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Case Report

Myofibrillar myopathy caused by a novel FHL1 mutation presenting a mild myopathy with ankle contracture

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ABSTRACT

FHL1-related myopathies are clinically heterogeneous, involving skeletal and cardiac muscles. Overlapping clinical features include joint contractures, rigid spine, scapuloperoneal weakness and cardiac diseases. Histopathologically, reducing bodies are the most characteristic finding, but not present in all FHL1-related cases. Non-specific dystrophic pathology without reducing body is usual in the forms of X-linked myopathy with postural muscle atrophy, Emery-Dreifuss muscular dystrophy and isolated hypertrophic cardiomyopathy. Here, we describe a patient with mild weakness with ankle contracture. We finally concluded he has a FHL1-related myopathy at an extreme end of phenotypic spectrum of FHL1 myopathy, which one might miss to recognize as a form of myopathy. The genetic variant was detected by whole exome sequencing, and its pathogenicity was clearly confirmed with pathological and biochemical studies. This is the first FHL1 case with a mildest phenotype backed by biochemical/genetic evidence. This report will help clinicians hesitating to further evaluate mild cases to better correlate the genotype to the phenotype.

1. Introduction

The FHL1 protein has four and a half LIM domains, comprised of highly conserved sequences with cysteine-rich double zinc finger motifs. [1] FHL1 has 3 isoforms with different LIM domain composition (FHL1A, FHL1B and FHL1C). It is abundant in striated muscles, and known to have roles in sarcomere assembly, cytoskeletal rearrangement, transcriptional regulation and also satellite cell activation. [1] Six types of diseases caused by *FHL1* mutations include reducing body myopathy (RBM), X-linked recessive myopathy with postural muscle atrophy (X-MPMA), X-linked dominant scapuloperoneal myopathy (X-SPM), Emery-Dreifuss muscular dystrophy (EDMD), rigid spine syndrome (RSS) and hypertrophic cardiomyopathy (HCM). [2] Despite these heterogeneity in clinical manifestations, they tend to have joint contractures, rigid spine and cardiac involvement. Pathologically, myofibrillar myopathy or dystrophic changes are common findings, while reducing body is a most characteristic pathological feature detected in some of the FHL1-related cases.

The exact pathomechanism underlying various forms of FHL1-related myopathies has yet to be elucidated. However, it is of priority to be aware of the extent of the phenotypic spectrum to identify and correlate with the *FHL1* mutations in the clinical setting. We describe a patient with mild leg weakness with myofibrillar myopathy by a novel hemizygous *FHL1* mutation. This case further extends the phenotypic spectrum of FHL1-related myopathies.

2. Case report

A 20-year old man presented with mild leg weakness and resultant difficulty in running and climbing since his childhood. He recently noticed Achilles tendon contractures and bilateral calf atrophy. These symptoms were stationary and caused no limitation in daily living. He mentioned that an uncle on his mother's side had experienced gait disturbance, possibly due to his leg weakness. Both thighs and legs were equally graded as 4+ by MRC scale with his toe gait disturbed. Upper extremity power was normal. With the exception of ankle contractures, there were no other joint contractures or rigid spine. Serum creatine kinase level was elevated to 485 U/L (reference range, ˜ 213 U/L). Muscle CT scans revealed the affection of medial gastrocnemius, more prominent in the left, and minimal involvement in vastus lateralis and biceps femoris. He never complained of any symptoms suggestive of cardiac problems.

Muscle pathology obtained from his right gastrocnemius showed marked fiber size variation, internalized myonuclei, interstitial fibrosis,

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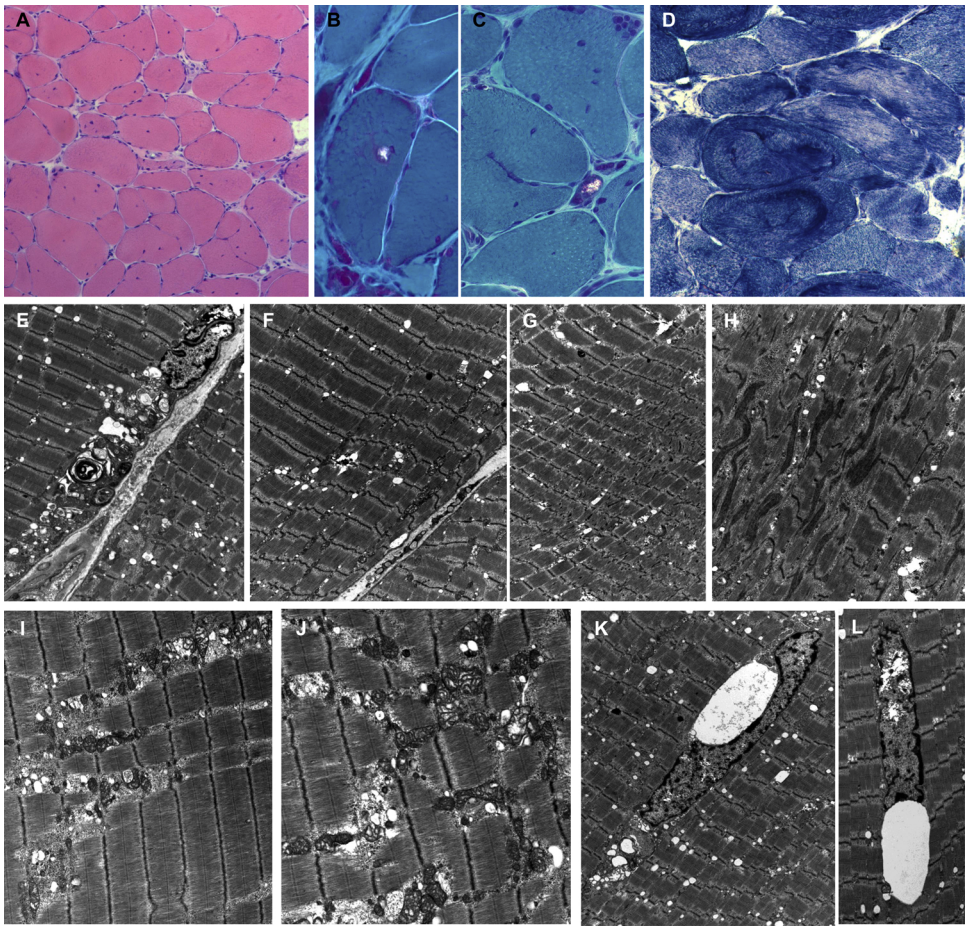

Fig. 1. Histochemistry and electron microscopy of the biopsied gastrocnemius muscle. (A) Hematoxylin and eosin stain shows chronic myopathic changes, such as marked fiber size variation, internal nuclei in many fibers, and splitting fibers. (B, C) Modified Gomori-trichrome stain highlights rimmed vacuoles in a few fibers. (D) The staining pattern on nicotinamide adenine dinucleotide dehydrogenase-tetrazolium reductase is inhomogeneous in some fibers. Whorled fibers are also noted. (E) Clusters of autophagic vacuoles are detected in a perinuclear region. Disarrangement in myofibrillar alignment (F, G) and Z-line streaming (H) are frequently noted. (I) Granulofilamentous materials are accumulated between neighboring myofibrils. (J) Enlarged mitochondria with prominent cristae are increased in number. (K, L) Juxta-nuclear vacuoles are noted in internalized myonuclei.

and splitting fibers (Fig. 1A-D). Rimmed vacuoles were found in several myofibers (Fig. 1B-C), and intermyofibrillar networks were markedly disorganized (Fig. 1D). However, overt protein aggregation as sarcoplasmic inclusion was not present on light microscope, and no reducing body was detected on menadione-NBT staining. On electron microscopy, clusters of autophagic vacuoles and multiple foci of myofibrillar derangement with Z-line streaming were compatible with the routine histochemistry findings (Fig. 1E-H). In addition, granulofilamentous materials between neighboring myofibrils (Fig. 1I), and accumulation of enlarged mitochondria with prominent cristae (Fig. 1I-J) were noted. A single, large vacuole was detected at juxta-nuclear position (Fig. 1K-L), which were detected in three of myonuclei among 10 myonuclei and three satellite cell nuclei observed in the specimen.

Whole exome sequencing identified a novel hemizygous variant (c.625_627delTGC, p.Cys209del) in exon 6 of *FHL1* (Fig. 2A). The missense mutation affecting the same amino acid (p.Cys209Arg) has been reported pathogenic. [3] Analyses *in silico* (MutationTaster, http://www.mutationtaster.org; Protein Variation Effect Analyzer (PROVEAN), http://provean.jcvi.org/index.php; and Polymorphism phenotyping v2 (PolyPhen-2), http://genetics.bwh.harvard.edu/pph2) also predicted the deletion to be deleterious.

Immunofluorescence staining showed markedly decreased FHL1 expression compared with that of normal muscle (Fig. 2B). Normal striated pattern of desmin expression was lost, while desmin-positive aggregates were frequently found (Fig. 2B, arrows and arrowheads). The aggregates were negative for FHL1, but they were co-stained with αB-crystalline and filamin C (data not shown). Western blot analysis confirmed marked reduction of FHL1 in the patient's muscle compared with the muscle from normal as well as other myofibrillar myopathy subjects (Fig. 2C).

3. Discussion

This case describes a novel phenotype of FHL1-related myopathy. The patient's presentation was a mild pure myopathy that was not accompanied by cardiac or respiratory problems. His muscle pathology corresponded to myofibrillar myopathy with desmin-positive/FHL1-negative aggregations. The hemizygous mutation of this patient affects a cysteine residue in the third LIM domain (LIM3), which is critically conserved to participate in zinc-binding. Substantial loss of FHL1 expression was confirmed by immunohistochemistry and immunoblotting.

The previous morphological study divided the FHL1-myopathies into two subgroups based on the presence of reducing bodies in muscle pathology. [2] The first group with reducing body pathology was related to the *FHL1* mutations in LIM2, while the other one without reducing bodies usually had the mutations in the distal exons corresponding to LIM3 or LIM4 domain. This rule also holds in the present case of non-reducing body pathology. In ultrastructural observation, myofibrillar derangement and vacuolar changes were highlighted in our patient, in contrasted to the previous report that non-reducing body pathology only showed mild dystrophic changes. [2] Also, the presence of mitochondrial changes and juxta-nuclear vacuoles were notable and unique. As for nuclear abnormalities, one report pointed out the relationship between FHL1B and nuclear envelope proteins, lamin A/C and emerin. [4] The finding might support our observation of nuclear vacuoles, which is much similar to those reported in skeletal muscle laminopathy. And, it could be the reason why FHL1 mutations can cause EDMD phenotype. Sarcoplasmic inclusion could eventually be visualized by immunohistochemical staining as desmin-positive subsarcolemmal aggregates, which have been noted in the cases of X-MPMA, [2] but not in the other diseases. FHL1 dysfunction rather than

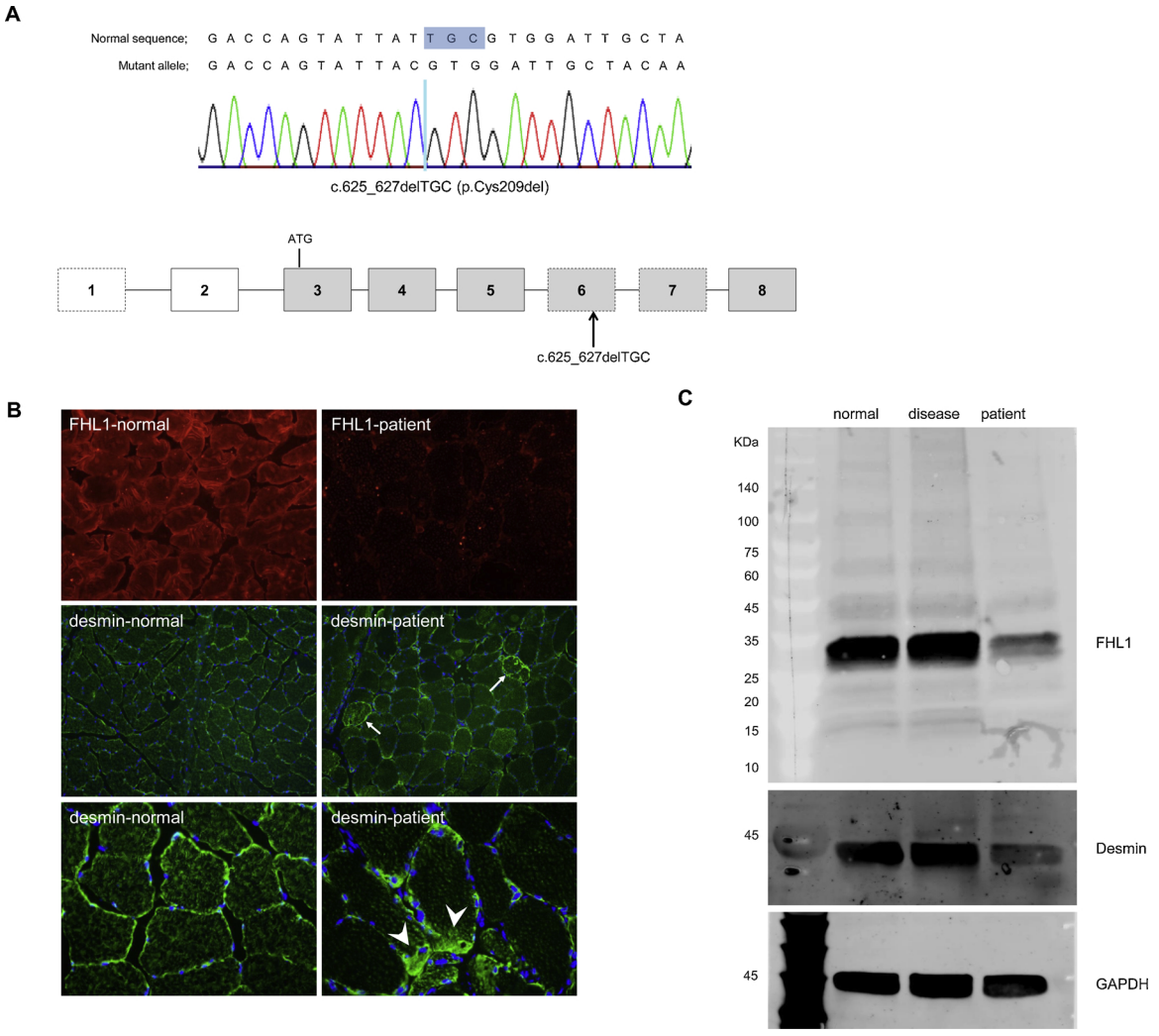

Fig. 2. FHL1 mutation identified in the patient and FHL1 protein expression. (A) A novel mutation c.625_627delTGC (p.Cys209Arg) in FHL1 was identified by whole exome sequencing and confirmed by Sanger sequencing. (B) FHL1 expression is markedly decreased in the patient's muscle (right upper) compared with the normal control (left upper). Desmin accumulated inside of a few muscle cells (arrows in right middle and arrowheads in right lower), and normal striated pattern of desmin expression was lost in the patient's muscle (right lower) compared with a normal control (left lower). (C) Immunoblot analysis revealed marked reduction of FHL1 protein compared with normal and other myofibriallar myopathy muscle.

aggregation itself is suggested to be the primary biologic defect, at least in this case, since FHL1-positive aggregations were absent and the FHL1 expression was markedly reduced even in the fibers with desmin-positive aggregations. Compared with the missense mutation affecting the same amino acid (p.Cys209Arg), our in-frame deletion mutation led to severe reduction of FHL1 expression. Considering the various protein levels caused by different FHL1 mutations, the protein expression might be determined by more complicated mechanisms, not just by the locations or types of FHL1 mutations.

Each of FHL1-related disorders presents distinct clinical courses, and may have specific manifestations, such as muscle hypertrophy mimicking athletic habitus in X-MPMA. Nevertheless, they have overlapping clinical features, including joint contractures, rigid spine, and cardiac diseases. Even an atypical case without evident muscular weakness has been reported to share the other features of rigid spine and cardiac disease. [3] The phenotype in our patient does not conform to any types of the FHL1-related disorders because key features are lacking except for the recent ankle contractures, which does not impair daily activities. A subgroup without reducing bodies usually causes severe decrease of FHL1 and showed EDMD or X-MPMA phenotypes, which was also contrasted to our case. Mild myopathic phenotype as in the present case is non-specific and difficult to confine the candidate genes for the genetic diagnosis. Whole exome sequencing finally led us to the diagnosis of FHL1-related myopathy, and immunohistochemistry and immunoblotting supported the diagnosis. One previous report about FHL1-related myofibrillar myopathy included 5 patients who were all lack of cardiac abnormalities. [5] Among those patients one even presented at 75 years of age. However, he had a mutation located between LIM1 and 2 domains, in which FHL1 mutations were rarely detected and the pathogenicity has not been proved. The other 4 patients had all reducing bodies in muscle pathologies, and demonstrated earlier onset, more rapid progression or at least one of overlapping clinical features. Thus clinical and pathological findings in the present case are beyond the general features published so far in FHL1-related myopathies, and further expand the phenotypic spectrum.

4. Conclusion

We propose a mild myopathic phenotype to be included within the spectrum of FHL1-related myopathies. Clinicians need to be aware of variable conditions which can be caused by mutations in *FHL1* gene.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2019.03.015.

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