

Two new rare pathogenic variants in DES gene causing distal myofibrillar myopathy

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Introduction

Myofibrillar myopathy (MFM) is a clinically and genetically heterogeneous disorder characterized by the abnormal finding of myofibrillar disruption on EM and excessive desmin deposition in muscle fibers^{1, 2}. Desmin deposits are not specific to MFM and can be found in other neuromuscular conditions such as x-linked myotubular myopathy, congenital myotonic dystrophy, SMA, nemaline rod myopathy, and inclusion body myositis³. On the other hand, MFM has been linked to mutations in desmin, alphaB-crystallin, myotilin, filamin C, and ZASP. MFM is associated with a broad spectrum of clinical phenotypes, affecting individuals between the ages of 25–45 with proximal, distal, or generalized weakness¹. MFM can be transmitted in an autosomal dominant, autosomal recessive, or x-linked pattern⁴. There are also a few sporadic cases. In addition to the skeletal muscle being involved, the heart can be affected, and congestive heart failure and arrhythmias can be the predominant feature of the disease. There is no proven medical therapy to improve skeletal muscle weakness. Cardiac transplantation can be lifesaving in patients with severe cardiomyopathy. Here, we present two new variants in DES causing desmin-myofibrillary myopathies demonstrated by muscle biopsies.

Case 1

This is the case of a young adult diagnosed with Epstein's anomaly of the tricuspid valve at birth. His cardiologic symptoms started at age 11 with chest pain and shortness of breath. His heart transplant was performed at the age of 13. He had a challenging course but eventually recovered and had a very active life, working in construction and playing soccer and the drums. At 26, he started noticing tiredness and difficulty climbing stairs. One year later, he developed atrial fibrillation, and he was cardioverted. At that point, he decided to stop working in construction and reduced his physical activities. This was followed by worsening his weakness, with progressive difficulty in walking and frequent trips and falls. His symptoms also progressed to involve his arms and hands. For the last eight months, he has also noticed neck extension weakness. He had no visual or hearing problems and no chewing or swallowing issues. He had no family history of neuromuscular diseases. His neurological examination was pertinent for distal more than proximal weakness in the lower and upper extremities, left worse than right, with significant bilateral foot drop. His reflexes were 1+ throughout. He had a steppage gait with a Trendelenburg component. His CPK was 800. HMGCR was negative. EMG showed diffuse, irritable myopathy. Muscle biopsy showed a progressive non-inflammatory chronic myopathy with rimmed vacuoles, favoring a myofibrillar myopathy (MFM). Immunostaining for Desmin in the muscle biopsy sample demonstrated immunoreactivity in myofibers with focal accumulations of Desmin-positive material in myofibers (figure 1 B).

Comprehensive Neuromuscular Disorders Panel was performed (Table 1), and a variant of uncertain significance in the DES gene c.1255C>A (p.Pro419Thr) in heterozygosis was found (Table 2).

A few months later, he developed shortness of breath at rest and chest pain. He was found to have severe coronary

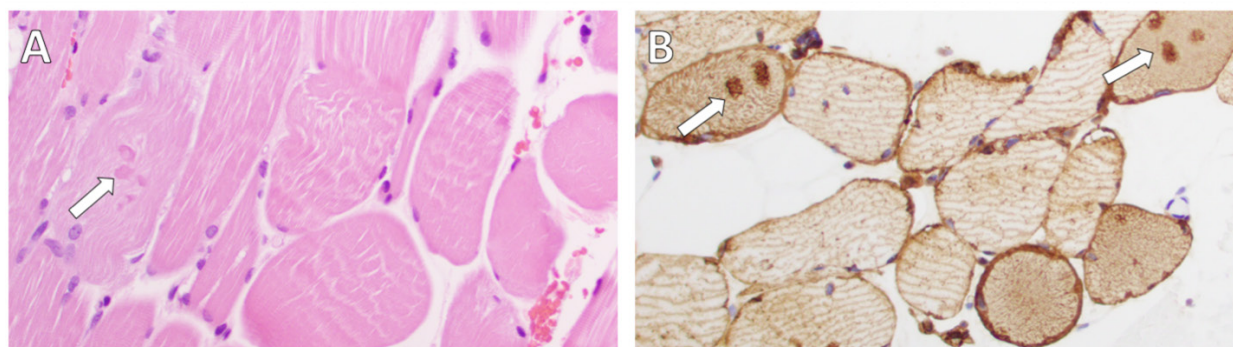


Figure 1: Muscle biopsy of Case 1. (A) H&E staining reveals cytoplasmic deposits in one fiber (arrow); (B) Desmin immunohistochemistry demonstrates the deposits to be Desmin-reactive (arrow).

Table 1: Features of the two new *DES* variants

	c.1243 C>T, p. Arg415Trp	c.1255C>A, p.Pro419Thr
Population frequency	Rare (Allele frequency on gnomAD: 0.00002172).	Private (no cases reported on gnomAD)
In silico prediction	Polyphen: probably damaging (Score: 1.0); SIFT: deleterious Mutation t@sting: prediction disease causing	Polyphen: probably damaging (Score: 0.988); SIFT: deleterious Mutation t@sting: prediction disease causing
Conservation	PhyloP: 5.344 PhastCons: 1	PhyloP: 5.11 PhastCons: 0.99
Further information	Missense variants in the same (R415Q) and nearby residues (E413K, P419S) have been reported in the Human Gene Mutation Database in association with DES-related disorders.	A different missense substitution at this codon (p.Pro419Ser) has been determined to be pathogenic ⁵⁻⁸ .

gnomAD: genome aggregation database

Table 2: Other variants identified in the two patients

	Variants identified	Genes tested
Case 1	<i>ANO5</i> , c.692G>T (p.Gly231Val) <i>DES</i> , c.1255C>A (p.Pro419Thr) <i>CHKB</i> , c.577G>A (p.Glu193Lys) <i>MYPN</i> , c.1952C>A (p.Pro651Gln) <i>NEB</i> , c.23753C>T (p.Ser7918Leu)	<i>ACTA1, AGRN, ALG2, ANO5, ATP2A1, B3GALNT2, B4GATI, BAG3, BIN1, CACNAIS, CAPN3, CAV3, CCDC78, CFL2, CHAT, CHKB, CHRNI, CHRNB1, CHRND, CHRNE, CLCN1, CNTN1, COL6A1, COL6A2, COL6A3, COLQ, CPT2, CRYAB, DAG1, DES, DMD, DNAJB6, DNM2, DOK7, DPAGT1, DPM1, DPM2, DPM3, DYSE, EMD, FHLL, FKBP14, FKRP, FKTN, FLNC, GAA, GFPT1, GMPPB, GNE, ISPD, ITGA7, KBTBD13, KCNJ2, KLHL40, KLHL41, LAMA2, LAMP2, LARGE1, LDB3, LMNA, LMOD3, MATR3, MEGF10, MTMI, MUSK, MYH2, MYH7, MYL2, MYOT, MYPN, NEB, PLEC, PNPLA2, POMGNT1, POMGNT2, POMK, POMT1, POMT2, RAPSN, RYR1, SCN4A, SELENON, SGCA, SGCB, SGCD, SGCG, SMN1, SMN2, SQSTM1, STAC3, STIM1, TAZ, TCAP, TIA1, TMEM5, TNNT1, TNPO3, TPM2, TPM3, TRAPPC11, TRIM32, TTN, VCP, VMA21</i>
Case 2	<i>BAG3</i> , c.1634C>G (p.Pro545Arg) <i>DES</i> , c.1243C>T (p.Arg415Trp) <i>SGCB</i> , c.419A>G (p.Asn140Ser)	<i>ACTA1, ANO5, ASAHI, ATP2A1, B3GALNT2, B4GATI, BAG3, BICD2, BIN1, BVES, CACNAIS, CAPN3, CAV3, CCDC78, CFL2, CHKB, CLCN1, CNTN1, COL12A1, COL6A1, COL6A2, COL6A3, CRYAB, DAG1, DES, DMD, DNAJB2, DNAJB6, DNM2, DOK7, DPM1, DPM2, DPM3, DYNCH1, DYSE, EGR2, EMD, FHLL, FKRP, FKTN, FLNC, GAA, GBEL, GMPPB, GNE, IGHMBP2, ISPD, ITGA7, KBTBD13, KLHL40, KLHL41, LAMA2, LAMP2, LARGE, LDB3, LMNA, LMOD3, MEGF10, MICU1, MTMI, MYH2, MYH7, MYOT, NEB, PHKAI, PLEC, PLEKHG5, POMGNT1, POMK, POMT1, POMT2, PYGM, RYR1, SCN4A, SEPNI, SGCA, SGCB, SGCD, SGCG, SIL1, SLC52A2, SLC52A3, SYNE1, TCAP, TMEM5, TNNT2, TNNT1, TNPO3, TORIAIPI, TPM2, TPM3, TRAPPC11, TRIM32, TRIP4, TRPV4, TTN, UBA1, VCP, VRK1</i>

artery disease, presumed due to non-compliance with his medication over time. The patient passed away at 30 due to cardiac arrest, likely secondary to myocardial infarction.

Case 2

A 59-year-old man with no significant past medical history presents with slowly progressive distal lower extremity weakness. He refers that he used to be very active and was a runner but that his symptoms started around six years prior when he started noticing that he was walking differently. He noticed difficulty clearing his left foot during ambulation, and this caused his running to be difficult as well. Weakness gradually progressed to involve his right ankle. He also describes some muscle soreness and stiffness that appear as the day progresses. His physical exam is remarkable for bilateral calf hypertrophy, weakness limited to around his ankles bilaterally, but no significant sensory deficits. His father had similar calves and had died from congestive heart failure complications. He has had extensive testing done, including genetic testing (Table 2) that reported a variant of uncertain significance in the DES gene (c.1243 C>T, p. Arg415Trp) (Table 1), but likely pathogenic based on the predicted protein alteration, and also had a muscle biopsy which reported that desmin immunostaining revealed uneven immunoreactivity in myofibers with apparent focal accumulations of desmin positive material in some myofibers.

Discussion

These are 2 cases of adults presenting with a rare form of muscular dystrophy, myofibrillary myopathy. The comprehensive neuromuscular gene panel revealed in each case a variant of uncertain significance on the DES gene, c.1255C>A (p.Pro419Thr) and c.1243 C>T (p. Arg415Trp), respectively. These variants are not present in population databases, and it has not been reported in the literature in individuals with DES-related disease. However, given the clinical phenotypes and the muscle biopsy with findings of MFM and staining positive for desmin, the previously unreported DES gene mutations Pro419Thr and Arg415Trp are most likely pathogenic.

MFM is rare but should remain a diagnostic consideration in young adults presenting with slowly progressive proximal and distal weakness, and cardiomyopathy discovery of new pathogenic variants such as the ones discussed in these cases will help further understand this disease and facilitate the diagnosis in future patients.

Disclosure

Dr Olimpia Carbanar reports no disclosures relevant to the manuscript.

Dr Sakir “Hume” Gultekin reports no disclosures relevant to the manuscript.

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Author Contribution

- Olimpia Carbanar: Study concept and design, acquisition of data, lead role in writing manuscript, analysis and interpretation
- Sakir “Hume” Gultekin: Acquisition of data, intellectual contribution
- Mario A. Saporta: Study concept and design, acquisition of data, analysis and interpretation, critical revision of manuscript for intellectual content, intellectual contribution, study supervision

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