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Nemaline Rod/Cap Myopathy Due to Novel Homozygous *MYPN* Mutations: The First Report from South Asia and Comprehensive Literature Review

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Background and Purpose Pathogenic variants in the myopalladin gene (*MYPN*) are known to cause mildly progressive nemaline/cap myopathy. Only nine cases have been reported in the English literature.

Methods A detailed evaluation was conducted of the clinical, muscle magnetic resonance imaging (MRI), and genetic findings of two unrelated adults with *MYPN*-related cap myopathy. Genetic analysis was performed using whole-exome sequencing. MRI was performed on a 1.5-T device in patient 1.

Results Two unrelated adults born to consanguineous parents, a 28-year-old male and a 23-year-old female, were diagnosed with pathogenic variants in *MYPN* that cause cap myopathy. Both patients presented with early-onset, insidiously progressive, and minimally disabling proximodistal weakness with mild ptosis, facial weakness, and bulbar symptoms. Patient 1 had a prominent foot drop from the onset. Both patients were followed up at age 30 years, at which point serum creatine kinase concentrations were minimally elevated. There were no cardiac symptoms; electrocardiograms and two-dimensional echocardiograms were normal in both patients. Muscle MRI revealed preferential involvement of the glutei, posterior thigh muscles, and anterior leg muscles. Whole-exome sequencing revealed significant homozygous splice-site variants in both of the probands, affecting intron 10 of *MYPN*: c.1973+1G>C (patient 1) and c.1974-2A>C (patient 2).

Conclusions This study elaborates on two patients with homozygous *MYPN* pathogenic variants, presenting as slowly progressive congenital myopathy. These patients are only the tenth and eleventh cases reported in the English literature, and the first from South Asia. The clinical phenotype reiterates the mild form of nemaline rod/cap myopathy. A comprehensive literature review is presented.

Key Words myopalladin, *MYPN*, nemaline rod myopathy, cap myopathy, muscle.

INTRODUCTION

Myopalladin is a 145-kDa sarcomeric protein that is expressed specifically in striated muscle.[1,2] Heterozygous variants in the gene (*MYPN*) encoding myopalladin are associated with different cardiac phenotypes.[3-6] Recessive *MYPN* mutations have been reported in only nine patients from seven families thus far, manifesting in some patients as a mildly progressive nemaline or cap myopathy with associated cardiomyopathy. The first report documented four individuals of Japanese ethnicity having cap myopathy secondary to biallelic pathogenic *MYPN* variants.[7] Homozygous truncating mutations in this gene were subsequently reported in three patients: two of French and one of African descent.[8] The most recent report is from Italy, with two siblings confirmed as having autosomal recessive *MYPN*-related cap myopa-

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thy.[9] Here we describe the clinical condition of two unrelated individuals with confirmed *MYPN*-related cap myopathy secondary to pathogenic variants in *MYPN*. These are only the tenth and eleventh genetically confirmed cases reported in the English literature, and the first from South Asia.

METHODS

Subjects and clinical evaluation

Institutional Ethics Committee approval was obtained for this retrospective study (NIMHANS/IEC/2020-21). Permission was granted to collect the clinical, electrophysiological, imaging, and genetic data of two unrelated patients with confirmed *MYPN*-related cap myopathy secondary to pathogenic variants in *MYPN*, and their family members. The pedigree of the families—family 1 (F1) and family 2 (F2)—are presented in Fig. 1. A detailed description of the clinical, muscle magnetic resonance imaging (MRI) and genetic findings is presented. The study participants provided written informed consent for publication of their case details and the investigation results. In patient 1 (F1-IV:2), MRI of the pelvis and lower limbs was performed on a 1.5-T device (Aera, Siemens Medical Systems, Erlangen, Germany). The standard protocol comprised contiguous T1-weighted, T2-weighted (T2w), and T2w fat-saturated axial sections. Patient 2 (F2-IV:7) provided written consent for the use of face recognition in the photographs and video. Muscle analysis involved visual assessment for fatty infiltration, muscle volume loss, and interstitial edema. Objective evaluation was performed using analytical methods that are described elsewhere.[10,11]

Genetic analysis

The DNA was extracted from blood samples using the QIAamp DNA Blood Mini Kit (Qiagen: Hilden, Germany). The DNA was sheared to produce 150- to 250-bp fragments for library preparation. Hybridization was conducted using a whole-exome 39-Mb Exome Research Panel (IDT: Coralville, IA, USA), following size selection, end repair, phosphorylation, and adapter ligation to the DNA fragments according to the manufacturer's protocol. The Exome Library quality control was checked on a Bioanalyzer (Agilent: Santa Clara, CA, USA) and quantified using Qubit (Invitrogen: Carlsbad, CA, USA). The libraries were sequenced as paired-end reads (2×150) for 70−80× coverage on a HiSeq X device (Illumina: San Diego, CA, USA). Germ-line variants were identified by aligning the obtained sequences to the human reference genome (GRCh37/hg19) using the BWA program and analyzed using the Genome Analysis Toolkit best-practices variant-calling pipeline.[12,13] The variants were annotated using the Ensembl (release 89) human gene model, disease annotations against ClinVar, SwissVar, and the licensed Human Gene Mutation Database; population frequencies from the 1000Genome Phase 3, ExAC, gnomAD, and dbSNP databases, and the internal Indian-specific database; and *in silico* prediction algorithms in PolyPhen-2, SIFT, Mutation Taster2, and LRT. The variants were filtered sequentially as follows: 1) variants with a minor allele frequency of ≥0.1 were excluded, 2) phenotype-specific genes with symptoms of congenital myopathy and muscular dystrophy (n=114) (Supplementary Table 1 in the online-only Data Supplement), and 3) segregation of the filtered variants in the family (affected/unaffected). The samples were analyzed based on clinical symptoms using the MedGenome variant interpretation tool Varminer, and the pathogenicity of the variants was assessed based on 2015 American College of Medical Genetics (ACMG) guidelines.[14]

RESULTS

Clinical findings

Patient 1 (F1-IV:2)

Patient 1 was a 28-year-old male born to consanguineous parents, who was evaluated in June 2017 (Fig. 1). He had a normal birth and developmental history, but he experienced difficulty attaining the milestone of running fast. predominant symptom since childhood was frequent tripping while running on uneven surfaces due to foot drop. This patient also had a history since childhood of difficulty in spitting with force, lagophthalmos, hypophonia of speech, mild shoulder girdle weakness, and calf hypertrophy. At 8 years of age he developed progressive lower-limb proximal and distal upper-limb weakness, including in the long flexors and extensors. He also presented with severe truncal and neck muscle weakness.

Ten days prior to the present evaluation, the patient developed exertion-induced palpitations lasting for 20−30 minutes. There was no positive family history. An examination revealed severe and bilateral facial weakness, trismus, hypermobility of the elbow joint, winging of the scapula, a protuberant abdomen, and exaggerated lumbar lordosis. No contractures were present. The motor strength according to modified Medical Research Council (MRC) grading is presented in Table 1. Tendon reflexes were normal except for absent ankle jerks. The patient had an asymmetrical high stepping gait.

The serum concentrations of creatine kinase (CK), lactate dehydrogenase, and lactate were 131 U/L, 267 U/L, and 22 mg/dL, respectively. Liver enzymes and thyroid function were normal. Motor and sensory nerve conduction studies were normal, but electromyography revealed a pattern of chronic denervation and myopathy. Results of repetitive nerve stimulation of the deltoid, trapezius, and nasalis were negative.

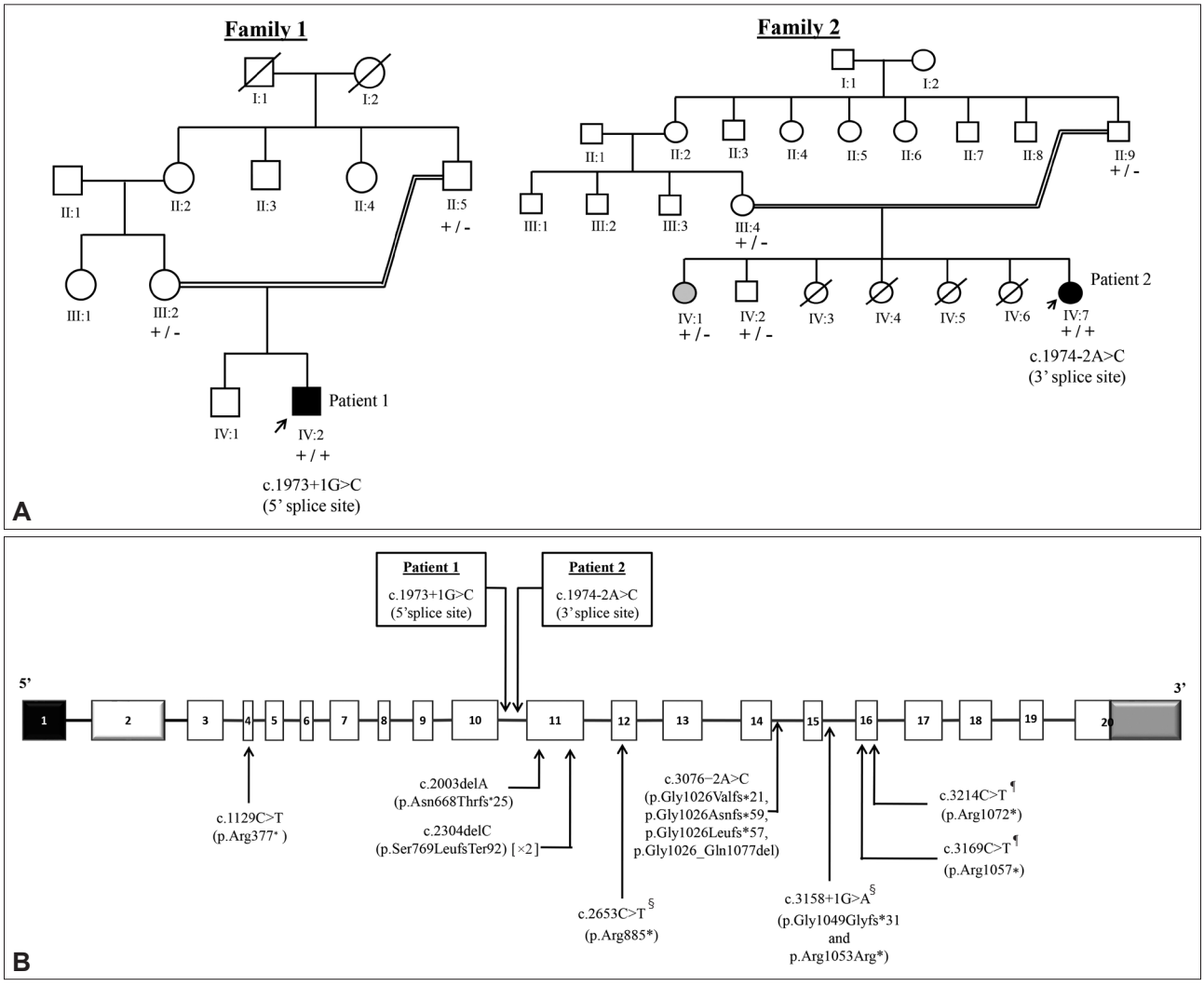

Fig. 1. Family trees of the patients (A) and *MYPN* mutational spectrum (B). A: Pedigree charts of two patients harboring pathogenic variants in the gene (*MYPN*) encoding myopalladin that cause cap myopathy. Males and females are indicated by squares and circles, respectively. Filled and unfilled symbols indicate affected and unaffected individuals, respectively, and an oblique line on the symbol indicates a deceased individual. The gray-shaded individual presented with encephalopathy and seizures. The arrows show the probands. The connecting double line between individuals indicates a consanguineous marriage. The homozygous and heterozygous states for the pathogenic variants are designated +/+ and +/−, respectively. B: Schematic representation of all reported and current mutations and their location on *MYPN*. The pathogenic variants identified in this study are enclosed in the box above the structure and the mutations reported in the literature are shown below it. Variant c.2304delC was reported in two cases from one family and is indicated as "[×2]." Unfilled boxes indicate coding exons, the black box indicates the 5' noncoding region, and the gray box indicates the 3' noncoding region. Introns are indicated by dark lines. Exon numbers are indicated inside the boxes. The sizes of exons/introns are not to scale (transcript ID: NM_032578.4). §The positions of c.2653C>T and c.3158+1G>A were originally reported as exon 13 and intron 16, respectively, according to NM_001256267.1.[8] ¶Compound heterozygous variant.

MRI revealed grade 2b fatty infiltration in the glutei, in the posterior, anterior, and medial compartments of the thigh (2a), and in the anterior leg muscles (right, 2a; left, 2b).[10] An especially noteworthy finding was of pronounced volume loss and fatty infiltration in both the sartorius and gracilis (2b) muscles. There was no evidence of edema on axial T2w fat-saturated imaging (Fig. 2).

Patient 2 (F2-IV:7)

A 23-year-old female, also born to consanguineous parents (Fig. 1), presented in 2013, and had been unable to run fast from early childhood. She had experienced slowly progressive/nonprogressive lower-limb proximal muscle weakness from the age of 11 years and truncal muscle weakness from the age of 20 years. She has easy fatigability while climbing stairs. There were no bulbar symptoms. On examination, this patient had an elongated face, low-set ears, a high arched palate, pes planus, mild ptosis, dysconjugate eye movements, wasting of the temporalis muscle, bilateral facial weakness, and mild scapular winging [Fig. 3, Supplementary Video 1 (in the online-

Table 1. Motor strength according to modified Medical Research Council grading

Muscles	Patient 1 (F1-IV:2)	Patient 2 (F2-IV:7)
Neck muscles		
Neck flexors	1	3
Neck extensors	4	3
Upper limb		
Shoulder abductor	3	4
Shoulder adductor	3	4
Biceps brachialis	4	4
Triceps	4	4
Brachioradialis	4	4
Wrist flexors	4	4
Wrist extensors	4	4
Finger flexors	4	3
Finger extensors	4	3
Small muscles of hand	4	3
Lower limb		
Hip flexors	3	3
Hip extensors	4	3
Hip abductors	5	3
Hip adductors	5	3
Knee flexors	4	3
Knee extensors	5	3
Ankle dorsiflexors	Grades 3 (right) and 2 (left)	3
Ankle plantar flexors	4	4

only Data Supplement)]. The motor strength according to modified MRC grading is presented in Table 1. The tendon reflexes were normal. This patient had a waddling gait and a serum CK concentration of 331 U/L. Motor and sensory nerve conduction studies were normal with no evidence of decrement on repetitive nerve stimulation. At a follow-up conducted by telephone in July 2020 (6 years after presentation) when the patient was 30 years old, her neurological status was stable except for mild dysphagia and slowness in eating from the age of 27 years. She had no cardiac or respiratory symptoms and was able to perform all of the normal activities of daily living, albeit slowly. Her current electrocardiogram (ECG) and two-dimensional echocardiogram (2D-ECHO) were normal.

The proband's elder sister was aged 41 years, and had experienced an encephalopathic illness episode with seizures and cerebellar ataxia at the age of 35 years but made a spontaneous and significant recovery. Unlike the proband, she had no history of muscle weakness and was apparently normal before the encephalopathy episode.

Genetic findings

Genetic sequencing was performed for seven consented individuals (samples from two affected and five unaffected family members). An average of 5.6±0.4 Gb data were generated per samples sequenced with >95% coverage obtained at a depth of ≥20×. Detailed sequencing data and quality metrics shared in Supplementary Table 2 (in the online only Data Supplement). Approximately 30,200 variants per sample were detected, including single-nucleotide variants and indels. Application of the variant filtering strategy (Supplementary Table 3 in the online-only Data Supplement) four variants were shortlisted in each family. Based on clinical correlation and segregation, two different splice-site variants affecting intron 10 in *MYPN* were prioritized in F1 and F2. A homozygous variant, NM_032578.4:c.1973+1G>C, affecting the canonical 5' end splice site of intron 10 of *MYPN*, was found in patient 1 (F1-IV:2) [Fig. 1, Supplementary Table 3 (in the online-only Data Supplement)]. His parents (F1-II:5 and F1-III:2) were confirmed to be heterozygous for the same variant [Fig. 1, Supplementary Table 3 (in the online-only Data Supplement)]. Patient 2 (F2-IV:7) was found to have a homozygous variant, NM_032578.4:c.1974-2A>C, affecting the canonical 3' splice site of intron 10 (Fig. 1). Her unaffected brother (F2-IV:2) and parents (F2-II:9 and F2-III:4) were heterozygous for the splice-site variant [Fig. 1, Supplementary Table 3 (in the online-only Data Supplement)].

Integrative Genome Viewer screenshots of the c.1973+1G>C variant in F1 and the c.1974-2A>C variant in F2 are shown in Supplementary Figs. 1 and 2 (in the online-only Data Supplement), respectively. The splice-site variants found in these patients were not present in reference population databases or an internal Indian-specific database. Both the acceptor and donor splice sites were conserved across species. The Combined Annotation Dependent Depletion (CADD) Phred quality score was 32 for c.1973+1G>C and 35 for c.1974-2A>C. The variants were predicted to affect the mRNA splicing, leading to aberrant transcripts by *in silico* tools such as MaxEntScan, SpliceAI, and MutationTaster2 (NNSplice). The variants were classified as pathogenic according to ACMG guidelines.[14] The elder sister of patient 2 (F2-IV:1), who had an unrelated episodic encephalopathic illness, was heterozygous for the splice-site variant c.1974-2A>C, as confirmed by Sanger sequencing.

DISCUSSION

This report describes two unrelated patients with congenital myopathy secondary to novel homozygous *MYPN* pathogenic variants [intron 10, c.1973+1G>C (5' splice site); intron 10, c.1974-2A>C (3' splice site)]. The patients presented with the early-childhood onset of slowly progressive/nonprogressive proximodistal muscle weakness. Patient 1 had predominant foot drop and finger weakness, and prominent facial and axial muscle weakness. Previously reported patients demonstrated

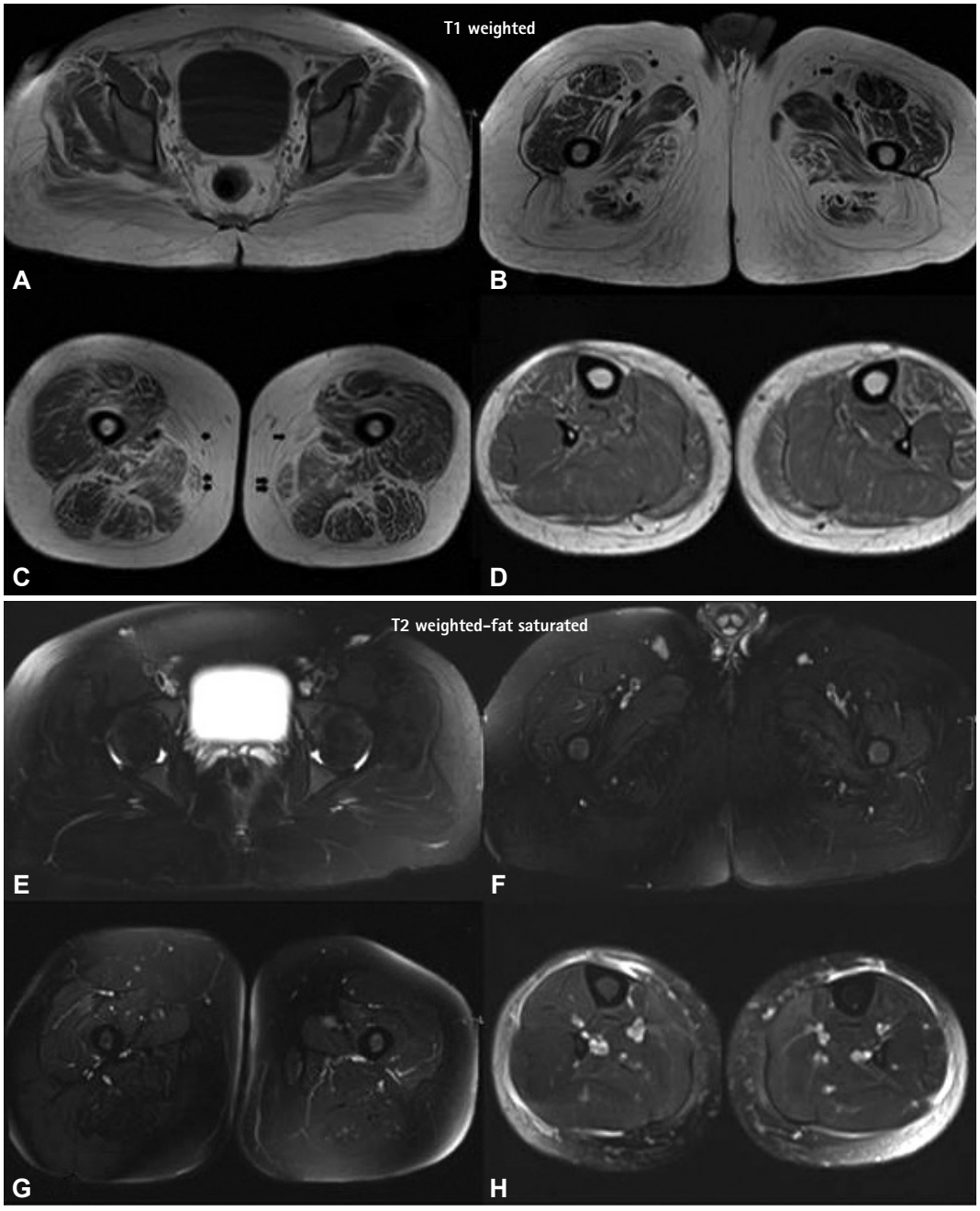

Fig. 2. Patient 1. Axial T1-weighted magnetic resonance imaging (MRI) of the lower-limb muscles with the Mercuri score, showing fat replacement and atrophy: (A-D) in the gluteus maximus and medius (2b), the gluteus minimus (2a), the posterior compartment of the thigh (2b), and the anterior and medial compartments of the thigh (2a). Note the distinctive and severe volume loss and fatty changes in the sartorius (2b) and gracilis (2b). (E–H) Axial T2-weighted fat-saturated MRI of the lower-limb musculature showing no significant edema in the involved muscles. Lt: left, Rt: right.

consistent features of childhood-onset proximodistal weakness with foot drop, finger flexor and extensor weakness, profound axial muscle weakness, and (less commonly) cardiac dysfunction.[7-9]

The recessive inheritance of *MYPN* mutations was first reported by Miyatake et al.[7] in 2017. They described four unrelated Japanese patients with childhood-onset, slowly progressive muscle weakness, initially involving the distal extremities and the neck flexors. Cardiac hypertrophy and diffuse hypokinetic heart with a first-degree atrioventricular block were noted in one case each.[7] The second report came from France and involved three patients who had a neonatal to childhood-onset, slowly progressive proximodistal myopathy,[8] and the third report from Italy described two siblings with congenital

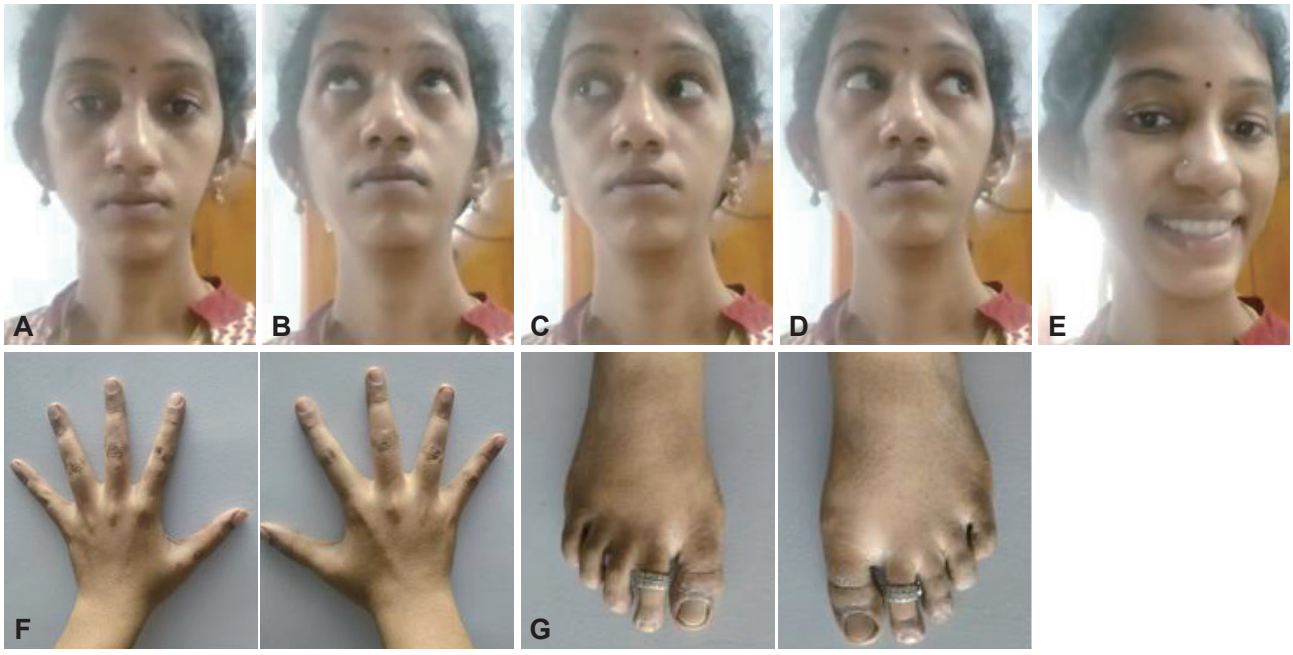

Fig. 3. Patient 2. A–E: Photographs of the patient taken at age 30 years. Note the elongated face, low-set ears, mild ptosis, mild facial weakness, and normal eye movements. F and G: Hands and feet appear normal except for mild hammertoes.

to adult-onset, slowly progressive distal predominant weakness.[9] To date, recessive *MYPN*-related pathogenic variants causing congenital myopathy have been reported in nine patients from seven families (Table 2).[7,8]

All *MYPN*-related cap myopathy patients reported to date had biallelic truncating or loss-of-function mutations.[7,8] Similarly, both of the unrelated patients in the present study had homozygous splice-site *MYPN*-related pathogenic variants affecting intron 10, implying a loss-of-function mechanism.

The preferential muscle involvement pattern in our patients is similar to that described in previous reports, but the distal muscle involvement in patient 2 was mild. Patient 1 had hypophonia of speech, while one of the two Italian patients described by Merlini et al.[9] had hypernasal speech. At 30 years of age, the patients described in the present study had minimal motor disability, similar to most previously reported cases.[7-9]

Lornage et al.[8] described three adult patients in France with cap myopathy with neonatal hypotonia, swallowing difficulties, facial weakness, respiratory difficulty, and upper-limb weakness from early childhood, along with skeletal deformities and progressive limb-girdle, axial, and distal weakness. Cardiac rhythm abnormalities and ventricular hypokinesia have been described for five of the nine cases in the three previously published reports.[7-9] Patient 1 in the present study had a brief episode of intermittent palpitations at the age of 28 years, but ECG and 2D-ECHO findings were normal.

Merlini et al.[9] reported marked intrafamilial variability in age at onset and disease severity. The proband had the classical "hanging great toe sign" and mild finger contractures. His sister, in her 30s, also had a milder phenotype but was not symptomatic. The patients in the present study had variability in the severity and degree of distal muscle involvement. Neither patient had contractures, but patient 1 had hyperextensibility at the elbows. In 2006, Cuisset et al.[15] reported on three patients in France with pathologically confirmed cap myopathy from the same kindred, all of whom had congenital to childhood-onset weakness with a variable phenotype.

The term "cap myopathy" was first coined by Fidziańska et al.[16] in 1981, based on muscle histopathology findings in a 7-year-old male. A vastus lateralis muscle biopsy revealed a densely staining substance forming a partial ring around the fibers, appearing like a cap, that lacked ATPase activity. Electron microscopy (EM) demonstrated that these cap-like structures contained abnormally arranged myofibrils with abnormal sarcomeres. Loosely organized filaments that extended between the Z lines appeared to lack myosin filaments and projected along the sarcomere. The authors concluded that these morphological changes occurred due to a failure of the fusion process and filament synthesis during muscle development; however, no genetic tests were conducted.[16]

In 2002, Fidziańska[17] reported on four unrelated individuals with childhood-onset muscle hypotonia, weakness, skeletal abnormalities, and respiratory insufficiency. Histopathology and EM examinations revealed that the muscle tissue contained peripherally located structures resembling caps that lacked ATPase and fast myosin activity, but which were rich in desmin, tropomyosin, and alpha-actinin, and abnormally arranged myofibrils. These cases were believed to have con-

Table 2. Comprehensive details of salient features of current patients and published individuals

Parameters	Current study		Miyatake et al.[7]				Lornage et al.[8]			Merlini et al.[9]	
	Patient 1	Patient 2	Patient 1	Patient 2	Patient 3	Patient 4	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2
Origin	South Indian	South Indian	Japanese	Japanese	Japanese	Japanese	French (siblings)	French (siblings)	African	Italian (siblings)	Italian (siblings)
Sex	M	F	F	M	F	M	F	M	M	M	F
Consanguinity	Yes	Yes	Yes	No	NA	No	Yes	Yes	Yes	Yes	Yes
Family history	No	No	Yes	No	No	No	Yes	Yes	No	Yes	Yes
Age(s) at evaluation (years)	27, 30	23	48	35	55	37	34	50	44	14, 23, 26, 35	26
Age at onset (years)	Early childhood	Early childhood	25	4-5	First decade	First decade	Birth	3 months	Early childhood	Infantile	Not clear
Disease course	Slowly progressive	Slowly Progressive	Slowly progressive	Slowly progressive	Slowly progressive	Slowly progressive	Slowly progressive	Progressive (wheelchair bound at 49)	Slowly progressive	Slowly progressive	Slow, non-progressive
Symptom at onset	Falls due to tripping (foot drop)	Difficulty in running fast	Gait abnormality with foot drop	Foot drop	Foot drop	Foot drop	Mild hypotonia, swallowing difficulties, lower limbs contractures	Swallowing difficulties, delayed motor development	UL limb weakness	Distal extremity weakness	Distal extremity weakness
Proximal muscle weakness	Yes, moderate	Yes, UL – mild, LL - moderate	Yes, severe	Yes, mild	Yes, moderate	Yes, moderate	Yes	Yes	Yes	Yes, moderate	Yes, mild
Distal muscle weakness	Yes, mild	Yes, moderate	Yes, severe	Yes, mild	Yes, moderate	Yes, moderate	Yes	Yes, severe finger extensors and flexors	Yes, severe finger extensors and flexors	Yes, severe	Yes, mild
Axial muscle weakness	Yes, severe	Yes moderate	Yes, severe	Yes, mild	Yes, moderate	Yes, moderate	Yes	Yes	Yes	Yes, severe	Yes, mild
Atrophy of muscles	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes, mild
Foot drop	Yes, severe	Yes, mild	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Foot drop with hanging great toe	Yes, mild
Ptosis	No	Yes	No	No	No	No	Yes	Yes	No	Yes	No
Facial weakness	Moderate	Moderate	Yes	Yes	No	Yes	Yes	Yes, severe	No	Yes	Yes, mild
Bulbar symptoms	Hypophonia	Yes, mild	No	No	No	No	No	No	No	Nasal speech	No

Table 2. Comprehensive details of salient features of current patients and published individuals (continued)

Parameters	Current study		Miyatake et al.[7]				Lornage et al.[8]			Merlini et al.[9]	
	Patient 1	Patient 2	Patient 1	Patient 2	Patient 3	Patient 4	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2
Respiratory problems	No	No	No	No	No	No	Reduced FEV 57%, NIV ventilation	Recurrent respiratory infections	Reduced pulmonary vital capacity 46%	No	No
Skeletal deformities	None	Yes	Pectus excavatum	Pes cavus	Equinus foot, scapulae alatae	NA	Pectus excavatum, elongated face, tubular nose and low-set ears,	Elongated face, low-set ears, and tubular nose	Elongated face, tubular nose and low-set ears, pectus excavatum	Pes Cavus	NA
Cardiac abnormality	Intermittent palpitations EKG, 2D-ECHO normal	No symptoms, EKG and 2D-ECHO normal	Hypertrophy	Nil	Nil	Diffuse hypokinesia, EF 52%, first-degree AVB	Nil	Sinus tachycardia, increased QRS duration and left axis deviation	Nil	1st-degree AV block (PR 208 ms), leftanteriorhemiblock (QRS 122 ms) with high ventricular voltages. 24-hour Holter: marked sinus arrhythmia with 42 to 120 beats/min	NA
Status at evaluation time	Ambulant with high stepping gait	Ambulant, slow	Severe weakness, wheelchair bound 15 years after onset	Mild and diffuse	Mild to moderate weakness, ambulant	Moderate weakness in LL, ambulant	Moderate weakness, ambulant	Moderate weakness, ambulant	Moderate weakness, ambulant	Ambulant with waddling gait	Ambulant
Serum CK level (IU/L)	131	33	18 (normal 45–163)	13 (normal 0–40)	26 (normal 40–160)	35 (normal 62–289)	NA	NA	NA	Normal	Normal
Muscle CT/ MRI	Gluteus maximus, Hamstrings> Quadriceps: fatty infiltration. Fatty atrophy in EDL, EHL, TA and posterior compartment	Not done	Not done	Not done	Not done	Not done	Globally thin muscle bulk, fatty infiltrations in tongue, latissimus dorsi, pelvic girdle, lower limbs	Not done	Not done	Muscle CT at age 14: hypodensity of the sartoriusand upper part of gracilis. MRI at age 35: scattered abnormal high-intensity in tongue	NA

AV: atrioventricular block, EDL: extensor digitorum longus, EHL: extensor hallucis longus, LL: lower limb, NIV: non-invasive ventilation, TA: tibialis anterior, UL: upper limb, 2D-ECHO: two-dimensional echocardiogram.

genital myopathy with cap structures, and the entities were regarded as "Z-line disorders," possibly caused by defective myofibrillogenesis. These cases were divided into fatal and nonfatal forms, correlating disease outcome with the degree of cap structures identified.[17]

Whole-body muscle MRI performed on one patient by Lornage et al.[8] demonstrated patchy fatty infiltration of the tongue. The scapular girdle muscles were thin and atrophic, and without fatty infiltration, while marked fat replacement of the latissimus dorsi, rotator, and extensor muscles of the back at the lumbar area was observed. The pelvic muscles were thin and infiltrated with fat, and the thighs exhibited mild atrophy and fatty infiltration in sartorius and gracilis muscles, which were remarkably atrophic; fatty infiltrations of the peroneus muscles were noted in the leg muscles.[8] Muscle computed tomography conducted on the index case at the age of 14 years in the study of Merlini et al.[9] revealed distinct hypodensity of the sartorius muscle and to a lesser extent of the upper part of the gracilis. MRI performed when the patient was aged 35 years revealed scattered abnormal high-intensity areas in the internal tongue muscles and the posterior cervical muscles.[9] Similar to these reports, patient 1 in the present study exhibited striking and pronounced involvement of the sartorius and gracilis muscles. In contrast to the previously described whole-body report, the gluteus maximus, other thigh muscles, tibialis anterior, and peroneus longus also demonstrated mild to moderate fat infiltration.

While the recessive loss-of-function pathogenic variants in *MYPN* (nonsense, frameshift, and splice-site variants) are attributed to the cap myopathy phenotype, heterozygous missense mutations have been reported in various forms of inherited cardiomyopathies due to aberrant protein–protein interactions.[4,6] However, Purevjav et al.[4] found two heterozygous nonsense mutations (p.R885X and p.Q529X) in hypertrophic and restrictive cardiomyopathy patients, respectively, and suggested that the pathogenicity in *MYPN*-related cardiomyopathy patients can be attributed to both dominant-negative and haploinsufficiency mechanisms. It was particularly notable that none of the heterozygous carriers in *MYPN*-related cap myopathy families were reported to have cardiomyopathies, including the two families described herein.

All previously reported cases as well as those presented here had normal serum CK concentrations. The muscle histology of patients with *MYPN*-related pathogenic variants demonstrated type 1 fiber predominance and the presence of subsarcolemmal caps,[7,8] which were associated with a dramatic reduction of myopalladin protein expression. In the case reported by Merlini et al.,[9] the muscle biopsy pathology demonstrated only minimal changes, with internal nuclei and type 1 fiber predominance, but no caps or nemaline bodies. Since the genetic analyses for both patients reported herein revealed homozygous pathogenic mutations in *MYPN* with a good phenotype correlation, an invasive muscle biopsy procedure was not considered. The first line of investigation for suspected cases of inherited neuromuscular disorders is currently genetic testing.

In conclusion, this is the first description of recessive *MYPN*-related cap myopathy coming out of from South Asia, with the present patients being only the tenth and eleventh genetically confirmed cases reported in the English literature. The course is generally slow, with minimal motor disability, similar to other milder forms of nemaline rod myopathy. However, it may be essential to identify such cases early since they may have cardiac abnormalities that can be detected and treated appropriately. Nevertheless, the patients reported here had not yet displayed any cardiac manifestations. Not finding nemaline rods in the muscle biopsies is a limitation of this study.

Supplementary Video Legend

Video 1. Video of patient 2 taken at age 30 years. Note the elongated face, low-set ears, and facial weakness. The eye movements are normal and physical disability is minimal.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2021.17.3.409.

Author Contributions

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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