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Case Report

Novel LDB3 Mutation in a Patient With Autosomal Dominant Myofibrillar Myopathy

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Abstract

Introduction: Myofibrillar myopathy (MFM) is a rare human disease, characterized by a distinct histopathological pattern of myofibrillar degeneration and protein aggregates. LDB3 protein encoded by this gene is a key Z-disk protein that interacts with a-actinin and protein kinase C.

Case Presentation: In this paper, we identified the novel heterozygous, and hence, dominant mutation in the LIM domain-binding protein 3 gene (LDB3) in a patient affected by myofibrillar myopathy (MFM). We performed direct sequencing in an Iranian patient with autosomal-dominant inheritance of MFM characterized by clinical features, and we identified a heterozygous missense mutation in exon 10, c.1687A > G (p.Ile563Val) in the LDB3 gene on chromosome 10:88476524.

Conclusions: Bioinformatics analyses using SIFT, Mutation Taster and Polyphen-2 indicated that p.Ile563Val was predicted to be damaging, disease causing, and probably damaging to and causing LDB3 dysfunction. As such, this mutation produces novel protein coding transcripts, which might explain the MFM phenotype in the patient.

Keywords: Myofibrillar Myopathy, LDB3 Protein, Human, Sequence Analysis, DNA

1. Introduction

Myofibrillar myopathies (MFM, [MIM 601419]) are a group of clinically and genetically heterogeneous neuromuscular disorders defined by ectopic expression of proteins, such as desmin, and myofibrillar disorganization starting at the Z-disk and protein aggregates in muscle fibers (1). The clinical phenotypes of myofibrillar myopathies are widely heterogeneous. Patients usually present with progressive muscle weakness that can involve both proximal and distal muscles, with the age of onset ranging from infancy to late in adulthood, but in most cases the symptoms appear in the fourth and fifth decades. However, other features are extremely variable. The diagnosis of MFM is frequently difficult because of the substantial phenotypic and pathomorphological variability (2, 3). In recent years, an increasing number of genes have been recognized to be involved in MFM pathogenesis, causing subgroups of the disease. Until now, mutations in nine genes have been identified to cause MFM: titin (TTN), DNA J homolog subfamily B member 6 (DNAJB6), bcl-2 associated athanogene protein 3 (BAG3), four and a half LIM domain protein 1 (FHL1), Z-band alternatively spliced PDZ containing protein (ZASP, also LDB3), α B-crystallin (CRYAB), desmin (DES), filamin C (FLNC) and myotilin (MYOT, also TTID) (4-11). More than 50% of cases are caused by unresolved gene defects. In this report, we describe the first dominant acting heterozygous mutation in the LDB3 gene, which affects a family with severe myofibrillar myopathy. This mutation produces novel protein coding transcripts that might explain the MFM phenotype in the patient.

2. Case Presentation

The patient was a 21-year-old man, and the last child of consanguineous parents of southwest Iran. He was admitted to the neurologist for investigation of slowly progressive walking difficulties that began two years previously. He also had slowly progressive hand and foot weakness (distal muscles) and occasional stiffness and cramping of the leg muscles after exercise. He had severe weakness of toe extensor, anterior tibial and peroneal muscles, and mild weakness of iliopsoas, quadriceps, hamstring and finger extensor muscles. His parents were relative (his father died at age 70 and had suffered from Parkinson and his mother was 60 years old and was reported to be unaffected).

Genomic DNA was extracted from peripheral leukocytes of the patient and controls, using standard procedures (12), and PCR sequencing was performed to investigate the possible cause of muscular dystrophies, including analysis of the mutations in LDB3 (ZASP) in the patient with MFM phenotypes.

PCR was conducted under the following conditions: 200 µM deoxyribonucleotide triphosphates (dNTPs), 100 ng genomic DNA, 2.5 units supertaq polymerase, 1.5 mm

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MgCl, and 25 pmol each primer (Table 1) (13). Amplification was carried out in 25 μ L volumes and 35 cycles: 94°C for one minute, 65°C for 35 seconds and 72°C for one minute. The sequencing reactions were carried out and the sequences were compared to the reported gene sequence using the BLASTN program.

Exon/PrimerPrimer Sequence (5 - 3) TPCR Product Size, bp1221ZASP IFGTGCCCTTCCACACCACCZASP IRACACATGCCCTCCTCAGACCACZASP IRTGGCCTTTCCTCAGGACCACZASP 2FTGGCCTTTCCTCAGGACCACZASP 3RTCCAGGAACCAGGGCTGAGT3CCACGGACCAGGGCTGAGTZASP 3RTCCAGGAACCAGGGCTGAGT4S06ZASP 4FGGCTCGCCTAACACATCTGZASP 3RCCACCTGTGGAGAGCTGAGTZASP 4FGCCACCTGTGCACACACAC5266ZASP 4FGCCACCTGTGCTCTCCTCACCZASP 4FCTCTATCCACGCCACCACAA6380ZASP 5FCACTCCTTGCTCCTCACCZASP 6FTGTAACCGCCACCTGTTGCCZASP 6FTGTAACCGCCACCTGTGAG7353ZASP 7FCCACCAATGGGCATGAGCA7353ZASP 7FCCACCAATGGCATGAGCA8178ZASP 7FCCACCAATGGCATGAGCA2ASP 7FCCACCACATGGCATGAGCA2ASP 7FGGGTGACACATTCCTAACCZASP 8FTTGCTGTGTCTCCCTGAGTGZASP 9FGGTGACACATTCCTAACC2ASP 9FGGTGACACATTCCTAACCZASP 9FGGCTGTCCTTGTGGCTCTZASP 10FGCTCCTTGAGCATGATACTTGZASP 10FGCCTGTCCTTGTGGGCTACAZASP 10FGGCTGTCCTTGTGGGCTACAZASP 10FGGCTGTCCTTGTGGGCTACAZASP 10FGGCTGTCCTTGTGGGCTACAZASP 10FGGCACCCTGGGGAGAGCTATCATCTGZASP 10FGGCACCCTGGGGCAGGCTACA3352ZASP 10FGGCACCCT	Table 1. Primers Used for the Screening of the LDB3 Gene					
1221ZASP IFGTGCCCTCTCACTCAACCCTZASP IRACACATGCCCTCCTCAAGC2335ZASP 2FTGGCCTTTCCTCAGGACCACZASP 2RTCCTGCACAGTTTTGTAGCC3230ZASP 3FTGACTCTGGCTCTCTTGTGCTZASP 3RTCCAGGAACCAGGCTGAGT4506ZASP 4FGGCTCGCGCTAACACATCTGZASP 4FGGCTCGCCGCTAACACATCGZASP 4RCCCACCTGTGGAGAGCTGTA5266ZASP 5FCTCTATCCAGCCCACACACA6380ZASP 6FTGTAACCGCCACCTGTTGCCZASP 6RTCCAGGAGGTCCACGTGGAGCA7353ZASP 7FCCACCAATGGGCATGGAGCA7353ZASP 7FCCACCAATGGGCATGGAGCA8178ZASP 7FCCACCAATGGGCATGGAGCA9317ZASP 8FTTGCTGTCTCCCGTGAGT2ASP 9FGGTGAACACATTCCCTAACC2ASP 9FGGTGAACACATTCCCTAACC2ASP 9FGGTGAACACATTCCCTAACC2ASP 10FGCCCTAACTACCTTGGACAC10331ZASP 10FGCCCTAACTACCTGGACAC12A352ZASP 10FGGCTGTCCTTGTGGGTGTAZASP 10RCCCCACCCGGGGCCTAAC21B352ZASP 12BFTGCACCCTCGGTGCCTACA2ASP 12BFGGAAGAGACATGGTCAGAG14200ZASP 13FGTTCTGGGAGTGCTCTACTZASP 13FGTACTGGGGAGAGCTGTGTCT2ASP 13FGTACTAGGCGCTCACAC14200ZASP 13FGTACTGGGAGAGCTGTGTCT <th>Exon/Primer</th> <th>Primer Sequence (5 - 3) T</th> <th>PCR Product Size, bp</th>	Exon/Primer	Primer Sequence (5 - 3) T	PCR Product Size, bp			
ZASP IFGTGCCCTCTCACTCAACCCTZASP JRACACATGCCCTCCTCAGGC2335ZASP JFTGGCCTTTCCTCAGGACCACZASP JRTCCTGCACAGTTTGTAGCC3230ZASP JRTCCTGCACAGGCTCTCTTGCTZASP JFTGACTCTGGCTCTCTTGCTZASP JFGGCTGCCGCTAACACATCTGZASP JFGGCTCGCGCTAACACATCTGZASP JFCACTCCTTGCTCCTCACCZASP JFCACTCCTTGCTCTCCTCACCZASP JFCACTCCTTGCTCTCCTCACCZASP JFCACTCCTTGCTCCCCCCACACA6380ZASP GFTGTAACCGCCACCTGTTGCCZASP GRTCCAGGAGGCTCAACGTGAG7353ZASP JFCCCACCAATGGGCATGGAGCAZASP JFCCCACCAATGGGCATGGAGCAZASP JFCCCACAATGGCCATGGAGCA2ASP JFGGTGAACACATTCCCTAACCZASP JFGGTGAACACATTCCCTAACCZASP JFGGTGAACACATTCCCTAACCZASP JFGGTGAACACATTCCCTAACCZASP JFGCTCCCTTGAGGTGTAAZASP JARCCCAGCAGGTTATACATTG10331ZASP JAFGCTTCCTTGTGGGTGTAAZASP JARCTGGGCAGAAGCTATCATCTGZASP JARCTGGGAGAAGCTATCATCTGZASP J2BFTGCACCCTCGGTGGCCTACAZASP J2BFGGTCACACACAGGGTCAGAG14200ZASP J3FGTACTGGGGAGGCCTACAZASP J3FGTACTGGGGAGGCGTAGGAG14200ZASP J3FGTACTGGGGAGGCTGTACTZASP J3FTGATTGGGGTTTGTCTGGZASP J3FGTACTGGGGAGAGTATGGTCGCTCTCZASP J3FGG	1		221			
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ZASP 5FCACTCCTTGCTCTCCTCACCZASP 5RCTCTATCCACGCCAGACACA6380ZASP 6FTGTAACCGCCACCTGTTGCCZASP 6RTCCAGGAGGTCCAACGTGAG7353ZASP 7RACCAGCATGGAGACA8178ZASP 7RAGCAGGACTCCTGGGTG8178ZASP 8FTTGCTGTGTCTCCCGTGAGT2ASP 9FGGTGAACACATTCCCTAGCA9317ZASP 9RGCCCAGCAGAGTTATACATTG10331ZASP 10FGCTCCCTTGACTGTGTCTZASP 10FGCTCCCTTGGCTGTGTCTZASP 10RGCCCTAACTACCTGGGCTAA2ASP 11RTCTTGGCTGTTGGGTGTAZASP 12AFCAGGGAAGCTATCATCTG14257ZASP 12BFTGCACCCTCGGTGGCTACAZASP 13FGTTCTGGGAGCTGCCTTACTZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BFTGCACCCTCGGTGGCCTACAZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13FGTTCTGGGGAGCTGCCTTACTZASP 13FGTTCTGGGGAGCTGCCTACAZASP 13FGTACAGCCGCCTCCCTCCZASP 13FTGATTTGGGGTTGGCTAGAGG14200ZASP 13FTGATTTGGGGTTGCTTGGZASP 13FTGATTTGGGGTTGCTTGGZASP 13FTGATTTGGGGTTGCTGTGZASP 13FTGATTTGGGGTTGCTGTGTZASP 13FTGATTTGGGGTTGCTGTGTZASP 13FTGATTTGGGGTTGCTGTGTCTZASP 13FTGATTTGGGGTTGCTGTGTCTZASP 13FTGATTTGGGGTGGCAGGGTCTGTTCTZASP 13FTGATTGGGGAGGCAGGTCTGTT	5		266			
ZASP 5RCTCTATCCACGCCAGACACA6380ZASP 6FTGTAACCGCCACCTGTTGCCZASP 6RTCCAGGAGGTCCAACGTGAG7353ZASP 7FCCACCAATGGGCATGGAGCAZASP 7RAGCAGGACTCCCTGGCTTCT8178ZASP 8FTTGCTGTGTCTCCCGTGAGTZASP 9RGAGGTCCCTTCATGAGTGA9317ZASP 9RGCTGACACATTCCCTAACCZASP 9RGCCGACAGAGTTATACATTG10331ZASP 10FGCTCCCTTGACCTGTGTCTZASP 10RGCCCTAACTATCCTTGGACAC11257ZASP 10RGCCCTATGCTTGTGGCTCT12A348ZASP 12AFCATTTCTGGCTAGGAGTGZASP 12AFCATTTCTGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13RGGAAGAGCATGGTCAGAG14200ZASP 14RCACATGCCGTCCTCTCZASP 14RCACATGCCATCGAAGGGTCAGAG15290ZASP 15FTGATTTGGGGAGTATGTTZASP 15RCTACGCTGCAGGGTAGTATCTZASP 15RCTACGCTGGCAAGGTATGTA24SP 15FTGATTTGGCGTTGCTTGTGZASP 15FTGATTTGGCGTGTGTTCTZASP 15FTGATTTGGCAGGCAGGTATGTA2ASP 15FTGATTTGGCGTGTGTTCTZASP 15FTGATTTGGCAGGGAGGTATGTATCTGZASP 15FTGATTTGGCGAGGGTGTGTTCTZASP 16FGTCCACGCAGGGTGTGTTCT <td>ZASP 5F</td> <td>CACTCCTTGCTCTCCTCACC</td> <td></td>	ZASP 5F	CACTCCTTGCTCTCCTCACC				
6380ZASP 6FTGTAACCGCCACCTGTTGCCZASP 6RTCCAGGAGGTCCAACGTGAG7353ZASP 7FCCACCAATGGGCATGGAGCAZASP 7RAGCAGGACTCCCTGGCTTCT8178ZASP 8FTTGCTGTGTCTCCCGTGAGT2ASP 8FGAGGTCCCTTCCATGAGTGA9317ZASP 9FGGTGAACACATTCCCTAACCZASP 9RCCCCACGAGGTTATACATTG10331ZASP 10FGCTCCCTTGACCTGTGTCTZASP 10FGCTCCCTTGACCTGTGTGTZASP 10RGCCCTAACTACCTTGGGCTGTAAZASP 11FGGCTGTCCTTGGGTGTAAZASP 12AFCATTTCTGGCTATGGCTCCT12A348ZASP 12AFCTGGGAGAAGCTATCATCTG12B352ZASP 12ARCTGGGAGAAGCTATCATCTG13267ZASP 13FGTTCTGGGTGCCTACA2ASP 13RGGAAGAGCTGCCTACA2ASP 13RGGAAGAGCATGGTCAGAG14200ZASP 14RCACATGCCATCGAAGGT15290ZASP 14RCTAGCGTGGCATGAGTG2ASP 14RCTAGCGTGGCAGGTATGTTCZASP 15FTGATTTGGGAGCTGCTTTCTGGZASP 14RCTAGCGTGGCAAGGATATGAT15290ZASP 15FTGATTTGGCAGGGAGGTATGTAT2ASP 16FGTCTCACGCAGGGTGTGTTCTZASP 16FGTCTCACGCAGGGTGTGTTCTZASP 16RGTCTCACGCAGGGTGTGTTCTZASP 16RGTCTCACGCAGGGTGTGTTCTZASP 16RGTCTCACGCAGGGTGTGTTCTZASP 16RGTCTCACGCAGGGTGTGTTCTZASP 16RGTCTCACGCAGGGTGTGTTCT </td <td>ZASP 5R</td> <td>CTCTATCCACGCCAGACACA</td> <td></td>	ZASP 5R	CTCTATCCACGCCAGACACA				
ZASP 6FTGTAACCGCCACCTGTTGCCZASP 6RTCCAGGAGGTCCAACGTGAG7353ZASP 7FCCACCAATGGGCATGGAGCAZASP 7RAGCAGGACTCCCTGGCTTCT8178ZASP 8FTTGCTGTGTCTCCCGTGAGTZASP 8FTTGCTGTGTCTCCCGTGAGTZASP 9FGGTGAACACATTCCCTAGAGTGA9317ZASP 9FGGTGAACACATTCCCTAACCZASP 9RCCCAGCAGAGTTATACATTG10331ZASP 10FGCTCCCTTGACTGTGTCTZASP 10RGCCCTAACTACCTTGGACAC11257ZASP 10RGCCTATCTTGGGTGTAAZASP 11RTCTTGGCTCTTGTGGCTCAT12A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATTG12B352ZASP 12BRTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGTCAGAC13267ZASP 12BRCTCCCGACCGGTGCCTACAZASP 13FGGTAGAGAGCAGTGGCTTACTZASP 13FGGAAGAGACATGGGTCAGAG14200ZASP 13RGGAAGAGCATGGGTCAGAG15290ZASP 15FTGATTTGGGGAGTGGCTAGA16229ZASP 16FGTCTCACGCAGGGTCTGTTCTZASP 16RGCTCCCTCTCTCCCCCATT	6		380			
ZASP 6RTCCAGGAGGTCCAACGTGAG7353ZASP 7FCCACCAATGGGCATGGAGCAZASP 7RAGCAGGACTCCCTGGCTTCT8178ZASP 8FTTGCTGTGTCTCCCGTGAGTZASP 8RGAGGTCCCTTCCATGAGTGA9317ZASP 9FGGTGAACACATTCCCTAACCZASP 9RCCCAGCAGAGTTATACATTG10331ZASP 10FGCTCCCTTGACCTGTGTCTZASP 10RGCCCTACTACCTTGGACAC11257ZASP 11FGGCTGTCCTTGGGCTGTAAZASP 12AFCATTTCTGGCTAGTGGGCTCT12A348ZASP 12AFCATTTCTCTGGCTGGTGGGCTACAZASP 12AFCATTTCTCTGGCTGGGGCCTACAZASP 12BR352ZASP 12BRCTCCCAACCAGGGCCTACAZASP 13FGTACTAGGAGACGTATCATCTG13267ZASP 13FGTACTAGGCGGCCTACAZASP 13FGTACTAGGCAGCGCCTACAZASP 13FGTACTAGGCAGCGCCTACAZASP 13FGTACTGGGAGACATGGGTCAGAG14200ZASP 13FTGATTGGGAGCTGCAGAGGAGAGTAGTGTC15290ZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 15FTGATTTGGGGAGTTGTTGTGGZASP 15FTGATTGGGGACTAGAGTATGTA16229ZASP 16FGTCTCACGCAGGAGGTGTTCTZASP 16RGCTCCCTCTCTCCCCATT	ZASP 6F	TGTAACCGCCACCTGTTGCC				
7353ZASP 7FCCACCAATGGGCATGGAGCAZASP 7RAGCAGGACTCCCTGGCTTCT8178ZASP 8FTTGCTGTGTCTCCCGTGAGTZASP 8RGAGGTCCCTTCCATGAGTGA9317ZASP 9FGGTGAACACATTCCCTAACCZASP 9RCCCAGCAGAGTTATACATTG10331ZASP 10FGCTCCCTTGACCTGTGTCTZASP 10RGCCCTAACTACCTTGGACAC11257ZASP 11FGGCTGTCCTTGTGGCTCCT12A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGGAGAGCTATCATCTG13267ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13FGTTCTGGGAGCTGCCTTACTZASP 14FAGTCAAGCCCGCTCCCTCCZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14FCACATGCCATCGAAGTATCATCTG15290ZASP 15FTGATTTGGGGTTTGTCTTGGZASP 16FGTCTCACGCAGGCTGAGTGT16229ZASP 16FGTCTCACGCAGGCTGCTTCTZASP 16FGTCTCACGCAGGTCGTTCT	ZASP 6R	TCCAGGAGGTCCAACGTGAG				
ZASP 7FCCACCAATGGGCATGGAGCAZASP 7RAGCAGGACTCCCTGGCTTCT8178ZASP 8FTTGCTGTGTCTCCCGTGAGTZASP 8RGAGGTCCCTTCCATGAGTGA9317ZASP 9FGGTGAACACATTCCCTAACCZASP 9RCCCAGCAGAGTTATACATTG10331ZASP 10FGCTCCCTTGACCTGTTGTCTZASP 10RGCCCTAACTACCTTGGACAC11257ZASP 11FGGCTGTCCTTGTGGCTGTAAZASP 11RTCTTGGCTCTTGTGGCTCCT12A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BFGTCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGGAGCTGCCTTACTZASP 14FAGTCAAGCCCGCTCCCTCCZASP 14FAGTCAAGCCCGCTCCCTCCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGATTGTTGTGTG2ASP 15RCTACCACGCAGGCTAGAGTATGTA16229ZASP 16FGTCTCACGCAGGCTGCTTCZASP 16RGCTCCCTCCTCCCCATT	7		353			
ZASP 7RAGCAGGACTCCCTGGCTTCT8178ZASP 8FTTGCTGTGTCTCCCGTGAGTZASP 8RGAGGTCCCTTCCATGAGTGA9317ZASP 9FGGTGAACACATTCCCTAACCZASP 9RCCCAGCAGAGTTATACATTG10331ZASP 10FGCTCCCTTGACCTGTGTCTZASP 10RGCCCATACTACCTTGGACAC11257ZASP 11FGGCTGTCCTTCTGGGTGTAAZASP 11RTCTTGGCTCTTGTGGCTCT12A348ZASP 12AFCATTTCTCTGGCTAGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13FGTTCTGGGAGCTGCCTACA2ASP 13FGTACAGCCCGCTCCCTCTCZASP 13FGTACTGCAACCAGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTTCCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGACTAGCTATGTA16229ZASP 16FGTTCCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCCCCATT	ZASP 7F	CCACCAATGGGCATGGAGCA				
8178ZASP 8FTIGCIGIGTCICCCGIGAGTZASP 8RGAGGTCCCTTCCATGAGTGA9317ZASP 9FGGTGAACACATTCCCTAACCZASP 9RCCCAGCAGAGTTATACATTG10331ZASP 10FGCTCCCTTGACCTGTGTCTZASP 10RGCCCTAACTACCTTGGACAC11257ZASP 11FGGCTGTCCTTCTGGGTGTAAZASP 11FGGCTGTCCTTGTGGCTCCT12A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12AFCATTTCTCTGGCTAGAGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG13267ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13FGTTCTGGGAGCTGCCTACAZASP 13FGTTCTGGGAGCTGCCTACAZASP 13FGTTCTGGGAGCTGCCTTACTZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTGCTTGGG16229ZASP 16FGTTCTCACGCAGGTCTGTTCTZASP 16FGTTCTCCTCTCTCCCCATT	ZASP 7R	AGCAGGACTCCCTGGCTTCT				
ZASP 8FTTGCTGTGTCTCCCGTGAGTZASP 8RGAGGTCCCTTCCATGAGTGA9317ZASP 9FGGTGAACACATTCCCTAACCZASP 9RCCCAGCAGAGTTATACATTG10331ZASP 10FGCTCCCTTGACCTGTGTCTZASP 10RGCCCTAACTACCTTGGACAC11257ZASP 11FGGCTGTCCTTCTGGGTGTAAZASP 11RTCTTGGCTCTTGTGGCTCCT12A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC14200ZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCTCTCZASP 14FGCAAGGAGCAGTGTC15290ZASP 15FTGATTTGGGGTTGTCTTGG2ASP 15FTGATTTGGGGATATGATGA16229ZASP 16FGTTCTCACGCAGGTCTGTTCTZASP 16FGTTCTCCTCTCTCCCCATT	8		178			
ZASP 8RGAGGTCCCTTCCATGAGTGA9317ZASP 9FGGTGAACACATTCCCTAACCZASP 9RCCCAGCAGAGTTATACATTG10331ZASP 10FGCTCCCTTGACCTGTGTCTZASP 10RGCCCTAACTACCTTGGACAC11257ZASP 11FGGCTGTCCTTCTGGGTGTAAZASP 11RTCTTGGCTCTTGTGGCTCCT12A348ZASP 12AFCATTTCTCTGGGTAGCAC12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCACAZASP 13FGTTCTGGGAGAGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCTCTCZASP 14FGCACAGCCGCTCCCTCTCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTIGGGATTGTTTGTG2ASP 15RCTACGCTGGCCAAGTATGTA16229ZASP 16FGTTCTCACGCAGGTCTGTTCTZASP 16FGTTCTCACCCAGGGTCTGTTCTZASP 16RGCTTCCTCTCTCCCCCATT	ZASP 8F	TTGCTGTGTCTCCCGTGAGT				
9317ZASP 9FGGTGAACACATTCCCTAACCZASP 9RCCCAGCAGAGTTATACATTG10331ZASP 10FGCTCCCTTGACCTGTIGTCTZASP 10RGCCCTAACTACCTTGGACAC11257ZASP 11FGGCTGTCCTTCTGGGTGTAAZASP 11RTCTTGGCTCTTGTGGCTCCT12A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGGAGAGTGCCTACAZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13FGTTCTGGGAGCTGCCTACA2ASP 13FGTTCTGGGAGCTGCCTTACTZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTGTTTGTGT2ASP 15FGTATCGGCGCAAGGTATGTA16229ZASP 16FGTTCTCACCGCAGGTCTGTTCTZASP 16FGTTCCTCTCTCTCCCCCATT	ZASP 8R	GAGGTCCCTTCCATGAGTGA				
ZASP 9FGGTGAACACATTCCCTAACCZASP 9RCCCAGCAGAGTTATACATTG10331ZASP 10FGCTCCCTTGACCTGTGTCTZASP 10RGCCCTAACTACCTTGGACAC11257ZASP 11FGGCTGTCCTTCTGGGTGTAAZASP 11RTCTTGGCTCTTGTGGCTCCT12A348ZASP 12AFCATTTCTCIGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGCCTCACAZASP 13FGTTCTGGGAGAGTGC2ASP 13FGTTCTGGGAGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCCZASP 14FAGTCAAGCCCGCTCCCTCCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTTTGGZASP 15FGTCTCACGCAGGTATGTA16229ZASP 16FGTTCCACGCAGGTCTGTTCTZASP 16FGTTCCCTCTCTCCCCCATT	9		317			
ZASP 9RCCCAGCAGAGTTATACATTG10331ZASP 10FGCTCCCTTGACCTGTGTCTZASP 10RGCCCTAACTACCTTGGACAC11257ZASP 11FGGCTGTCCTTCTGGGTGTAAZASP 11RTCTTGGCTCTTGTGGCTCT12A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGGAGACTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCCZASP 15FTGATTTGGGGTTTGTTGGZASP 15FTGATTTGGGGATATGATC16229ZASP 16FGTTCTCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCCCCATT	ZASP 9F	GGTGAACACATTCCCTAACC				
10331ZASP 10FGCTCCCTTGACCTGTTGTCTZASP 10RGCCCTAACTACCTTGGACAC11257ZASP 11FGGCTGTCCTTCTGGGTGTAAZASP 11RTCTTGGCTCTTGTGGCTCCT12A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BFGTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGAGAGCACCTGCTACAZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTTTGGZASP 15FTGATTTGGGGAGCTAGTAT16229ZASP 16FGTTCCACGCAGGTCTGTTCTZASP 16FGCTTCCTCTCTCCCCCATT	ZASP 9R	CCCAGCAGAGTTATACATTG				
ZASP 10FGCTCCCTTGACCTGTTGTCTZASP 10RGCCCTAACTACCTTGGACAC11257ZASP 11FGGCTGTCCTTCTGGGTGTAAZASP 11RTCTTGGCTCTTGTGGCTCCT12A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGAGAGCGCTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTTTGG2ASP 15FGTCTCACGCAGGTCAGTATCA16229ZASP 16FGTTCCACCACGAGGTCTGTTCTZASP 16RGCTTCCTCTCTCCCCATT	10		331			
ZASP 10RGCCCTAACTACCTTGGACAC11257ZASP 11FGGCTGTCCTTCTGGGTGTAAZASP 11RTCTTGGCTCTTGTGGCTCCT12A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGAGGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTTTGGZASP 15FGTGTCACGCAGGTATGTA16229ZASP 16FGTTCTCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCCCCATT	ZASP 10F	GCTCCCTTGACCTGTTGTCT				
II257ZASP 11FGGCTGTCCTTCTGGGTGTAAZASP 11RTCTTGGCTCTTGTGGCTCCTI2A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATCTGI2B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGACI3267ZASP 13FGTTCTGGAGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAGI4200ZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14FCACATGCCATCGAAGTGTTCI5290ZASP 15FTGATTTGGGGTTTGTCTTGGZASP 15RCTAGCGTGGCAAGGTATGTAI6229ZASP 16FGTTCCACGCAGGTCTGTTCTZASP 16FGCTTCCTCTCTCCCCATT	ZASP 10R	GCCCTAACTACCTTGGACAC				
ZASP 11FGGCTGTCCTTCTGGGTGTAAZASP 11RTCTTGGCTCTTGTGGCTCCT12A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGAAGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTCTTGG2ASP 15FGTACTGGCGCAAGGTATGTA16229ZASP 16FGTTCCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCCCCATT	11		257			
ZASP 11RTCTTGGCTCTTGTGGCTCCT12A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTCTTGG2ASP 15RCTAGCGTGGCAAGGTATGTA16229ZASP 16FGTTCCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCCCCATT	ZASP 11F	GGCTGTCCTTCTGGGTGTAA				
12A348ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTCTTGGZASP 15RCTAGCGTGGCCAAGGTATGTA16229ZASP 16FGTTCTCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCCCCCATT	ZASP 11R	TCTTGGCTCTTGTGGCTCCT				
ZASP 12AFCATTTCTCTGGCTAGGAGTGZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTCTTGGZASP 15RCTAGCGTGGCCAAGGTATGTA16229ZASP 16FGTTCTCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCCCCCATT	12A		348			
ZASP 12ARCTGGGAGAAGCTATCATCTG12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTCTTGG2ASP 15FGTACTGCGTGGCAAGGTATGTA16229ZASP 16FGTTCTCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCCCCATT	ZASP 12AF	CATTTCTCTGGCTAGGAGTG				
12B352ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14FCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTCTTGGZASP 15FGTACGTGGCAAGGTATGTA16229ZASP 16FGTTCCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCCCCCATT	ZASP 12AR	CTGGGAGAAGCTATCATCTG				
ZASP 12BFTGCACCCTCGGTGGCCTACAZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14RCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTCTTGGZASP 15RCTAGCGTGGCAAGGTATGTA16229ZASP 16FGTCTCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCCCCCATT	12B		352			
ZASP 12BRCTCCCAACCAGGGCTCAGAC13267ZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14RCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTCTTGGZASP 15RCTAGCGTGGCAAGGTATGTA16229ZASP 16FGTCTCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCTCCCCATT	ZASP 12BF	TGCACCCTCGGTGGCCTACA				
13267ZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14RCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTCTTGGZASP 15RCTAGCGTGGCAAGGTATGTA16229ZASP 16FGTTCCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCCCCCATT	ZASP 12BR	CTCCCAACCAGGGCTCAGAC				
ZASP 13FGTTCTGGGAGCTGCCTTACTZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14RCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTCTTGGZASP 15RCTAGCGTGGCAAGGTATGTA16229ZASP 16FGTCTCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCTCCCCATT	13		267			
ZASP 13RGGAAGAGACATGGGTCAGAG14200ZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14RCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTCTTGGZASP 15RCTAGCGTGGCAAGGTATGTA16229ZASP 16FGTCTCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCTCCCCCATT	ZASP 13F	GTTCTGGGAGCTGCCTTACT				
14200ZASP 14FAGTCAAGCCCGCTCCCTCTCZASP 14RCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTCTTGGZASP 15RCTAGCGTGGCAAGGTATGTA16229ZASP 16FGTCTCACGCAGGTCIGTTCTZASP 16RGCTTCCTCTCTCTCCCCCATT	ZASP 13R	GGAAGAGACATGGGTCAGAG				
ZASP 14F AGTCAAGCCCGCTCCCTCTC ZASP 14R CACATGCCATCGAAGTGTTC 15 290 ZASP 15F TGATTTGGGGTTTGTCTTGG ZASP 15R CTAGCGTGGCAAGGTATGTA 16 229 ZASP 16F GTCTCACGCAGGTCTGTTCT ZASP 16R GCTTCCTCTCTCTCCCCCATT	14		200			
ZASP 14RCACATGCCATCGAAGTGTTC15290ZASP 15FTGATTTGGGGTTTGTCTTGGZASP 15RCTAGCGTGGCAAGGTATGTA16229ZASP 16FGTCTCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCTCCCCCATT	ZASP 14F	AGTCAAGCCCGCTCCCTCTC				
15 290 ZASP 15F TGATTTGGGGTTTGTCTTGG ZASP 15R CTAGCGTGGCAAGGTATGTA 16 229 ZASP 16F GTCTCACGCAGGTCTGTTCT ZASP 16R GCTTCCTCTCTCTCCCCATT	ZASP 14R	CACATGCCATCGAAGTGTTC				
ZASP 15FTGATTTGGGGTTTGTCTTGGZASP 15RCTAGCGTGGCAAGGTATGTA16229ZASP 16FGTCTCACGCAGGTCTGTTCTZASP 16RGCTTCCTCTCTCTCCCCCATT	15		290			
ZASP 15R CTAGCGTGGCAAGGTATGTA 16 229 ZASP 16F GTCTCACGCAGGTCTGTTCT ZASP 16R GCTTCCTCTCTCCCCCATT	ZASP 15F	TGATTTGGGGGTTTGTCTTGG				
16 229 ZASP 16F GTCTCACGCAGGTCTGTTCT ZASP 16R GCTTCCTCTCTCCCCCATT	ZASP 15R	CTAGCGTGGCAAGGTATGTA				
ZASP 16F GTCTCACGCAGGTCTGTTCT ZASP 16R GCTTCCTCTCTCCCCCATT	16		229			
ZASP 16R GCTTCCTCTCTCCCCATT	ZASP 16F	GTCTCACGCAGGTCTGTTCT				
	ZASP 16R	GCTTCCTCTCTCTCCCCATT				

The search for rare variants (MAF, 1%) that were specifically found in the affected man was carried out with different open access Web tools. The effect of the candidate variant in protein structure and phylogenetic conservation was predicted by using bioinformatics tools, such as PolyPhen-2 (Polymorphism Phenotyping v2), SIFT (Sort Intolerant from Tolerant) and Mutation Taster, to estimate the pathogenicity risk for the variant.

Analysis of DNA sequences in coding exons of the LDB3 gene represents a novel heterozygous missense. So far, the substitution (the c.1687A > G, p.Ile563Val mutation in exon 10 of LDB3 (Figure 1)) has neither been observed as a polymorphism in the latest 1000 Genomes Project databases, nor as a causative mutation in any accessible disease mutation database (for example, HGMD: Human Gene Mutation Database) (Table 2).



A, Normal Control; B, a Patient; c.1687ATC > GTC heterozygous missense mutation (p.lle563Val) in exon 10 of LDB3 gene was detected in the patient.

Codon Change	Amino Acid Change	Codon Number	Phenotype	Reference
GAC/AAC	Asp/Asn	117	Cardiomyopathy, dilated	(13)
AAG/ATG	Lys/Met	136	Cardiomyopathy, dilated	(13)
GCC/ACC	Ala/Thr	147	Myofibrillar myopathy	(8)
GCC/GTC	Ala/Val	165	Myofibrillar myopathy	(8)
GCC/ACC	Ala/Thr	174	Myofibrillar myopathy	(14)
CGC/TGC	Arg/Cys	268	Myofibrillar myopathy	(8)
ATC/GTC	Ile/Val	563	Myofibrillar myopathy	Present study. 2015

Table 3. Various in Silico Bioinformatics Tools Have Been Developed That Predict the Novel Mutation

LDB3/Software	SIFT Score	PolyPhen Score	Mutation Taster
ENST00000429277, I563V	0.01 (DAMAGING)	0.993 (PROBABLY DAMAGING)	Disease causing

LIM domain binding 3 (LDB3 [ENSG00000122367]) is at position chr10:88476524 A.G. In humans, LDB3 has nine annotated protein coding transcripts. The novel mutation produces an amino acid alter (Ile to Val) that modifies four of the nine coding isoforms predicted in the Ensembl database, and the function of this mutation is unknown.

Bioinformatics analyses indicate that the I563V mutation most probably causes LDB3 dysfunction, leading to the MFM clinical phenotype. Furthermore, analysis using various programs, e.g., SIFT (deleterious, score 0.00), Mutation Taster (disease causing, P value 1.0) and Polyphen-2 (probably damaging, score 1.00) indicated p.Ile563Val was predicted to be disease causing and probably damaging (Table 3). Unfixed muscle tissue of this patient was not accessible and no muscle biopsy could be obtained in order to conduct supplementary proteomic analyses for further clarification. Furthermore, family members were not accessible for segregation analysis to clarify the pathogenicity.

3. Discussion

In the present study, using direct sequencing, we looked for mutations in this patient in the LDB3 gene previously associated with MFM or muscular dystrophy. We identified the c.1687A > G (p.Ile563Val) mutation in exon 10 of this gene in members of a consanguineous family with an autosomal dominant mode of inheritance with severe MFM. So far, this mutation has not been reported in any of the information banks. All bioinformatics tools applied classified the identified substitution as pathogenic.

The LDB3 gene (OMIM: 605906) has 16 exons and spans approximately 70 kb (15). There are three isoforms of LDB3 in human skeletal muscle, which are produced by alternative splicing of exons 9 and 10. The prenatal long isoform (ZASP-L) contains exon 10 and the postnatal long isoform (ZASP-Ldelex10) lacks exon 10. Both long isoforms include a PDZ domain, ZASP-like motif encoded by exon 6 and 3 LIM domains. The short isoform (ZASP-S) lacks the LIM domains, because it has a stop codon in exon 9 (15). PDZ domain-containing proteins interact with a number of proteins involved in clustering and targeting of membrane proteins or with each other in cytoskeletal assembly. LIM domain-binding protein 3 encoded by this gene is a key Z-disk protein that interacts with α -actinin and protein kinase C. LDB3 protein also interacts with all members (MYOZ1, MYOZ2, MYOZ3) of the myozenin family (16, 17).

The three different missense mutations in the LDB3 gene (A147T, A165V, and R268C), recently published by Selcen and Engel, were found in patients in a heterozygous form, causing myofibrillar myopathy. The first two mutations occurred in exon 6, but R268C occurred in exon 9 (8). Since both mutations were detected on the same gene in LDB3, a similar phenotype might be expected in the patients of both families such as progressive proximal and/or distal weakness, cardiac involvement and peripheral neuropathy. Mutant LIM domain-binding protein 3 (ZASP) is predicted to weaken the linkage of Z-disk filaments to thin filaments. This novel mutation (c.1687A > G (p.Ile563Val) mutation in exon 10) may change the function of the ZASP-L and LIM domains.

In summary, in this study we identified by direct sequencing the first dominant and heterozygous mutation in the LDB3 gene causing MFM and the first in a non-European patient. Consequently, defects in this protein could destabilize the muscle cell membrane and, at the same time, weaken myofibrils. This may eventually result in clinical and molecular features resembling MFM. Our finding confirms previous reports that the muscle phenotype associated with LDB3 mutations is consistent.

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