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CASE REPORT

Novel mutation of the *FHL1* gene associated with congenital myopathy and early respiratory muscles involvement: a case report

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ABSTRACT

Background: Congenital myopathies are a diverse group of diseases that share features from the early onset of symptoms in the first year of life, such as hypotonia, muscle weakness, and developmental delays, and are often associated with respiratory insufficiency and feeding difficulties.

Case presentation: Here, we report an 8-year-old boy having hypotonia and signs of respiratory insufficiency that ended with tracheostomy and ventilator-dependent status. Muscle biopsy showed histological findings of congenital fiber-type disproportion myopathy. The whole exome sequencing revealed a novel hemizygous missense variant (c.530A > C p.Gln177Pro) that confirms the diagnosis of *FHL1*-associated congenital myopathy.

Conclusion: The findings in this study help to expand the genetic and mutational spectrum of the *FHL1* gene associated with respiratory insufficiency and help in formulating a precise strategy for prognosis and future management of patients.

Keywords: Congenital myopathy, *FHL1*, hypotonia, congenital fiber-type disproportion myopathy, and X-linked myopathy.

Introduction

Congenital myopathy (CM) refers to a heterogeneous group of inherited neuromuscular disorders that are exhibited at birth or within the first few months of life (1). CMs are characterized by a delay in gross motor milestones, nonprogressive muscular hypotonia, and immunohistochemical findings, which ranges from myopathic to overtly dystrophic changes on muscle biopsy. These features impair the ability of muscles to contract, ultimately resulting in the loss of muscle fibers (2). CMs are associated with structural changes in some rare disorders with variable degrees of severity, including central core disease, nemaline myopathy, and congenital fiber-type disproportion myopathy (2).

FHL1 is a member of four-and-a-half LIM domains protein 1 located on the Xq26.3 chromosome. The LIM domain proteins play an important role in sarcomeres synthesis and muscle mass regulation, and act as docking sites in a protein complex assembly based on a highly conserved cysteine-rich zinc-binding motif having a double zinc finger domain (3). Furthermore, *FHL1* has three isoforms that are highly expressed in skeletal and cardiac muscles known as FHL1A, FHL1B, and FHL1C (4). Recently, *FHL1* was identified as a causative gene in several muscle myopathies, including X-linked myopathy with postural muscle atrophy [Online Mendelian Inheritance in Man (OMIM) 300696], X-linked dominant scapuloperoneal myopathy (OMIM 300695), reducing body myopathy (OMIM 300717), rigid spine syndrome, and Emery–Dreifuss muscular dystrophy (OMIM 300696) (5). Up until now, the exact pathomechanism associated with *FHL1* mutations is unknown; however, proper genotype–phenotype correlations help in understanding the underlying *FHL1* gene pathogenesis.

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CMs are not regarded as progressive disorders; however, additional factors such as respiratory muscle weakness, scoliosis, and kyphoscoliosis may coexist, which are associated with extrapulmonary restriction of the lungs, resulting in the impairment of the pulmonary function. Additionally, they compromise the ability of the airways to clear the secretion and to predispose pneumonia and aspiration. As CMs usually involve the muscles of respiration, many patients require ventilatory assistance for a few months or years after the onset of the symptoms.

Herein, using whole exome sequencing, we report a novel hemizygous missense mutation in the *FHL1* gene in a patient with congenital fiber-type disproportion myopathy with recurrent aspiration. We reviewed all the previously reported cases to identify the different *FHL1* gene mutations that may lead to respiratory impairment in patients with CM and carried out genotype–phenotype correlation for *FHL1*-associated CM.

Case Presentation

The patient is an 8-year-old boy, who is the first and only child of healthy, non-consanguineous parents (Figure 1A). After an uneventful full-term pregnancy, the baby was born by an uncomplicated cesarean section due to prolonged rupture of the membrane; subsequently, he was discharged with his mother in a good condition. At the age of 5 months, the proband had hypotonia with failure to thrive and a relatively weak cry. The proband had developmental delays in the form of gross motor, speech, and language delays. In the following months, he required frequent admissions to the hospital and Pediatrics Intensive Care Unit (PICU) due to respiratory failure, recurrent chocking attacks, and aspiration pneumonia. His medical history included chronic lung disease and bronchial asthma. The family history was unremarkable, except for recurrent miscarriages for the mother where routine investigations were conducted,

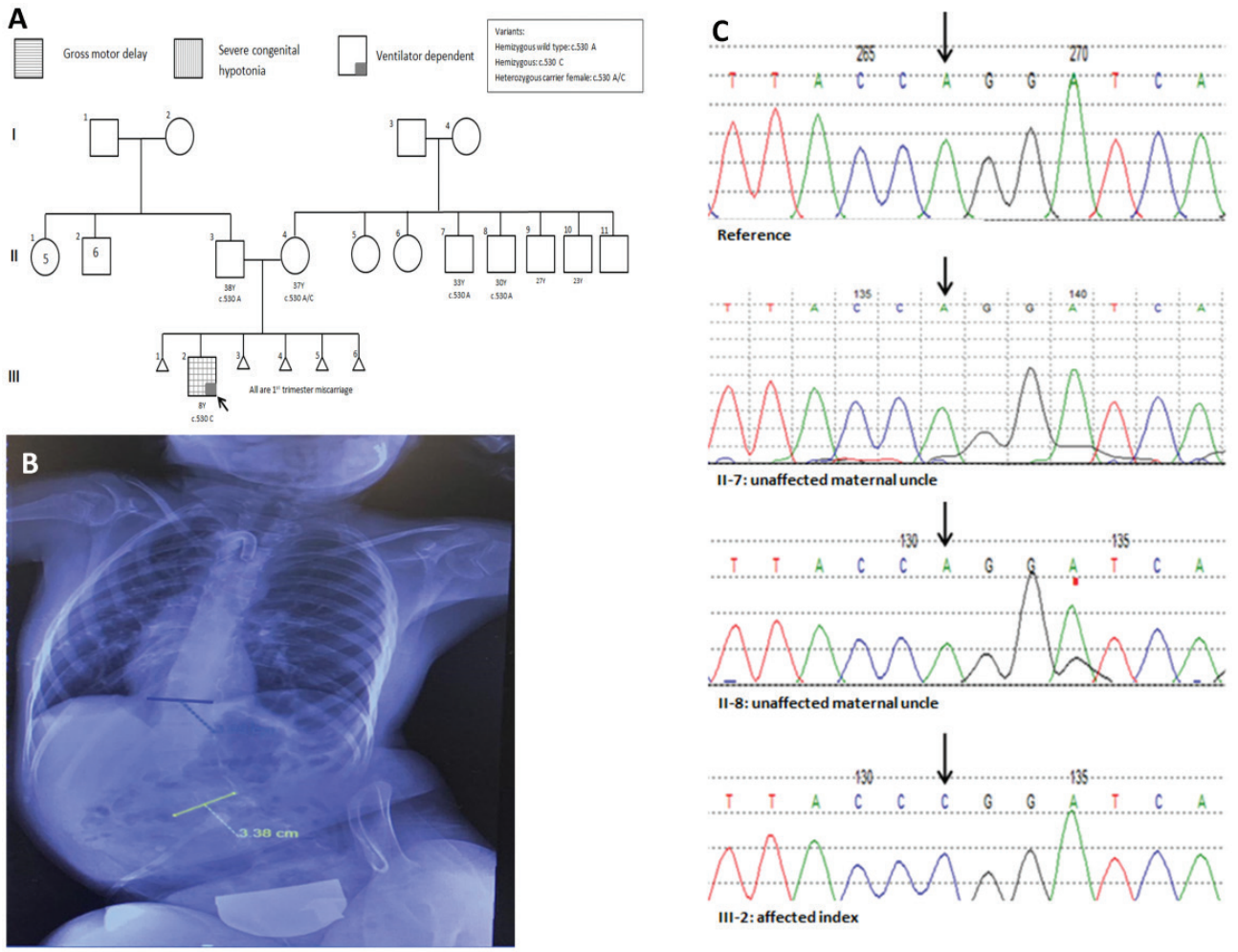

Figure 1. *(A) Pedigree of the index family. (B) Thoracic-spine radiograph showing moderate thoracolumbar dextroscoliosis estimated by Cobb's angle measuring 37° taken from the upper end plate of T12-2 lower end plate of the vertebral bodies, and there is a significant downward right-sided pelvic tilt. (C) DNA chromatogram, the index, and two healthy family members.*

and all were normal including chromosomal analysis and placental histological findings.

On physical examination, the boy weighted 17.8 kg (< 3rd percentile), was 108 cm long (< 3rd percentile), and his head circumference was 50.5 cm (10th–25th percentile). He had dysmorphic features, including the myopathic face, low hairline, bilateral epicanthal folds, and gingival hyperplasia.

Neurological examination revealed a generalized weakness that mainly involved both upper and lower limbs with poor head control and hyporeflexia. Joint hyperlaxity was observed through musculoskeletal examination without any signs of contracture. On auscultation, the air entry was reduced and crackles were heard over all the lung fields. A thoracic spine X-ray revealed bilateral perihilar air space opacity and dextroscoliosis with a Cobb angle of 37° taken from the upper end plate of T12-2 lower end plate of the vertebral bodies (Figure 1B). His electromyogram (EMG), nerve conduction study, and brain Magnetic resonance imaging (MRI) were all normal. During his disease course, his condition did not improve and he was frequently admitted and also needed to be intubated and ventilated; he was admitted to the PICU several times due to hypercarbia. By the age of 18 months, the patient was tracheotomized and became ventilator-dependent. Now, at the age of 8, the patient is stable and saturating well on a home ventilator. The proband is having a global developmental delay, wherein he is unable to sit or stand independently; however, according to his mother, he can write alphabets, numbers, and talk fluently for his age.

Muscle biopsy, from an unspecified site, was carried out at the age of 9 months. Histological analyses of the muscle showed a marked variation in muscle fibers size, due to the presence of evenly distributed fibers around the atrophic fibers, alternating with the normal-sized fibers. Additionally, ATPase reactions revealed type 1 fiber atrophy, up to 50% smaller in size than type 2 fibers, with a tendency of type 1 fibers clustering. The presence of atrophic fibers with sarcolemmal folds was confirmed using ultrastructural examination. The fiber illustrated disorganization of myofibrils; however, no ring fibers were observed. There were occasional collections of enlarged mitochondria with cristae. Therefore, congenital fiber-type disproportion myopathy was compatible with the histomorphology of the biopsied muscle.

Chromosomal analysis, array Array based comparative genomic hybridization (CGH), and Sanger sequencing of *RYR1* and *TMP3* genes were unremarkable. Additionally, molecular testing for *SMN* gene and *SNRPN* gene was carried out using standard methods and the result were unremarkable. Subsequently, trio-Whole Exome Sequencing (WES) was carried out for the proband and parents using standard methods. The WES revealed a novel hemizygous missense variant (c.530A>C; p.Gln177Pro) in exon 6 of the *FHL1* gene (NM_001159702.3) located on chromosome Xq26.3 (Figure 1). Using Sanger sequencing, the identified variant segregated perfectly from the disease phenotype and was found in the mother in a heterozygous status, while the father and two maternal uncles' results revealed normal wild type. This variant classified as likely pathogenic based on the American College of Medical Genetics (ACMG) guidelines and has not been previously observed in large-scale sequencing databases, such as Exome Aggregation Consortium, dbSNP/1,000 genome, Exome Sequencing Projects or Genome Aggregation Database, and local database. This substitution (c.530A>C; p.Gln177Pro) was predicted to be deleterious by several online computational prediction tools [PolyPhen2, MutationTaster, and Sorting Intolerant From Tolerant (SIFT)]. Complete attention to the *TPM3*, *ACTA1*, and *RYR1* genes did not reveal any possible diseases-causing variants in any of them. Furthermore, manual analysis of the raw data generated from WES, including Binary Alignment Map (BAM) file, failed to identify deletion or duplication in the above-mentioned gene.

Discussion

CMs are diagnosed based on clinical features associated with respiratory insufficiency, feeding difficulties, and histological changes that are seen in the patients' biopsied muscles. However, of late, genetic testing is considered as one of the preferred methods since it can detect a breadth of phenotypic variability associated with each gene (2). Recently, most of the studies have identified the mutations in the *FHL1* (which plays a critical role in the development and function of the skeletal muscles) as a causative gene in different human myopathies, considering its high level of expression in the skeletal as well as cardiac muscles (6).

In the previous studies, *FHL1* mutation has been identified in various phenotypes of X-linked myopathy, such as X-linked dominant scapuloperoneal myopathy, distal myopathy with hypertrophic cardiomyopathy, Emery–Dreifuss muscular dystrophy with rigid spine, and many other phenotypes (7). However, the association between *FHL1* mutation and respiratory insufficiency is discussed without clear phenotype delineation. Only a few studies have identified the coexistence of respiratory impairment in association with *FHL1* mutation in their patients (Table 1).

In this study, we report a patient with a novel hemizygous missense mutation (c.530A>C; p.Gln177Pro) in exon 6 of the *FHL1* gene associated with congenital myopathy and early respiratory muscle involvement. The identified mutation changes a highly conserved Gln amino acid at position 177 into a Pro amino acid. Glutamine is a polar amino acid, while proline is a hydrophobic aliphatic amino acid. This mutation (p.Gln177Pro) results in secondary structure disability and improper *FHL1* function. There are around 12 different isoforms in the RefSeq and Ensemble database for the *FHL1* gene, and 9 out of 12 results in the same protein changes from Gln to Pro at different amino acid positions (177 or 206), and in the three remaining isoforms the variant is considered as a non-coding exon. The *FHL1* protein consists of four

Table 1. *FHL1 mutations, clinical characteristics and respiratory involvement of the reported cases.*

Gender	Onset of symptoms	Phenotype/Muscle statues/Major clinical findings	Course of respiratory disease	Mutation	Reference
M	5 months	CFTD phenotype/generalized weakness and scoliosis	Recurrent respiratory failure and aspiration pneumonia since the age of 5 months/tracheostomy at the age of 18 months	c.530A > C	Present report
M	6 years	EMDM phenotype/muscle hypertrophy, dysphonia due to vocal cord palsy and swallowing difficulties	Respiratory insufficiency, FVC was reduced/required NIV support died at the age of 31.	c.817dup	(4)
M	1 year	EMDM phenotype/stiff neck and scoliosis	Respiratory insufficiency, FVC was reduced/required NIV support died from respiratory failure at the age of 37.	c.332_688del	(4)
N.A	30 years	XMPMA phenotype/myopathic change seen on the biopsied muscle.	Respiratory insufficiency	672 C > G	(9)
N.A.	35 years	Becker muscular dystrophy phenotype/and muscle hypertrophy.	Respiratory insufficiency	c.381_382insATC	(9)
M	42 years	Becker muscular dystrophy phenotype/experience difficulties with walking at the age of 42, and wheelchair-bound.	Respiratory insufficiency, died at the age of 52.	c.381_382insATC	(9)
F	6 years	XMPMA phenotype/and kyphoscoliosis	Respiratory Insufficiency	c.672 C > G	(10)
M	15 years	XMPMA phenotype/EMG showed myopathic and neurogenic changes	Respiratory insufficiency	c.672 C > G	(10)
M	45 years	XMPMA phenotype/EMG showed myopathic and neurogenic changes	Respiratory insufficiency	c.672 C > G	(10)
M	47 years	XMPMA phenotype/EMG showed myopathic and neurogenic changes.	Respiratory failure started in adulthood and died at the age of 47	c.672 C > G	(10)
F	4 months	Head lag/axial hypotonia	Respiratory insufficiency	c.367G > A	(11)
M	1 year	Head drop, scapular muscle amyotrophy, abolished reflexes/ proximal muscle weakness, and muscle hypotrophy	Respiratory insufficiency, cardiac arrest at the age of 3.	c.369C > A	(11)
M	2 years	Axial and limb girdle symmetric weakness/wheelchair-bound and diffuse weakness.	Respiratory insufficiency	c.395G > T	(11)
M	6 years	Multiple contractures/severe axial weakness with associated mild limb-girdle weakness, dysphonia, and dysphagia/rigid spine, and hypertrophic cardiomyopathy	Respiratory insufficiency	c.817dup	(11)
M	9 years	Difficulties in sport activities/axial and limb-girdle weakness, distal weakness, and rigid spine	Mild respiratory involvement	c.377G > A	(11)
M	48 years	Lower limb-girdle weakness, axial weakness, hypertrophic cardiomyopathy, cardiac arrhythmia/severe axial weakness, and difficulties in walking	Respiratory insufficiency	c.827G > A	(11)

Continued

Gender	Onset of symptoms	Phenotype/Muscle statues/Major clinical findings	Course of respiratory disease	Mutation	Reference
F	<2 years	Wheelchair-dependent at the age of 3/proximally pronounced diffuse weakness/spinal rigidity, and scoliosis	Respiratory insufficiency, BiPAP at the age of 4, tracheotomy at the age of 7.	c.367C > T	(8,12)
M	1 year	Progressive loss of ambulation and generalized muscle hypotrophy, wheelchair-dependent at the age of 31 months, progressive severe contractures, and mild scoliosis	Respiratory insufficiency, NIV support	c.369C > A	(8,12)
F	2 years	Progressive generalized muscle hypotrophy with severe truncal and limb weakness at the age of 5, inability to sit or ambulate eventual flaccid paralysis.	Respiratory insufficiency died at the age of 6.5.	c.395G > T	(8,12)
F	5 years	Limb-girdle weakness and scapular winging, dysphagia. Wheelchair-dependent at the age of 8/progressive weakness, pronounced in neck and trunk, and scoliosis	Respiratory insufficiency, night BiPAP at the age of 8.	c.369C > G	(8,12)
M	5 years	Predominantly proximal muscle weakness, wheelchair-bound at the age of 8 , and mild scoliosis.	Respiratory insufficiency, ventilatory support at the age of 11	c.458G > A	(8,12)
M	7 years	Predominantly proximal muscle weakness, generalized muscle hypotrophy, kyphoscoliosis, contracture, wheelchair dependent at the age of 14.	Moderate respiratory insufficiency on BiPAP at the age of 17.	c.457T > C	(8,12)
M	13 years	RSS/scoliosis/muscle weakness and atrophy in the sternomastoid, trapezius, paravertebral, pelvic girdle, and proximal lower limb muscles.	Mild respiratory involvement	c.451–459del	(14)

F = Female; M = Male; CFTD = congenital fiber-type disproportion myopathy; XMPMA = X-Linked Myopathy with Postural Muscle Atrophy; RSS = Rigid spine syndrome; EDMD = Emery-Dreifuss muscular dystrophy; EMG = Electromyogram; NIV = Non-invasive ventilation; BiPAP = Bilevel Positive Airway Pressure; FVC = Forced Vital Capacity.

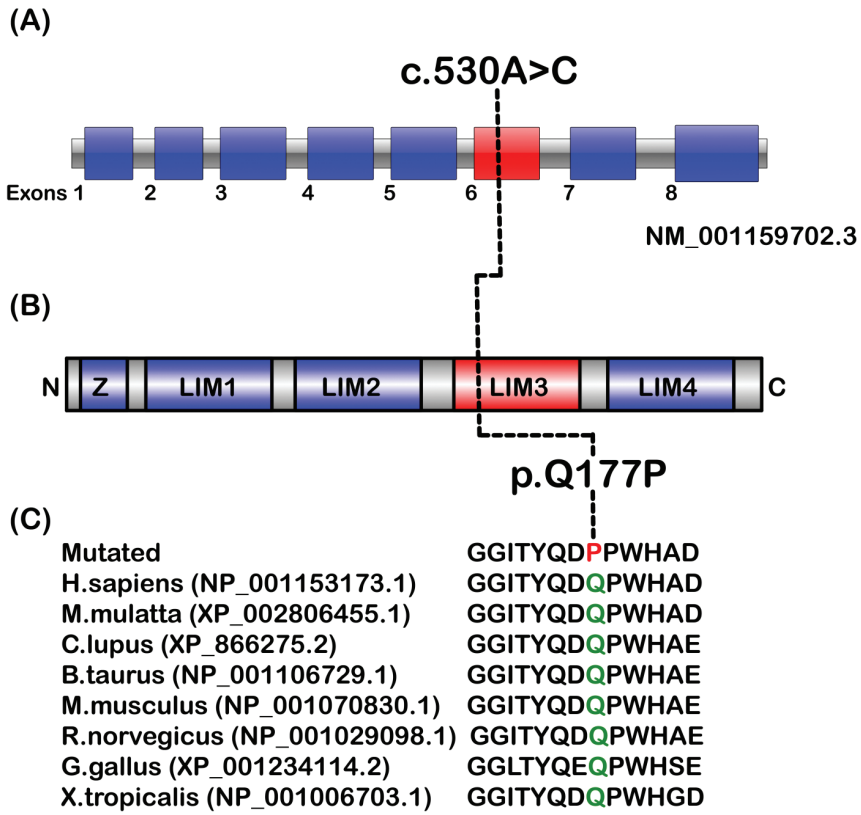

Figure 2. *(A-B) Schematic representation of FHL1 exons and protein domain representation. FHL1 consists of four LIM domains (LIM1–4), an N-terminal, and a half-LIM domain [Z]. (C) The mutation identified in the present study is located in the highly conserved LIM 3 domain.*

LIM domains (LIM1–4), a half-LIM domain (Z), and an N-terminal and C-terminal (Figure 2B). The mutation (p.Gln177Pro) identified in our patient is located in the highly conserved LIM3 domain (Figure 2B,C).

Some of the previously reported patients who had *FHL1* mutations were severely affected, as they required ventilatory support either permanently or while sleeping, and had various symptoms from childhood to late adulthood (4,8). About five patients died from respiratory failure and the age of the deceased individuals ranged widely from the age of 6 to 50 (4,8–10). Until now, few pathogenic mutations in the *FHL1* gene have been reported and mostly they appear in the second and fourth LIM domains. The mutations in the *FHL1* gene were identified at positions c.367C>T, c.369C>G, c.395G>T, and c.672C>G, where c.367C>T, c.369C>G, and c.395G>T were reported mostly in early childhood, while the c.672C>G variant has been associated with the later onset of the symptoms (4,8–10). Other mutations, such as c.381_382insATC, c.827G>A, c.457T>C, c.377G>A, and c.451–459del, have been associated with various phenotypes. However, most of them present at a later stage with respiratory insufficiency (8,9,11–14). Because of the small number of available patients with an unclear description of respiratory status, there is no clear phenotype–genotype correlation neither with the onset nor with severity of the respiratory complications.

Conclusion

The findings in this study increase the mutational spectrum of the *FHL1* gene associated with respiratory insufficiency and also ensure that clinicians and respiratory therapists are aware of the respiratory involvement in the patients with *FHL1* gene mutations. Further studies are required to dissect the pathophysiology of the *FHL1* mutations in terms of respiratory muscle involvement to obtain a precise future management strategy.

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List of Abbreviations

ACMG	American College of Medical Genetics
ATP	Adenosine triphosphate
BAM	Binary Alignment Map
CGH	Array based comparative genomic hybridization

FHL1	Four-and-a-Half Lim Domains 1
LIM	LIM-domain proteins 1
MRI	Magnetic resonance imaging
OMIM	Online Mendelian Inheritance in Man
PICU	Pediatrics Intensive Care Unit
SIFT	Sorting Intolerant From Tolerant
WES	Whole Exome Sequencing

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The authors of this article have no affiliations or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

Consent for publication
Informed consent was obtained from the parents.

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