



## CASE REPORT

### Rare Genetic Variant of Distal Myopathy with Posterior Leg and Anterior Hand Involvement: Case Report

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#### Abstract:

Distal myopathies are a heterogeneous group of genetic muscle disorders characterized by weakness of distal muscle groups of the upper and lower extremities. The various types of distal myopathies can be clinically differentiated based on age at onset, pattern of muscle involvement, disease severity, and the mode of inheritance. We described a case of slowly progressive muscle weakness that involved one of the patients' hand and posterior leg muscles. Her genetic study showed a rare variant that likely contributed to distal myopathy with posterior leg and anterior hand involvement (distal actin-binding domain [ABD]-filaminopathy). The disease is due to mutations on the actin-binding domain of the FLNC gene that encodes filamin C. This variant has been described only in one Italian family. This rare variant will expand our knowledge about the rare phenotype of distal myopathy with posterior leg and anterior hand involvement.

**Keywords:** ABD-Filaminopathy, Distal myopathy, Distal myopathy with posterior leg and ABD-Filaminopathy, Progressive muscle weakness, Electromyography, Serum creatine kinase.

#### Article History

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## 1. INTRODUCTION

Distal myopathies are a heterogeneous group of genetic muscle disorders characterized by weakness of distal muscle groups of the upper and lower extremities [1]. The various types of distal myopathies can be clinically differentiated based on age at onset, pattern of muscle involvement, disease severity, and the mode of inheritance. Distal myopathies show a dominant or recessive mode of inheritance.

## 2. CASE REPORT

We describe a 30-year-old woman who presented with features suggestive of probable muscle disease. We discovered a family history of similar issues in her mother; however, her mother was diagnosed with spinal stenosis and eventually required the use of a wheelchair. The patient was well until her first trimester of pregnancy when she developed lower limb weakness and had difficulty getting out of low seat chairs or climbing stairs. She observed that she needed to hold the hand rail when climbing stairs and was not confident wearing high heels. Her weakness worsened; her upper limbs were initially unaffected, and she did not observe symptoms of ocular or bulbar weakness, numbness or tingling, neck weakness, myalgia, or a change in urine color. Her bowel and bladder

control was normal. She reported falling on one occasion owing to leg weakness. The patient showed clear deterioration in her condition on subsequent visits. She reported increasing difficulty with using a computer mouse, with opening jars, doing up buttons and wearing slippers and observed significant difficulty using her arms and hands.

Physical examination showed a well-appearing woman with painless cervical and lumbosacral spinal motion. Cranial nerves and speech were normal. The thighs and upper arm muscles (particularly the biceps) showed mild muscular atrophy. Muscle strength was as follows: hand grip 4/5, finger extensor 4/5, wrist extension and flexion 4/5, biceps 5/5, deltoid 5/5, hip flexors and extensors 5/5, knee flexors 5/5, knee extensors 5/5, foot dorsiflexion 5/5, and planter flexion 3/5. Motor tone, coordination, and sensory examination were normal. She developed a waddling gait, and although she could stand and walk on her heels, she was unable to walk on her toes. She could perform the tandem gait test but with difficulty. She was able to stand from a seated position without difficulty; however, she required support to stand from a squatting position.

Laboratory investigations revealed a serum creatine kinase (CK) level of 726 U/L. Electromyography revealed a shift toward lower frequencies indicating mild myopathy; however, nerve conduction studies were normal. Biceps biopsy revealed

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mild non-specific changes with variation in fiber size. No inflammation and degenerating or regenerating fibers were observed. The muscle specimen showed low fat content, and staining performed for various types of limb girdle dystrophy revealed normal results. Genetic testing for facioscapulohumeral muscular dystrophy was within the normal range, and Pompe disease testing revealed negative results. We performed muscle genetic panel testing, which showed a variant that likely contributed to distal myopathy with posterior leg and anterior hand involvement (distal actin-binding domain [ABD]-filaminopathy). The pathogenic variant was identified as FLNC (NM\_001127487.1): heterozygous, c.577G>A (p.Ala193Thr).

### **3. DISCUSSION**

Distal ABD-filaminopathy is an autosomal distal myopathy. The genetic culprit is identified as a missense mutation in the ABD. Notably, met251Thr and Ala193Thr mutations have been reported in such cases [2]. It could also present as an allelic disorder with overlapping myofibrillar myopathy or distal myopathy features with upper limb predominance. The prevalence is < 1/1,000,000. This disease usually manifests during the third decade of life with intrinsic hand muscle weakness, which may progress to calf muscle atrophy. This condition shows a slow progressive course and often spares the anterior leg and respiratory muscles. Serum CK levels are normal or mildly elevated. Nerve conduction studies are normal; however, electromyography reveals myopathic motor unit potentials. Magnetic resonance imaging usually reveals the involvement of the posterior leg muscles. Muscle biopsy usually shows a variation in fiber size without myofibrillar aggregates, vacuoles, or inflammation. Previous studies have reported this condition in two families. A study performed in 2005 reported this condition in a large family from Victoria, Australia [3]. Patients presented with distal myopathy, also called distal ABD-filaminopathy or William's disease. It was not associated with any known distal myopathy loci at that time. However, in 2011, the clinical phenotype was reanalyzed, and members of that family were reclassified and subsequently underwent whole genome analysis [2]. The mutation was identified on chromosome 7. Reportedly, an Italian family also presented with the same phenotype, and the disease in this family was similarly associated with the same region of chromosome 7.

### **CONCLUSION**

Two different missense mutations were identified in the N-terminal ABD of FLNC (MIM 102565), and both mutations

segregated with the disease in both families. Analysis of cDNA from affected family members revealed a c.752T>C (p.Met251Thr) FLNC mutation located in the N-terminal ABD. The p.Met251Thr variant segregated with the disease in the family but was not observed in 400 control chromosomes. A c.577G>A (p.Ala193Thr) mutation was subsequently identified within the filamin C ABD in the Italian family. The pathogenic variant identified in our patient was similar to the one discovered in the Italian family.

### **ETHICAL APPROVAL AND CONSENT TO PARTICIPATE**

Not applicable.

### **HUMAN AND ANIMAL RIGHTS**

Not applicable.

### **CONSENT FOR PUBLICATION**

Informed consent was obtained from the patient.

### **STANDARD OF REPORTING**

CARE guidelines and methodology were used.

### **FUNDING**

None.

### **CONFLICT OF INTEREST**

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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