

[CASE REPORT]

Characteristic Posterior-dominant Lower Limb Muscle Involvement in Limb-girdle Muscular Dystrophy due to a *DNAJB6* Phe93Leu Mutation

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Abstract:

A 41-year-old man presented with gradually progressing proximal-dominant lower limb atrophy and weakness. His brother, mother and maternal aunt had the same symptoms. A physical examination and muscle imaging (CT and ultrasound) showed selective muscle involvement of the bilateral paraspinal, gluteus and posterior groups of lower limb muscles. Based on the characteristic muscle involvement pattern, the clinical findings and the muscle biopsy results, we made a straightforward diagnosis of limb-girdle muscular dystrophy (LGMD) due to a *DNAJB6* Phe93Leu mutation based on a targeted gene analysis. In the differential diagnosis of adult-onset LGMD syndromes, in addition to investigating the family history, it is important to perform an extensive physical examination to determine the pattern of muscle involvement, and to perform a muscle biopsy. Our case suggests that posterior-dominant lower limb muscle impairment with gluteus and truncal muscle involvement and the detection of rimmed vacuoles on a muscle biopsy could be clues for the diagnosis of LGMD due to *DNAJB6* mutations.

Key words: limb-girdle muscular dystrophy (LGMD), LGMD1D, LGMD1E, *DNAJB6*, Phe93Leu, LGMD syndrome

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Introduction

Limb-girdle muscular dystrophy (LGMD) is a group of hereditary myopathies that are characterized by predominant proximal muscle weakness and atrophy (1). LGMD is genetically heterogeneous and is classified into two major categories based on the pattern of inheritance: LGMD type 1, autosomal dominant; and LGMD type 2, autosomal recessive. Given the significant advances in the understanding of the genetic background of LGMD, it has become possible to make a definitive diagnosis by genetic testing in selected cases (2). However, LGMD is often difficult to diagnose because of its wide phenotypic variation. For the differential

diagnosis of the LGMD subtypes and related disorders (LGMD syndromes), it is essential to perform targeted genetic testing based on the clinical, muscle imaging and muscle biopsy findings and to narrow down the candidates for further testing. We herein report a case of LGMD due to a *DNAJB6* Phe93Leu mutation, in which we could make a straightforward diagnosis based on the findings of a detailed clinical assessment, muscle CT/ultrasound (US) and muscle biopsy and targeted genetic testing of *DNAJB6*.

Case Report

A 41-year-old man presented with proximal-dominant lower limb atrophy and weakness that had gradually pro-

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Figure 1. Axial CT images of the L2 level (A), L4 level (B), pelvic level (C), thigh level (D) and lower leg level (E) in a 41-year-old patient with LGMD due to a *DNAJB6* mutation. No muscle abnormalities were present in the psoas muscle (A, B), or the anterior compartment muscles of the lower limbs (D, E). The images show muscle atrophy and fatty degenerative changes in the paraspinal (A), gluteus (C), biceps femoris (D) and gastrocnemius (E) muscles.

gressed since he was 25 years of age. He first noticed that he ran slower than his colleagues did when he was 25 years of age. A medical check-up at 31 years of age revealed that his creatine kinase (CK) level was high (1,082 U/L). His brother, mother, and maternal aunt had the same symptoms. His 48-year-old brother had slowly progressive weakness of the lower limbs that started at 38 years of age; he was able to walk without assistance. His 70-year-old mother had mild gait disturbance when walking without assistance and difficulty rising from a squatting position. The onset of her symptoms occurred at 50 years of age. Her muscle strength based on the Medical Research Council (MRC) grading system, showed symmetrical proximal-dominant lower limb and hip weakness of the gluteus (MRC 2), biceps femoris (MRC 3), tibialis anterior (MRC 4) and gastrocnemius (MRC 2) muscles. His aunt also had gait disturbance and lower limb muscle atrophy, however the details of her activities of daily living and the timing of the onset of her symptoms were not available.

A physical examination of the patient revealed muscle weakness of the bilateral gluteus and lower limb muscles, with muscle atrophy that was milder than his mother's: gluteus maximus (MRC 4), gluteus medius (MRC 4), biceps femoris (MRC 4) and gastrocnemius muscles (MRC 2). His paraspinal muscles showed mild atrophy. He presented with no atrophy or weakness of the facial, shoulder, upper limb or abdominal muscles. Furthermore, the anterior part of his lower limbs showed no atrophy or weakness. Although he had no gait disturbance or Gowers' sign, he required assistance to climb stairs and could not run. He had no difficulty swallowing or speaking and had no tongue atrophy or nasal voice. The results of electrocardiography and echocardiography were normal. A respiratory function test revealed that his forced vital capacity was 3.43 L (78.9% of predicted normal value). Muscle imaging (CT and US) also showed selective muscle involvement of the paraspinal, bilateral gluteus and lower limb muscles, which was in accordance with the clinical presentation (Fig. 1, 2). A muscle biopsy of the left biceps brachii revealed muscle fibers of various sizes, scattered atrophic fibers, and a few fibers with rimmed vacuoles or cytoplasmic inclusions (Fig. 3). The symmetrical posterior-dominant muscle involvement without foot drop or scapular wing, the patient's family history that suggested an autosomal dominant pattern of inheritance and the existence of rimmed vacuoles in the muscle biopsy were important clues in the differential diagnosis of LGMD syndromes. Based on these findings and previous reports (3, 4), we initially suspected LGMD due to a *DNAJB6* mutation. This was confirmed by the direct sequencing of *DNAJB6*, which revealed a heterozygous c.279C > G p.Phe93Leu mutation. We also confirmed the same heterozygous mutation in his mother.

Discussion

We encountered a case of typical LGMD due to a

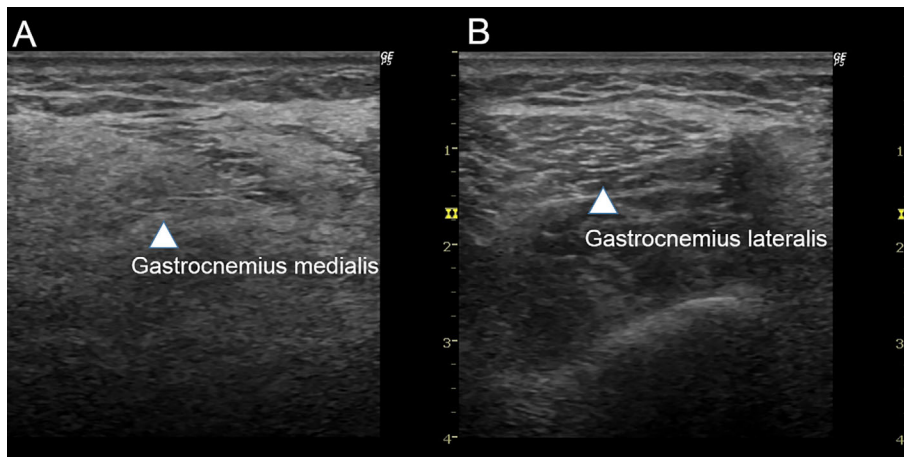


Figure 2. Ultrasound images of the gastrocnemius medialis (A) and lateralis (B) muscles on the right side of a 41-year-old patient with LGMD due to a *DNAJB6* mutation. The echo intensity strongly increased in the gastrocnemius medialis muscle (A) and moderately increased in the gastrocnemius lateralis muscle (B).

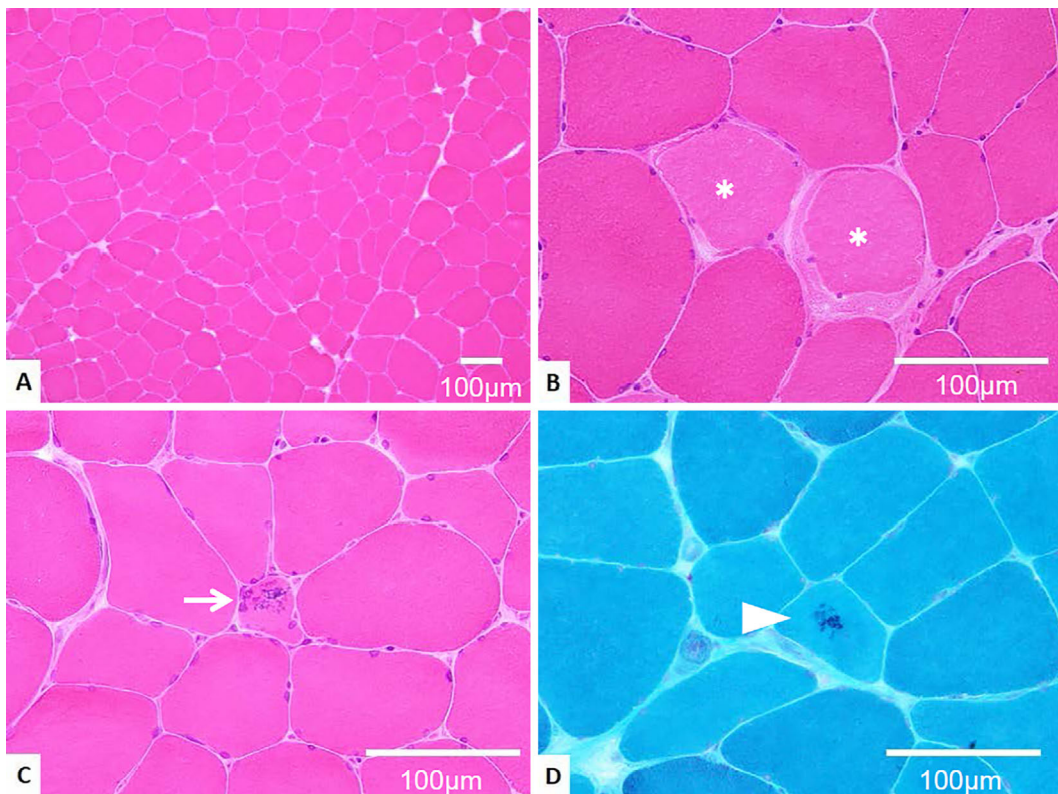


Figure 3. The examination of a biopsy specimen of the biceps brachii muscle from a 41-year-old patient with LGMD due to a *DNAJB6* mutation. Hematoxylin and Eosin staining (A, B, and C) and modified Gomori trichrome staining (D). Moderate variation was observed in the fiber size (A). There were some degenerating fibers (*) (B). A fiber with a rimmed vacuole (arrow) (C). Cytoplasmic inclusions in the fiber (arrowhead) (D).

DNAJB6 Phe93Leu mutation that could be definitively diagnosed based on the characteristic muscle involvement pattern, the clinical symptoms and the results of a muscle biopsy. Phe93Leu mutations have been previously reported (5, 6). In patients with LGMD due to *DNAJB6* mutations, the onset of symptoms occurs in adulthood and an autosomal dominant pattern of inheritance is observed.

Some missense mutations of the *DNAJB6* gene have been reported (7). The disease is characterized by the involvement of the dorsal lower limbs, as well as the gluteus and truncal muscles. The rectus femoris, sartorius, and the anterolateral group of lower leg muscles are preserved until the late stage. The upper limb muscles are also spared (3, 4). Rimmed vacuoles are a characteristic muscle biopsy find-

ing (8). In the present case, the gluteus, paraspinal and posterior-dominant lower limb muscle involvement (identified by a clinical examination and imaging), family history (suggesting an autosomal-dominant pattern of inheritance), onset of symptoms in adulthood, detection of rimmed vacuoles in the muscle biopsy and the moderately elevated CK level were valuable clues that facilitated the smooth diagnosis of LGMD due to a *DNAJB6* Phe93Leu mutation. Separately, Ruggieri et al. identified genotype-phenotype linkage in LGMD due to *DNAJB6* mutation and reported that the Phe93Leu mutation was the least severe phenotype among six mutations (7). If the patient in the present case had a different mutation with more severe or broader muscle impairment, it might have been difficult to diagnose.

The differential diagnosis of patients with LGMD syndrome is made based on the inheritance pattern and clinical features. When a patient is suspected of having adult-onset LGMD syndrome with a family history that suggests an autosomal-dominant pattern of inheritance, we should consider other LGMD1 subtypes in the differential diagnosis (LGMD type 1A [LGMD1A], LGMD due to *Filamin C* mutation, and LGMD due to *Desmin* mutation), facioscapulo-humeral muscular dystrophy (FSHD), oculopharyngeal muscular dystrophy (OPMD), and late-onset centronuclear myopathy due to Dynamin 2 mutation (CNM1). Although the muscle involvement patterns of these diseases are similar to those of LGMD due to *DNAJB6* mutation, the gastrocnemius muscle involvement can be a clue for the differential diagnosis. In contrast to LGMD due to a *DNAJB6* mutation, the gastrocnemius muscles are commonly spared in OPMD (9). However, it is difficult to narrow down the diagnosis based on the pattern of muscle involvement alone, because there is wide variation in the lower limb muscle impairment in each subtype (10, 11). When a patient's family history suggests an autosomal recessive pattern, LGMD type 2A (LGMD2A), LGMD type 2B (LGMD2B), LGMD type 2L (LGMD2L) and GNE myopathy should be considered in the differential diagnosis. LGMD2A is the most common type of autosomal recessive LGMD, and the truncal and hamstring muscle involvement and scapular wings are often seen in the limb-girdle phenotype of LGMD2A (12). The lower limb muscle involvement pattern in patients with LGMD2A is similar to that in patients with LGMD due to a *DNAJB6* mutation (3). Patients with LGMD2B or LGMD2L can also present hamstring muscle wasting and often have proximal upper limb weakness (13, 14). In terms of the incidence, the possibility of LGMD2A should be noted when a posterior-dominant lower limb muscle involvement pattern is seen. In GNE myopathy, the quadriceps muscle is spared in most patients, whereas foot drop can usually be seen and the neck, truncal and upper limb muscles are generally affected (15). Late-onset Becker muscular dystrophy (BMD) can be a differential diagnosis if an X-linked recessive pattern is suspected. The muscle imaging findings, including CT and US, also helped us to determine the pattern of involvement more precisely. Muscle CT is suitable for deter-

mining whether muscles are affected or spared; thus, the findings clearly and objectively show the pattern of muscle involvement. Affected muscles show a low density on muscle CT due to degeneration. Furthermore, muscle US is a useful tool for assessing the pattern of muscle involvement noninvasively. As shown in Fig. 2, the affected muscles show a high intensity, which indicates muscle degeneration or increased connective tissues (16). However, the reason for the muscle selectivity in each type of LGMD syndrome remains unknown.

Regarding the muscle biopsy findings, rimmed vacuoles are often observed in LGMD1A, OPMD, and GNE myopathy. Central nuclei are a characteristic of CNM1 (17). As such, the combination of an accurate assessment of the systemic pattern of muscle involvement and the muscle biopsy findings were helpful in the differential diagnosis. Although this was a typical mild case of LGMD due to *DNAJB6* mutation, there are some reports of cases with broad lower limb muscle involvement or scapular wing (3, 8). Specifically, the distribution of muscle impairment depends on the disease duration. In the diagnosis of LGMD syndrome, it is important to narrow down the various differential diagnoses using the clinical information, as well as the muscle imaging and biopsy findings with consideration of the clinical variations of each subtype.

In conclusion, we presented a case of LGMD due to a *DNAJB6* mutation, in which we could make a straightforward diagnosis based on the clinical, muscle imaging, and muscle biopsy findings. In the differential diagnosis of adult-onset LGMD syndromes, an extensive and careful examination of the systemic pattern of muscle involvement and a muscle biopsy are essential. Our case suggests that a posterior-dominant pattern of lower limb muscle impairment with gluteus and truncal muscle involvement and the finding of rimmed vacuoles on a muscle biopsy may be clues for the diagnosis of LGMD due to a *DNAJB6* mutation.

The authors state that they have no Conflict of Interest (COI).

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