 'sphinx' phenotype accounted for 43% of wheelchair-bound patients, making this the most severe form in our population.

In our cohort a striking intrafamilial variability concerning either the phenotype or the age at onset was found in five families. Indeed, two families had members presenting different phenotypes (either LDM or SP) and two other families had members presenting markedly different ages at onset (from early childhood to 18 years old). One family exhibited both the three different phenotypes and a variable age of disease-onset (from early childhood to 45 years old).

Paraclinical investigations

Paraclinical data are summarised in table 2.

Cardiac and respiratory involvement

Cardiomyopathy was diagnosed in seven patients (14%). Four (8%) had dilated cardiomyopathy (DCM), two (4%) had HCM and one (2%) had LVNC. Among these patients, a teenage patient with DCM died due to severe cardiac failure; another patient with DCM needed an implantable cardioverter-defibrillator (ICD) in his 40s. ECG was performed on 44 patients and was normal in 79% of these. The remaining 21% showed minimal conduction abnormalities such as bundle branch block or unspecific abnormal repolarisation deficits.

Respiratory assessment was available in 45 patients (79%). Restrictive respiratory syndrome was diagnosed in 14 patients (31%): 6 patients (median age 56 years) were treated with nocturnal non-invasive ventilation (NIV), and 1 patient needed a tracheostomy during the adolescence due to cardio-respiratory complications after spine fusion. Among the four patients with the 'sphinx' phenotype, all of them had a severe restrictive respiratory syndrome (FVC <40%) and three required NIV. In these patients, the spinal and thoracic deformations induced by scoliosis and vertebrae rotation, may have an additional mechanic impact on respiratory function, thus aggravating the restrictive syndrome.

Table 2 Summarised main paraclinical features

CK levels (N/A: 11)	n=46 * (81%)	
<250 UI/L	22 (48%)	AX (n=1) LDM (n=17) SP (n=4)
250–1000	23 (50%)	AX (n=1) LDM (n=15) SP (n=7)
>1000	1 (2%)	LDM (n=1)
Respiratory involvement (N/A: 12)	n=45 * (79%)	
FVC <80%	14 (31%)	AX (n=4) LDM (n=5) SP (n=5)
Non-invasive ventilation	6 (13%)	AX (n=3) LDM (n=2) SP (n=1)
Tracheostomy	1 (2%)	LDM (n=1)
Echocardiography cardiac involvement (N/A: 6)	n=51 * (90%)	
Normal	37 (72%)	AX (n=2) LDM (n=27) SP (n=8)
Hypertrophic cardiomyopathy	2 (4%)	LDM (n=1) SP (n=1)
Dilated cardiomyopathy	4 (8%)	LDM (n=3) SP (n=1)
Non-compaction of left ventricular myocardium	1 (2%)	LDM (n=1)
Other abnormalities	8 (16%)	AX (n=1) LDM (n=4) SP (n=3)

The denominator for percentage calculations was the number of cases with available data for each item (*).
AX, axial; FVC, forced vital capacity; LDM, Laing distal myopathy; N/A, not available; SP, scapuloperoneal.

Electroneuromyography

We analysed ENMG data from 43 patients. Spontaneous activity was present in eight patients (19%) and was characterised by fibrillation potentials, positive sharp waves or pseudomyotonic discharges. A myogenic interference pattern, with brief low-amplitude motor unit potentials (MUPs), was the most common in our cohort, found in 22 patients (51%). However, the coexistence of a myogenic and a pseudoneurogenic pattern, characterised by high-amplitude and/or long duration, with often polyphasic MUP and a reduced recruitment pattern, was observed in 18 patients (42%). An isolated pseudoneurogenic pattern was observed in three patients (7%), who were initially diagnosed as having dHMN.

Muscle imaging

The pattern of muscle involvement on MRI is summarised in figure 3. The main muscle imaging features are illustrated in figure 4.

Two patients showed normal muscle imaging. In general, the pattern of fibro-fatty substitution was symmetrical. In the posterior compartment of the pelvic girdle, a common severe

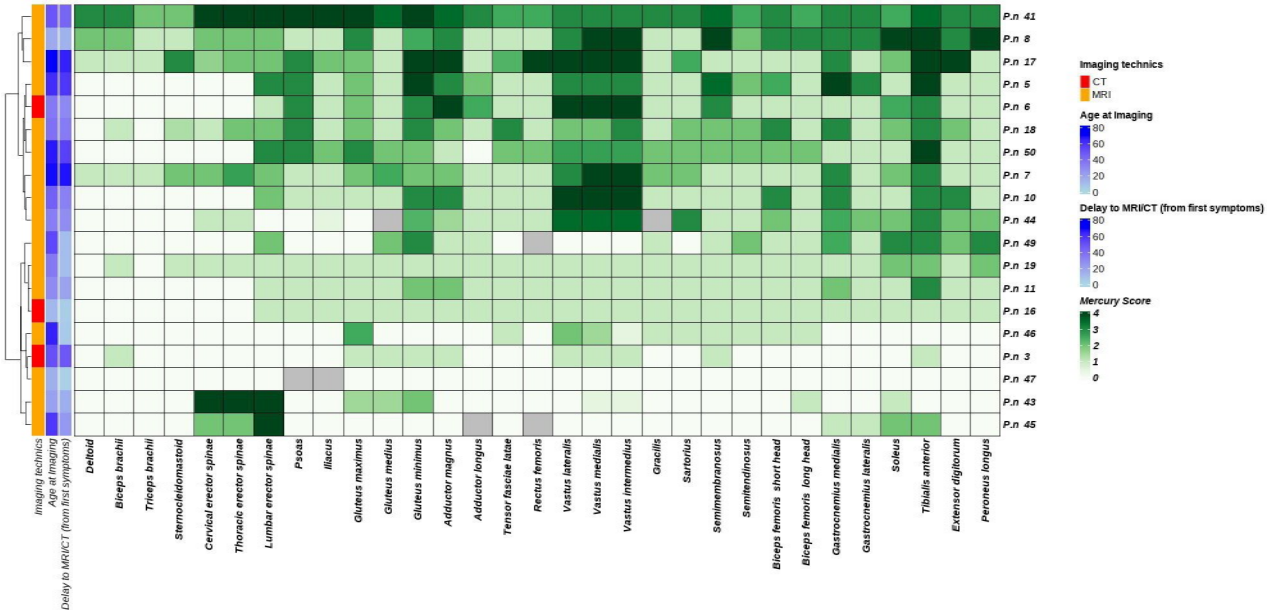

Figure 3 MRI pattern of muscle involvement. Mercuri score modified by Fisher: 0: normal appearance; 1: mild involvement, fatty infiltration <30%; 2: moderate involvement, fatty infiltration between 30% and 60%; 3: severe involvement, fatty infiltration >60%; 4: end-stage appearance, completely infiltrated.

involvement was seen in the gluteus minimus (n=16, 84%) and gluteus maximus (n=15, 79%), with a relative maintenance of the gluteus medius. Regarding the thigh adductors, the adductor magnus (n=15, 79%) was more frequently and more severely affected than the adductor longus. At the thigh level, quadriceps was the muscle most frequently impaired (n=16, 84%), with a pronounced involvement of the vastus lateralis, vastus intermedius and vastus medialis and a selective sparing of the rectus femoris. The hamstring muscles, semimembranosus, semitendinosus and biceps femoris muscles, were also frequently but less impaired (n=15, 79%). Regarding the legs, tibialis anterior involvement was the most frequent finding (n=16, 84%) and was the muscle most severely involved, followed by the extensor digitorum and the peroneus longus. In the posterior compartment, the gastrocnemius medial head was more strongly involved compared with the gastrocnemius lateral head and soleus. All erector spinae muscles were markedly affected in patients presenting a 'sphinx' phenotype.

Interestingly, patient 41, with the 'sphinx' phenotype, showed an inverted-collagen-VI sign, characterised by bands of fatty infiltration inside globally preserved muscle.

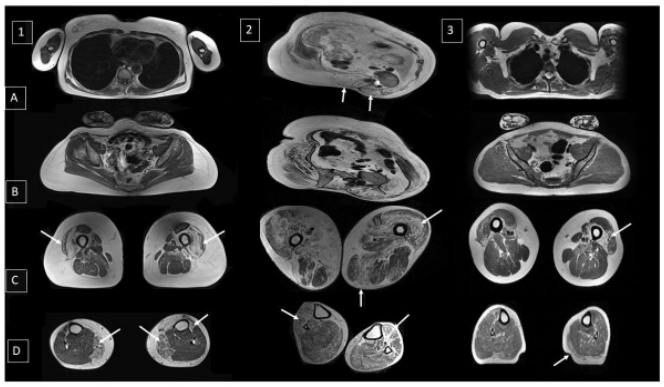

Figure 4 Muscle MRI patterns T1-weighed axial MRI images. Arms and trunk muscles (A); pelvic girdle (B); thighs (C); legs (D). (1) Laing distal phenotype. (C, D): fatty replacement of tibialis anterior, vastus lateralis, medialis and intermedius and gastrocnemius medialis (Mercuri grade 4, arrows). Mild fatty replacement of adductors magnus (Mercuri grade 2). (A, B): Pelvic girdle muscles, trunk and arms are well preserved. (2) Sphinx phenotype. (A, B): note the severe paravertebral fatty involvement (Mercuri grade 4) leading to major scoliosis and vertebrae rotation. (C, D): Fatty involvement of quadriceps, adductors magnus (Mercuri grade 3) whereas gracilis and hamstrings are better preserved. In legs, the fatty involvement is more pronounced in the tibialis anterior (Mercuri grade 3) than in the posterior compartment (Mercuri grade 2). (3) Atypical MRI phenotype (clinically Laing distal phenotype) (C, D) Atypical pattern of asymmetric fatty replacement of vastus intermedius and medialis, more pronounced on the left side (Mercuri grades 4 and 3, respectively). Note the fatty involvement of the left gastrocnemius medialis (Mercuri grade 3). (A, B): Pelvic girdle muscles, trunk and arms demonstrate normal appearance.

Muscle morphological features

A muscle biopsy was performed on 27 patients (figure 5, online supplemental table 1). The main findings were nuclear internalisation (n=12, 44%), fibre size variability (n=9, 33%), type 1 fibre predominance (n=12, 44%), type 1 fibre type disproportion (n=12, 44%), type 1 atrophy (n=7, 26%) and rimmed vacuoles (n=4, 15%). Six patients (22%) showed multiple necrotic regenerating fibres. Cores were observed in 13 patients (48%) and were the most frequent lesion. Hyaline bodies were found in only one patient and consisted of subsarcolemmal masses filled with amorphous material, strongly reacting with MyHC-slow antibody. Cap-like structures were found in one patient.

Genetic analyses

We identified 26 pathogenic and likely pathogenic heterozygous variants among the 41 index patients and their 16 affected relatives (online supplemental table 2). The vast majority were missense (n=18, 69%) followed by in-frame codon deletions (n=6, 23%). Two splice site mutations were found (n=2, 8%), one affecting the acceptor splice site of intron 37 and the other one affecting the donor splice site of intron 39. Their consequences

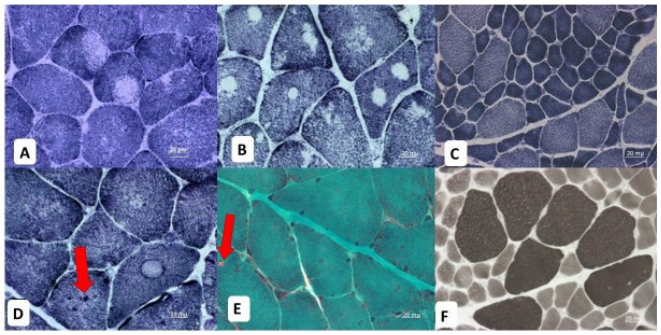

Figure 5 Myopathological findings. (A)SDH technique showing eccentric cores. (B) SDH, fibres showing either single or multiple cores. (C) NADH, type 1 fibres are smaller than type 2 fibres, corresponding to a significant type 1 fibre atrophy or CFTD (congenital fibre-type disproportion). The small lesion dark blue lesions in NADH (D) and reddish in mGT (E) correspond to tubular aggregates red (arrows). (F) ATPase 9.40 showing congenital type 1 fibre disproportion.

SDH: succinate dehydrogenase

mGT: modified Gömöri thricrome

NADH: nicotinamide adenine dinucleotide dehydrogenase

at the protein level could not be evaluated. The variants c.4522_4524del, p.(Glu1508del) and c.4850_4852delAGA, p.(Lys1617del) were the most frequent and were found, respectively, in 10 patients belonging to 5 families and in 5 patients from five different families.

We found nine novel variants classified as likely pathogenic. Among these (1) seven were missense variants: c.380C>T, p.(Pro127Leu), c.3092T>A, p.(Val1031Glu), c.4577T>C, p.(Leu1526Pro), c.4648T>C, p.(Ser1550Pro), c.4685A>C, p.(Gln1562Pro), c.4901G>C, p.(Arg1634Pro), c.5210T>C, p.(Leu1737Pro); (2) one was an in-frame codon deletion, c.4247_4249del, p.(Lys1416del) and (3) and the last one was an intronic splice site variant: c.5790+2T>G.

As shown in online supplemental table 2, most variants (n=21, 81%) were in the myosin tail (31–37 exons) (figure 6).

DISCUSSION

MYH7-RMs are a rare and clinically heterogeneous group of early-onset disorders with variable cardiac and respiratory involvement and variable myopathological features. In our cohort, LDM[7] was the most frequent phenotype, and age at onset ranged from infancy to adulthood, highlighting the importance of suspecting *MYH7*-RMs at any age.[14]

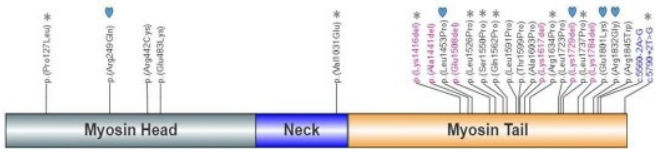

Figure 6 MYH7 pathogenic variants. Schematic representation of the distribution and nature of the pathogenic MYH7-variants identified in the reported cohort on the MYH7 corresponding protein (bMHC). The three main domains of the protein are indicated: the N-terminal globular myosin head is shown in grey, the neck domain in blue and the C-terminal myosin tail in orange: *indicates never reported variants, and the blue heart indicates variants associated with cardiomyopathy in the patients. Missense variants are indicated in black, in frame codon deletions in pink and splicing variants in blue.

Tibialis anterior and toe extensor weakness are pathognomonic features of LDM. Distal weakness, leading to foot drop, may lead to an initial misdiagnosis of HMN.[15]

The association of weakness of the finger extensors, with spared interosseous muscles and finger flexors in the hands, along with the preservation of the extensor digitorum brevis muscle in the feet, are the main clinical signs pointing towards *MYH7*-RMs.[16 17] These can help differentiate *MYH7*-RMs from dHMN, in which the intrinsic muscles of hands and feet are involved, along with the anterior and posterior compartments of the leg.[7] However, the weakness of finger extensors may appear later in the disease course.[8] Third, fourth and fifth finger extensor muscles are more affected whereas thumb abduction and second finger extension are less involved, giving a peculiar sign of 'pointed second finger'.[7 18 19] As previously reported, *MYH7*-RMs can also present with dropped head, rigid spine syndrome, axial,[20] proximal and SP muscle involvement[21 22] and asymptomatic hyperckaemia. Early axial involvement leading to a 'sphinx' phenotype is a rare clinical presentation of *MYH7*-RMs and the most severe phenotype of our cohort.

Rigid spine is a distinctive manifestation seen in various myopathies. Key features include contractures of the limb and spinal joints, limited flexion of the neck and trunk, weakness of the cervical or dorsolumbar spine muscles and progressive scoliosis. Variants in different genes, such as *LMNA*, *FHL1*, *EMD*, *COL6A1*, *COL6A2*, *COL6A3* and *SEPN1*, among others, have been associated with rigid spine. Early cardiac involvement points towards *LMNA*, *FHL1 or EMD*-related myopathies,[23–26] while *COL6*-related myopathies often present keloids and the coexistence of distal hypermobility and joint contractures.[27] In *SELENON*-related myopathies the severe axial involvement is often associated with preserved ambulation, even in adulthood.[28] In contrast, in patients presenting *MYH7*-RMs with axial involvement, a severe proximo-distal muscular weakness leads to the need for walking aids or a wheelchair in adulthood. Rigid spine may be an unusual clinical presentation of other disorders, such as Pompe disease[29–31] or *BAG3*-related myopathy, one of the rarest forms of myofibrillar myopathies, showing an early onset, progressive muscular weakness, rigid spine, severe cardiomyopathy and respiratory involvement.[32]

Clinical red flags that help to differentiate *MYH7*-RMs with early axial involvement leading to the 'sphinx' phenotype from other forms of myopathy associated with rigid spine are (1) a severe erector spinae weakness resulting in a forward bending of the trunk; (2) cervical spine rigidity leading to a hyperextended neck and (3) various degrees of facial involvement, such as ptosis, and orbicularis oris and orbicularis oculi weakness. Other, non-specific features that can help the clinical suspicion are large joint contractures, masseter retraction, scoliosis often needing arthrodesis and a severe restrictive respiratory pattern.

Electrophysiological studies can be misleading, as high amplitude of MUP and a reduced interference pattern can also be observed in myopathies with significant distal weakness and atrophy.[22 33 34] This pattern might reflect an abnormal motor unit remodelling process due to myocytic alterations[22] when associated with abnormal spontaneous activity and absent deep tendon reflexes, it may contribute to a misdiagnosis of neurogenic disease. Thus, in those patients measuring the duration of MUP is very useful, since their duration is shorter than those recorded in a neurogenic process.[35] Nevertheless, differentiating a motor neuropathy from myopathy can be difficult. In such cases, muscle imaging may be very useful since intrinsic foot

muscles are usually spared in patients with myopathy but not in patients with peripheral neuropathy. Moreover, paravertebral muscles also show an early fibro-fatty degeneration, a feature not seen in patients with dHMN.

In MYH7-RM patients, lower limb muscle MRI is characterised by a predominant distal pattern with an early and severe involvement of the tibialis anterior muscle, followed by extensor hallucis longus (online supplemental figure 1) and extensor digitorum longus muscles, whereas in the posterior compartment gastrocnemius medialis seems more affected.[7] Vastus lateralis and vastus medialis are the most affected thigh muscles, with a selective sparing of the rectus femoris, and adductor longus, gracilis and sartorius.[36] As previously reported and observed in some of our patients, it seems that fibro-fatty replacement of tibialis anterior begins from the periphery and progresses towards the centre of the muscle.[7] Although *MYH7*-RM usually presents a symmetrical pattern of muscle weakness distribution, muscle-MRI can reveal a clear asymmetrical fibro-fatty replacement occurring in both proximal (figure 4, 3–C) and distal (figure 4, 1–D) lower limbs in some cases. In contrast, and as described in the Italian cohort,[7] we found a frequent and severe involvement of quadriceps on muscle MRI, with relative sparing of the rectus femoris. In patients with the 'sphinx' phenotype, muscle MRI revealed a severe involvement of all cervical, thoracic and lumbar erector spinae muscles, with a complete fibro-fatty replacement.

The myopathological spectrum is large. Interestingly, most biopsies of our cohort showed cores, a type 1 fibre predominance or a fibre type disproportion. Additional findings were necrotic regenerating fibres, rimmed vacuoles and subsarcolemmal accumulation of material that looked hyaline in H&E corresponding to myosin storage myopathy.[2]

Genetically, the 26 encountered variants were evenly distributed along the different domains of the protein, with 21 variants clustered in the coiled-coil myosin tail. Thus, the main location of the variants resides in the myosin tail domain. This spectrum of variants was correlated to previous studies.[7 22] These variants alter the helical shape of the super helix.[37] However, four variants could be observed in the myosin head (motor domain) and one in the neck domain, all being missense. The latter variants were predicted to interfere with actin binding and ATP hydrolysis as well as light chain binding.

The six in-frame deletions (6/26 variants, 23%) resulting in one amino acid deletion were all located in the myosin tail domain. Only two splicing variants were observed and were located at the 3' end of the gene.

Interestingly, in two families, there were asymptomatic carriers and carriers with cardiomyopathy without muscular involvement. In the first family, harbouring the *MYH7* pathogenic variant c.1447G>A, p.(Glu483Lys), the index case presented with muscle and cardiac involvement and there was one asymptomatic carrier. In the second family, harbouring the *MYH7* pathogenic variant c.5186_5188del, p.(Lys1729del), the index case exhibited only muscle involvement and there were two cases of cardiomyopathy with ICDs without muscular involvement.

It would be of much interest to further study the familial segregation in a prospective study to detect the presence of asymptomatic carriers and patients with isolated *MYH7*-associated cardiomyopathy with no or very mild muscle involvement, which may only consult at cardiology clinics, in order to study and elucidate the penetrance of different mutations in the *MYH7* gene.

Correlations between the genotype and the phenotype are difficult to establish (online supplemental table 2). Pathogenic variants located in other, more proximal regions of the gene can be observed in patients with cardiopathy, as previously described.[38] Furthermore, among the variants located in the head domain, only one patient carrying the c.746G>A, p.(Arg249Gln) had a SP myopathy and a HCM, as previously reported.[38] This can be related to the description of several cases exhibiting both distal myopathy and cardiomyopathy (hypertrophic or dilated) and presenting a *MYH7* variant in the N-terminal domain.[39] Conversely, four variants c.4358T>C, p.(Leu1453Pro), c.5186_5188del, p.(Lys1729del), c.5401G>A, p.(Glu1801Lys) and c.5494C>G, p.(Arg1832Gly) observed in five probands with cardiomyopathy (DMC, HMC and LVMC) were detected in the myosin tail between exons 31 and 37. Three of them were previously reported in patients with both myopathy and cardiomyopathy while c.5494C>G, p.(Arg1832Gly) was described only in patients with cardiomyopathy without muscle damage.[40–42] The clinical and paraclinical assessment of the four patients harbouring pathogenic variants in the myosin head did not reveal any clear distinguishable clinical, muscle imaging, nor myopathological feature compared with the other patients presenting *MYH7*-RM due to myosin tail variants. These observations modulate the message of the preferential localisation of variants in the myosin head in the presence of cardiomyopathy reported in the literature.[43]

Prognostic factors and management

Focusing on motor performance, these results suggest that patients suffering from *MYH7*-RMs retain ambulation in the majority of cases; in our cohort only, a few patients were wheelchair-bound, and most of these presented an early axial phenotype (ie, 'sphinx'). Respiratory function was globally preserved, with rare cases requiring NIV, namely patients with the 'sphinx' phenotype showing a severe respiratory involvement (FVC<40%) compared with the other patients, likely due to mechanical alteration induced by severe scoliosis. This means that as well as being the rarest phenotype in our cohort, the 'sphinx' phenotype was the most severe. Cardiac management is crucial given that in the same family some patients can present with cardiomyopathy alone whereas others have only distal myopathy without any heart disease. Thus, cardiac investigations are mandatory in all patients carrying *MYH7* variants and in those patients who refuse presymptomatic genetic diagnosis.

EMG investigation can sometimes show a pseudoneurogenic pattern, in some cases, hindering diagnosis. Muscle biopsy reveals a wide myopathological spectrum with cores as the most frequent lesion. Muscle MRI shows concentric fibro-fatty replacement of tibialis anterior that could be considered as an early imaging feature of the disease.

In conclusion, our findings in a large cohort of *MYH7*-RMs patients expand the clinical and genetic spectrum of these rare myopathies, increasing awareness and facilitating their recognition.

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REFERENCES

1 Sellers JR. Myosins: a diverse superfamily. *Biochim Biophys Acta* 2000;1496:3–22.
2 Tajsharghi H, Oldfors A. Myosinopathies: pathology and mechanisms. *Acta Neuropathol* 2013;125:3–18.
3 Geisterfer-Lowrance AA, Kass S, Tanigawa G, *et al*. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. *Cell* 1990;62:999–1006.
4 Hershkovitz T, Kurolap A, Ruhrman-Shahar N, *et al*. Clinical diversity of MYH7-related cardiomyopathies: Insights into genotype-phenotype correlations. *Am J Med Genet A* 2019;179:365–72.
5 Tajsharghi H, Thornell L-E, Lindberg C, *et al*. Myosin storage myopathy associated with a heterozygous missense mutation in MYH7. *Ann Neurol* 2003;54:494–500.
6 Darin N, Tajsharghi H, Ostman-Smith I, *et al*. New skeletal myopathy and cardiomyopathy associated with a missense mutation in MYH7. *Neurology (ECronicon)* 2007;68:2041–2.
7 Fiorillo C, Astrea G, Savarese M, *et al*. MYH7-related myopathies: clinical, histopathological and imaging findings in a cohort of Italian patients. *Orphanet J Rare Dis* 2016;11:91.
8 Lamont PJ, Wallefeld W, Hilton-Jones D, *et al*. Novel mutations widen the phenotypic spectrum of slow skeletal/β-cardiac myosin (MYH7) distal myopathy. *Hum Mutat* 2014;35:868–79.
9 Beecroft SJ, van de Locht M, de Winter JM, *et al*. Recessive MYH7-related myopathy in two families. *Neuromuscul Disord* 2019;29:456–67.
10 Romero NB, Xie T, Malfatti E, *et al*. Autosomal dominant eccentric core disease caused by a heterozygous mutation in the MYH7 gene. *J Neurol Neurosurg Psychiatry* 2014;85:1149–52.
11 Mercuri E, Pichiecchio A, Allsop J, *et al*. Muscle MRI in inherited neuromuscular disorders: past, present, and future. *J Magn Reson Imaging* 2007;25:433–40.
12 Malfatti E, Romero NB. Diseases of the skeletal muscle. *Handb Clin Neurol* 2017;145:429–51.
13 Richards S, Aziz N, Bale S, *et al*. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405–24.
14 Lamont PJ, Udd B, Mastaglia FL, *et al*. Laing early onset distal myopathy: slow myosin defect with variable abnormalities on muscle biopsy. *J Neurol Neurosurg Psychiatry* 2006;77:208–15.
15 Laing NG, Laing BA, Meredith C, *et al*. Autosomal dominant distal myopathy: linkage to chromosome 14. *Am J Hum Genet* 1995;56:422–7.
16 Lamont P, Laing NG, Pagon RA. Laing distal myopathy. In: Adam MP, Feldman J, Mirzaa GM, eds. *GeneReviews®*. Seattle (WA): University of Washington, Seattle, 1993. Available: http://www.ncbi.nlm.nih.gov/books/NBK1433/
17 Felice KJ. Distal Myopathies. *Neurol Clin* 2020;38:637–59.
18 Dastgir J, Donkervoort S, Meilleur K, *et al*. G.P.31 MYH7 gene mutation related myopathies of skeletal and cardiac muscle. *Neuromuscul Disord* 2012;22:817.
19 Liu X-Y, Zhang Y-S, Sun A-P, *et al*. A novel MYH7 mutation resulting in Laing distal myopathy in a Chinese family. *Chin Med J* 2019;132:856–9.
20 Dabaj I, Carlier RY, Gómez-Andrés D, *et al*. Clinical and imaging hallmarks of the MYH7-related myopathy with severe axial involvement. *Muscle Nerve* 2018;58:224–34.
21 Pegoraro E, Gavassini BF, Borsato C, *et al*. MYH7 gene mutation in myosin storage myopathy and scapulo-peroneal myopathy. *Neuromuscul Disord* 2007;17:321–9.
22 Muelas N, Hackman P, Luque H, *et al*. MYH7 gene tail mutation causing myopathic profiles beyond Laing distal myopathy. *Neurology (ECronicon)* 2010;75:732–41.
23 Madej-Pilarczyk A. Clinical aspects of Emery-Dreifuss muscular dystrophy. *Nucleus* 2018;9:268–74.
24 Maggi L, Carboni N, Bernasconi P. Skeletal Muscle Laminopathies: A Review of Clinical and Molecular Features. *Cells* 2016;5:33.
25 Heller SA, Shih R, Kalra R, *et al*. Emery-Dreifuss muscular dystrophy. *Muscle Nerve* 2020;61:436–48.

26 Eymard B, Ferreiro A, Ben Yaou R, *et al*. Muscle diseases with prominent joint contractures: Main entities and diagnostic strategy. *Rev Neurol (Paris)* 2013;169:546–63.
27 Bönnemann CG. The collagen VI-related myopathies Ullrich congenital muscular dystrophy and Bethlem myopathy. *Handb Clin Neurol* 2011;101:81–96.
28 Villar-Quiles RN, von der Hagen M, Métay C, *et al*. The clinical, histologic, and genotypic spectrum of *SEPN1*-related myopathy: A case series. *Neurology (ECronicon)* 2020;95:e1512–27.
29 Laforêt P, Doppler V, Caillaud C, *et al*. Rigid spine syndrome revealing late-onset Pompe disease. *Neuromuscul Disord* 2010;20:128–30.
30 Kostera-Pruszczyk A, Opuchlik A, Lugowska A, *et al*. Juvenile onset acid maltase deficiency presenting as a rigid spine syndrome. *Neuromuscul Disord* 2006;16:282–5.
31 Panosyan FB, Fitzpatrick MF, Bolton CF. Late onset Pompe disease mimicking rigid spine syndrome. *Can J Neurol Sci* 2014;41:286–9.
32 Akaba Y, Takeguchi R, Tanaka R, *et al*. Wide Spectrum of Cardiac Phenotype in Myofibrillar Myopathy Associated With a Bcl-2-Associated Athanogene 3 Mutation: A Case Report and Literature Review. *J Clin Neuromuscul Dis* 2022;24:49–54.
33 Yu M, Zhu Y, Lu Y, *et al*. Clinical features and genotypes of Laing distal myopathy in a group of Chinese patients, with in-frame deletions of MYH7 as common mutations. *Orphanet J Rare Dis* 2020;15:344.
34 Dubourg O, Maisonobe T, Behin A, *et al*. A novel MYH7 mutation occurring independently in French and Norwegian Laing distal myopathy families and de novo in one Finnish patient. *J Neurol* 2011;258:1157–63.
35 Tannemaat MR, Kefalas M, Geraedts VJ, *et al*. Distinguishing normal, neuropathic and myopathic EMG with an automated machine learning approach. *Clin Neurophysiol* 2023;146:49–54.
36 Quijano-Roy S, Carlier RY, Fischer D. Muscle imaging in congenital myopathies. *Semin Pediatr Neurol* 2011;18:221–9.
37 Meredith C, Herrmann R, Parry C, *et al*. Mutations in the slow skeletal muscle fiber myosin heavy chain gene (MYH7) cause laing early-onset distal myopathy (MPD1). *Am J Hum Genet* 2004;75:703–8.
38 Díaz-Manera J, Alejaldre A, Llauger J, *et al*. Cranial, axial and proximal myopathy and hypertrophic cardiomyopathy caused by a mutation in the globular head region of the MYH7 gene. *Eur J Neurol* 2014;21:e51–2.
39 Overeem S, Schelhaas HJ, Blijham PJ, *et al*. Symptomatic distal myopathy with cardiomyopathy due to a MYH7 mutation. *Neuromuscul Disord* 2007;17:490–3.
40 Lefter S, Hardiman O, McLaughlin RL, *et al*. A novel MYH7 Leu1453pro mutation resulting in Laing distal myopathy in an Irish family. *Neuromuscul Disord* 2015;25:155–60.
41 Ruggiero L, Fiorillo C, Gibertini S, *et al*. A rare mutation in MYH7 gene occurs with overlapping phenotype. *Biochem Biophys Res Commun* 2015;457:262–6.
42 Golbus JR, Puckelwartz MJ, Fahrenbach JP, *et al*. Population-Based Variation in Cardiomyopathy Genes. *Circ Cardiovasc Genet* 2012;5:391–9.
43 Klaassen S, Probst S, Oechslin E, *et al*. Mutations in sarcomere protein genes in left ventricular noncompaction. *Circulation* 2008;117:2893–901.