

The DES R415W Mutation: Clinicopathological Report of Four Patients

Sadaf Khorasanizadeh, M.D.¹, Qian Wu, M.D.², Marie L. Rivera-Zengotita, M.D.³ and Kevin J. Felice, D.O.^{1*}

¹Muscular Dystrophy Association Care Center, Department of Neuromuscular Medicine, Hospital for Special Care, New Britain, Connecticut, USA.

²Department of Pathology and Laboratory Medicine, University of Connecticut School of Medicine, Farmington, Connecticut, USA.

³Department of Pathology, Immunology and Laboratory Medicine, University of Florida College of Medicine, Gainesville, FL, USA.

*Correspondence:

Dr. Kevin Felice, Muscular Dystrophy Association (MDA) Care Center, Department of Neuromuscular Medicine, Hospital for Special Care, New Britain, Connecticut 06053, USA, Tel: (860) 612-6305; Fax: (860) 612-6304; E-mail: felice@uchc.edu.

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ABSTRACT

The myofibrillar myopathies are a heterogeneous group of genetic disorders characterized pathologically by the disruption of myofibrils and accumulation of degradation products in intracellular inclusions. Most patients present with progressive limb muscle weakness – distal, proximal or both. Cardiomyopathy – dilated or hypertrophic – can be an isolated feature or may develop concurrently with the skeletal myopathy. Mutations in the DES gene account for approximately 7% of genetically-determined myofibrillar myopathies. DES encodes for the intermediate filament protein desmin which is an essential component of the extra-sarcomeric cytoskeleton in cardiac, skeletal and smooth muscle cells. Since the first report of DES gene mutations as a cause of a familial and skeletal myopathy in two families in 1998, 126 pathogenic mutations have been documented – including 24 involving the tail domain. The tail domain mutation, DES R415W, was previously described in a 30-year-old patient with leg weakness. Over the past 10 years, we have diagnosed and cared for four patients with progressive skeletal myopathy and muscle histopathology consistent with myofibrillar myopathy – all harboring the DES R415W mutation. In this report, we describe the clinicopathological findings in these four patients. In summary, we report four patients with the DES R415W mutation. This tail domain mutation causes a late-onset myopathy primarily affecting the lower extremities. Respiratory muscle weakness, mild hyperCKemia, and sensory neuropathy – but not overt cardiac involvement – are associated features.

Keywords

Myopathy, Muscular dystrophy, Myofibrillar myopathy, Desmin myopathy, DES gene.

Introduction

The myofibrillar myopathies are a heterogeneous group of genetic disorders characterized pathologically by disruption of myofibrils and accumulation of degradation products in intracellular inclusions [1-3]. Most patients present with progressive limb muscle weakness – distal, proximal or both. Cardiomyopathy – dilated or hypertrophic – can be an isolated feature or may develop concurrently with the skeletal myopathy. Other common phenotypic features include length-dependent sensorimotor axonal polyneuropathy and chest wall/diaphragmatic muscle weakness leading to chronic respiratory insufficiency. Thus far, ten genes – DES, CRYAB, SEPN1, LDB3, MYOT, FLNC, BAG3, TRIM54,

KY, TRIM63 – have been implicated in causing myofibrillar myopathy [4]. In addition, other gene disorders – PLEC, TTN, FHL1, ACTA1, HSPB8, DNAJB6 – have also been associated with myofibrillar histopathology, and upwards of 50% of reported cases have eluded a specific genetic diagnosis [5].

Mutations in the DES gene account for approximately 7% of genetically-determined myofibrillar myopathies [6]. DES encodes for the intermediate filament protein desmin which is an essential component of the extra-sarcomeric cytoskeleton in cardiac, skeletal and smooth muscle cells. Mutations in DES on chromosome 2q35 cause autosomal dominant, autosomal recessive, and sporadic skeletal myopathies, cardiomyopathy or both with marked phenotypic variability – including myofibrillar myopathy (MFM) (aka, desmin-related myopathy, desminopathy), limb-girdle muscular dystrophy, and dilated and hypertrophic

cardiomyopathy [7]. Since the first description of desmin-related myopathy by Goldfarb in 1998, 126 mutations in the DES gene have been categorized including the case of a 30-year-old patient with leg weakness who harbors the R415W mutation [8-10]. Over the past 10 years, we have diagnosed and cared for four patients with a progressive skeletal myopathy and muscle histopathology consistent with myofibrillar myopathy – all harboring the DES R415W mutation. In this report, we describe the clinicopathological findings in these four patients.

Material and Methods

Clinical exams and laboratory tests

This is a case study. The clinical exams and all investigations were performed with the informed consent of the patients for diagnostic purposes. The costs for all testing were funded by the patient's health care insurance providers.

Muscle biopsy studies

Muscle biopsies for patients 1-3 were processed and analyzed at the Pathology Laboratory at the University of Connecticut (QW) and for patient 4 at the University of Florida (MLRZ). Muscle tissue was obtained in open biopsy, snap frozen into the liquid phase of isopentane, previously cooled in liquid nitrogen. Transverse cryostat sections were cut at 10 μ m thickness and stained by hematoxylin and eosin, modified Gomori trichrome, NADH-tetrazolium reductase (NADH-TR), succinate dehydrogenase, Congo red, periodic acid Schiff, cytochrome c oxidase according to standard protocols. Immunohistochemical analyses of muscle biopsy sections were performed with monoclonal primary antibodies against desmin, fast and slow myosin, dystrophin (rod, C-terminus and N-terminus domains), dysferlin, merosin, emerin, alpha- and gamma-sarcoglycan, and calveolin-3 using standard techniques. Samples for electron microscopy were fixed in 4% glutaraldehyde and processed according to standard procedures.

Genetic studies

DNA testing

Next-gen DNA sequencing panels were performed by several commercial reference labs including Prevention Genetics (Marshfield, Wisconsin, USA) for patient 1, Eurofins Clinical Diagnostics (Tucker, Georgia, USA) for patient 2, Emory Genetics (Decatur, Georgia, USA) for patient 3, and GeneDx (Gaithersburg, Maryland, USA) for patient 4.

Case Reports

Patient 1

This 53-year-old man presented with progressive bilateral foot drop and gait difficulties. Twelve years prior, he was found to have restrictive lung disease during a screening pulmonary function test which was required for his employment as a volunteer firefighter. Five years prior, he began to notice increasing shortness of breath with exertion and gait difficulties with occasional falls. He also noted mild numbness and tingling in his toes and feet. Gait problems progressed to the point that he required bilateral ankle-foot orthoses for severe foot drop. Other medical problems included pre-diabetes, hypertension, nephrolithiasis, and seborrhic

dermatitis. Family history was remarkable for late-onset weakness and gait difficulties in his deceased father and older sister.

Exam was remarkable for a steppage-pattern gait. He was unable to stand on heels or tiptoes. He needed to push-off with both hands in order to arise from a chair. There were mild pes cavus foot deformities and tight heel cords, and prominent atrophy of foot and anterior foreleg muscles. Weakness was restricted to the lower extremities, affecting hip flexors (MRC grade 3), knee extensors and flexors (MRC grade 4), and foot and toe extensors (MRC grade 2). There was no myotonia. Ankle jerks were absent while other myotatic reflexes were normal. Sensory exam revealed mildly decreased perception of vibration and pin prick sensations in the toes and feet. Toe position sensation was intact.

Creatine kinase was 422 units/L (normal, <175). Complete blood count, chemistry panel, fasting blood glucose, thyroid function studies, serum protein electrophoresis, immunofixation, and vitamin B12 level were normal. Pulmonary function test revealed a forced vital capacity of 1.81 L (35% of predicted). Chest x-ray was normal. Electrocardiogram and echocardiogram were normal. Nerve conduction studies showed low-amplitude sural sensory nerve action potentials. Other sensory and motor nerve conduction studies were normal. Concentric needle electromyography showed increased insertional activity, sustained fibrillations and positive sharp waves, and increased (early) recruitment of small polyphasic motor unit action potentials in a diffuse pattern – abnormalities were particularly prominent in clinically weak muscles (e.g., tibialis anterior). Electromyography was consistent with a diffuse myopathy and concurrent length-dependent sensory neuropathy. Muscle biopsy of the right gastrocnemius showed marked variability in myofiber size, occasional necrosis and myophagocytosis, increased internalized nuclei, rare pyknotic nuclear clumps, increased endomysial fibrosis, sarcoplasmic masses on hematoxylin-eosin and Gomori trichrome stains, core-like lesions on NADH-TR stains, desmin-positive aggregates on immunostains, and granulofilamentous material on electron microscopy (Figure 1). Genetic testing disclosed a heterozygous R415W mutation (c.1243C>T nucleotide substitution) in exon 6 of the DES gene.

Patient 2

This 62-year-old right-handed woman is the sister of patient 1. She noted progressive leg weakness and gait difficulties for the past 12 years. She required a cane about 10 years prior. Leg weakness slowly progressed over the ensuing years to the point that she became bedbound 2 years prior to our evaluation. She reported recurrent pneumonia for many years, and, over last 5 years, had 1-3 bouts of pneumonia per year. Other medical problems include diabetes for 20 years and coronary artery disease requiring a left anterior descending artery stent.

On exam, she was bedbound and morbidly obese. Cranial nerve exam showed mild left upper eyelid ptosis. Strength testing revealed mild weakness of proximal upper extremity muscles (MRC grade 4) and severe diffuse lower extremity muscle weakness, especially

of hip flexors and foot dorsiflexors (MRC 1-2). Lower extremity myotatic reflexes were absent and other reflexes were hypoactive. Sensory exam revealed decreased vibration and proprioception at the toe and ankle level, and decreased pin prick sensation affecting the feet and ankles. Pulmonary function tests, EKG and echocardiogram, and lab test results were not available.

Muscle biopsy showed protein aggregates on Gomori trichrome, granulofilamentous aggregates on electron microscopy, and increased immunoreactivity on desmin stain (Figure 1). Next-Gen custom muscular dystrophy panel (35 genes) disclosed a heterozygous R415W mutation (c.1243C>T nucleotide substitution) in exon 6 of the DES gene. Excluded were other potential gene disorders associated with myofibrillar pathology including MYOT, TTN, PLEC and FHL1.

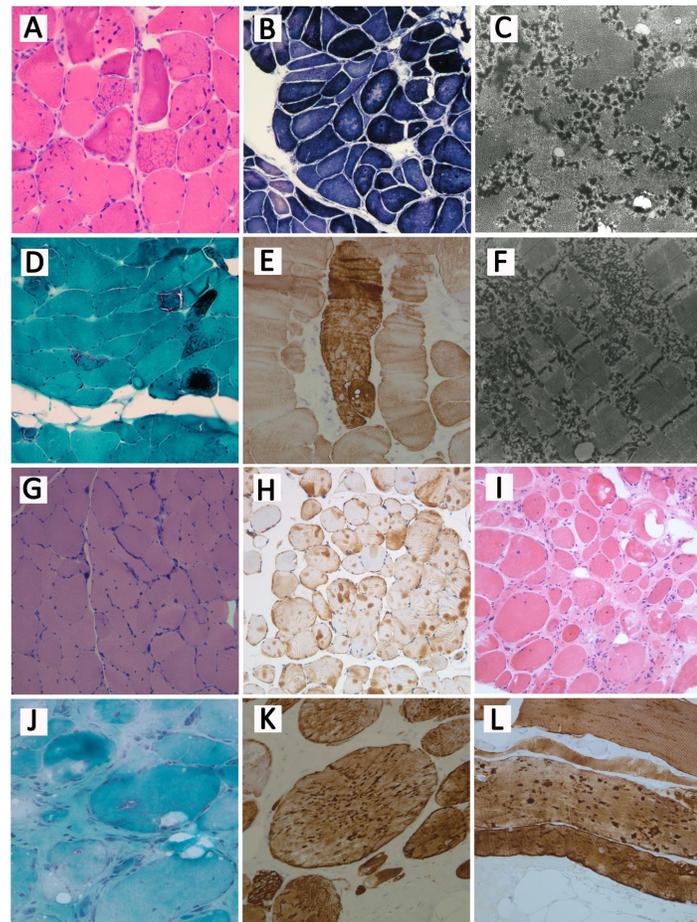


Figure 1: Muscle histopathology from patient 1 (A,B,C), patient 2 (D,E,F), patient 3 (G,H), and patient 4 (I,J,K,L) showing protein aggregates (A,G [H&E], D [Gomori trichrome]), moth-eaten fibers (B [NADH-TR]), granulofilamentous aggregates (C,F [electron microscopy]), increased immunoreactivity (E,H,K,L [desmin]), dystrophic changes (I [H&E]), and rimmed vacuoles (J [Gomori trichrome]).

Patient 3

This 83-year-old woman presented with progressive leg weakness and gait difficulties for the past 20 years. She had required a rolling walker for the past 2 years to assist with ambulation. She noted occasional low back pain – otherwise, she denied pain or

sensory symptoms. She noted increasing shortness of breath with exertion and utilized nocturnal continuous positive airway device for obstructive sleep apnea. Past medical history was also remarkable for pulmonary and systemic hypertension, glaucoma, atrial fibrillation, pacemaker placement, hyperlipidemia, gastroesophageal reflux disease, and late-onset cataracts. She had never taken statin or myotoxic medications. She was born in Philadelphia, Pennsylvania and of German ancestry. Family history was remarkable for father dying at age 65 years from a myocardial infarction. Her mother died at age 63 years of unclear cause. Exam was remarkable for slow and unsteady gait with slightly stooped posture, genu valgum, and Trendelenburg pattern. She was unable to stand on heels or tiptoes. She needed to push-off with both hands in order to arise from a chair. Cranial nerve exam showed mild partial bilateral upper eyelid ptosis but was otherwise normal. Strength testing revealed weakness of arm abductors, hip flexors, and foot dorsiflexors (MRC grade 4). There was no myotonia. Ankle jerks were absent and other myotatic reflexes were hypoactive. Sensory exam revealed mildly decreased perception of vibration and pin prick sensations in the toes and feet. Toe position sensation was intact.

Creatine kinase was 113 units/L (normal, <135). Complete blood count, chemistry panel, fasting blood glucose, thyroid function studies, serum protein electrophoresis, immunofixation, and vitamin B12 level were normal. Pulmonary function test revealed a forced vital capacity of 1.68 L (62% of predicted). Electrocardiogram showed a paced rhythm and echocardiogram showed mild left ventricular hypertrophy, and normal ejection fraction. MRI of the lumbosacral spine showed active disc disease with mild to moderate neural canal stenosis and neural foraminal narrowing as well as atrophy of paraspinal muscles bilaterally. Nerve conduction studies showed low amplitude sural sensory nerve action potentials, and peroneal/extensor digitorum brevis and tibial/abductor hallucis compound muscle action potentials. Other sensory and motor nerve conduction studies were normal. Concentric needle electromyography showed a mixed pattern with increased insertional activity, sustained fibrillations and positive sharp waves, and decreased recruitment of large motor unit action potentials in distal muscles of the lower extremity; and increased (early) recruitment of small polyphasic motor unit action potentials in proximal muscles of the upper and lower extremities. Electromyography was consistent with a proximal myopathy and concurrent length-dependent sensorimotor polyneuropathy.

Muscle biopsy of the left vastus lateralis showed moderate variability in myofiber size, rare regenerating myofibers, slightly smaller type I myofibers, rare pyknotic nuclear clumps, and desmin-positive aggregates on immunostains. Electron microscopy did not reveal vacuoles or inclusions. Immunohistochemical stains for dystrophin, dysferlin, alpha-sarcoglycan, gamma-sarcoglycan, emerin, merosin, and caveolin-3 were normal (Figure 1). Next-Gen custom muscular dystrophy panel (35 genes) disclosed a heterozygous R415W mutation (c.1243C>T nucleotide substitution) in exon 6 of the DES gene. Excluded were other potential gene disorders associated with myofibrillar pathology

including MYOT, TTN, PLEC and FHL1.

Patient 4

This 58-yr man was referred for 5 years of progressive bilateral foot drop and gait difficulties. He initially noticed difficulty standing on his heels. Over time, he developed a steppage-pattern gait, requiring bilateral ankle-foot orthoses. He had problems climbing stairs and arising from the floor. He noted occasional muscle cramps, but otherwise denied pain or sensory symptoms. He denied hand or arm weakness. Prior to the onset of symptoms, he was always physically strong and active. He recalled large calf muscles since childhood. Prior neurologic evaluation suggested a lower motor neuron disease as the diagnosis, probably a distal spinal muscular atrophy or hereditary motor neuropathy. Past medical history was remarkable for hyperlipidemia, mitral valve prolapse, and erectile dysfunction. He was a sober alcoholic for 20 years. He never took statin medications. He was born and resided in US. His father died at age 74 years from cardiac disease. He was of Scottish ancestry. His mother, aged 87 years, was in a nursing home. She had recently completed a course of radiation therapy for lung cancer. She was of Dutch-Irish ancestry. Patient's older sister and two daughters were in good health. To his knowledge, there was no known family history of neuromuscular disease.

Exam was remarkable for a steppage-pattern gait. He was unable to stand on heels or tiptoes. He was able to arise from a chair and perform a deep knee bend. There was prominent atrophy of foot and anterior foreleg muscles, and pseudohypertrophy of bilateral calf muscles (Figure 2). Weakness was restricted to the lower extremities, affecting foot and toe extensors (MRC grade 2), and plantar flexors (MRC grade 3). There was no myotonia. Ankle jerks were hypoactive while other myotatic reflexes were normal. Sensory exam revealed mildly decreased perception of vibration sensation in the toes and feet. Toe position sensation was intact.



Figure 2: Photograph of patient 4 showing calf muscle pseudohypertrophy.

Creatine kinase was 447 units/L (normal, <173). Complete blood count, chemistry panel, fasting blood glucose, thyroid function studies, serum protein electrophoresis, immunofixation, GM1

antibody test, and vitamin B12 level were normal. Pulmonary function test revealed a forced vital capacity of 2.99 L (62% of predicted). MRI of the lumbosacral spine reported diffuse multi-level degenerative changes without significant canal or foraminal stenosis. Nerve conduction studies were normal. Concentric needle electromyography showed increased insertional activity, sustained fibrillations and positive sharp waves, and increased (early) recruitment of small polyphasic motor unit action potentials in a diffuse pattern – abnormalities were particularly prominent in clinically weak muscles. Electromyography was consistent with a diffuse myopathy.

Muscle biopsy of the left gastrocnemius showed marked variability in myofiber size, occasional necrosis and myophagocytosis, increased internalized nuclei, rare pyknotic nuclear clumps, increased endomysial fibrosis, sarcoplasmic masses on hematoxylin-eosin and Gomori trichrome stains, core-like lesions on NADH-TR stains, desmin-positive aggregates on immunostains, and granulo-filamentous material on electron microscopy. Immunohistochemical stains for dystrophin, dysferlin, and the sarcoglycans (alpha, beta, delta, and gamma) were normal (Figure 1). Next-Gen custom muscular dystrophy panel (80 genes) disclosed three variants including a heterozygous R415W mutation (c.1243C>T nucleotide substitution) in exon 6 of the DES gene, heterozygous P545R mutation (c.1634C>T substitution) in exon 4 of the BAG3 gene, and heterozygous N140S mutation (c.419A>G substitution) in exon 3 of the SGCB gene. The report also documented the DES gene substitution to occur at a position that is conserved across species with in silico analysis predicting the variant to be “probably damaging” to protein structure and function. The BAG3 gene substitution occurred at a position that is not conserved, and in silico analysis was inconsistent in predictions about the pathogenicity of this variant. A second SGCB gene mutation was not identified. Excluded were other potential gene disorders associated with myofibrillar pathology including ACTA1, CRYAB, FHL1, MYOT, SEPN1, DNAJB6, FLNC, PLEC, LDB3, and TTN.

Discussion

This report provides strong clinicopathological evidence for the causative role of the DES R415W mutation in the myopathic weakness of our four patients. Inheritance pattern was autosomal dominant for patients 1 and 2, and dominant or sporadic for patients 3 and 4. All developed late-onset weakness – primarily of the lower extremities – with distal and proximal muscle involvement. For patients 1, 2, and 4, the presentation of bilateral foot drop and steppage-pattern gait is a common feature for the myofibrillar myopathies including those due to DES gene mutations. The calf muscle pseudohypertrophy for patient 4 seemed to be a novel feature for desmin-related myopathy, as we are not aware of a previously reported association. Clinical and EMG findings implicated concurrent sensory polyneuropathy for patients 1, 2, and 3. However, for patients 1 and 2, the neuropathy may have resulted from longstanding diabetes mellitus. The symptoms of dyspnea along with the reduced FVC values – implicating respiratory muscle weakness, and normal to mildly elevated

CK values were features previously reported in myofibrillar myopathies. Patients 1, 2 and 4 did not have symptomatic cardiac involvement or abnormalities noted on cardiac testing. The cardiologist for patient 3 noted that she had AV node ablation and pacemaker placement for control of persistent tachycardia related to atrial fibrillation. However, echocardiogram showed no evidence of systolic or diastolic cardiomyopathy, and patient had a normal left ventricular ejection fraction. Whether or not the atrial fibrillation was due to desmin-related cardiac involvement remains uncertain. Desmin-related myopathy was further supported by the muscle histopathology and electron microscopy – showing changes consistent with myofibrillar myopathy, and desmin immunohistochemistry – showing increased reactivity. Finally, comprehensive DNA analyses identified the heterozygous DES R415W mutation for all four patients, and excluded other gene disorders. For patient 4, we could not absolutely exclude the BAG3 P545R mutation as a primary or contributing pathogenic variant. Points that disfavor its pathogenic role include absence of previously reported cases harboring this mutation, inconsistent *in silico* analysis (GeneDx, Gathersburg, Maryland, USA), and the late-onset and relatively mild phenotype – somewhat atypical clinical features of the Bag3opathies [1].

The desmin protein is a major intermediate filament and essential component of the extra-sarcomeric cytoskeleton in muscle cells. Desmin is expressed in cardiac, skeletal, and smooth muscle. Desmin interacts with other proteins to form a continuous cytoskeletal network that maintains a spatial relationship between the contractile apparatus and other structural elements of the cell, therefore, providing maintenance of cellular integrity, force transmission, and mechanochemical signaling [3]. Human desmin is encoded by the single-copy DES gene localized on 2q35. The DES gene contains nine exons within an 8.4-kb region and encodes 470 amino acids. DES is organized into three domains including a highly conserved α -helical core flanked by globular N- and C-terminal structures known as the head and tail domains, respectively [11]. The helical rod is further subdivided into four consecutive helical segments – referred to as 1A, 1B, 2A and 2B – connected by three non-helical linkers. Since the first report of DES gene mutations as a cause of a familial and skeletal myopathy in two families in 1998, 126 pathogenic mutations have been documented – including 99 missense and nonsense, 11 small deletions, 9 splicing, 3 small indels, 2 small insertions, 1 large deletion, and 1 complex rearrangement [8,12]. Mutations have been described in all three DES gene domains – including the tail domain which extends from codons 410 to 470. Of the 24 tail domain mutations, 15 have been associated with the skeletal myopathy phenotype and 9 with cardiomyopathy. How tail domain mutations cause cardiac and skeletal muscle dysfunction is unclear. The tail domain lacks the heptad repeat pattern as noted in the rod domain and is involved mainly in interacting with other cytoskeletal proteins to establish a cytoplasmic intermediate filament network [9]. Experimental *in vitro* analyses using transfected myoblasts and viscometric assays have shown that several tail mutations including R454W cause a severe disturbance of filament formation competence and filament-filament interactions, indicating an inherent incompatibility of

mutation and wild-type protein to form mixed filaments [13,14]. Based on clinical and experimental data thus far, it is likely that tail mutations lead to altered interactions of the desmin tail domain with other components of the myoblast cytoskeleton.

The pathogenicity of the DES R415W is suspect for several reasons. First, this variant has been observed in a 30-year old individual with a lower limb skeletal myopathy [9,10]. Unfortunately, a detailed description of this case was not provided. Second, this variant has not been observed in approximately 6,500 individuals of European and African American ancestry in the NHLBI Exome Sequencing Project, indicating that it is not a common benign variant in these populations [15]. Third, R415W variant is a non-conservative amino acid substitution, which is likely to impact secondary protein structures as these residues differ in polarity, charge, size and other properties. This substitution occurs at a position that is conserved across species and *in silico* analysis predicts this variant is probably damaging to the protein structure/function (GeneDx, Gathersburg, Maryland, USA). Fourth, 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, supporting the functional importance of this region of the protein [16-19]. Finally, the pathogenicity of the more commonly-reported variant, R454W, sharing the same non-conservative amino acid substitution in the tail domain, has been shown to assemble aberrantly shortened and irregular filamentous structures and prominent aggregates in experimental *in vitro* assays [13,14]. Although not proven with similar assays to our knowledge, it is likely that the R415W mutation would have a similar negative affect on filament formation.

Although the DES R415W is the likely cause for the clinicopathological findings in the patients described, our study has several limitations. First, ours is a clinicopathological study only without experimental *in vitro* analyses of the R415W mutation. Second, this study lacks extensive clinical and genetic testing in other at-risk family members – including living parents (patient 4), siblings (patient 4), and children (patients 3 and 4). Third, our patients had extensive DNA studies – but not all of the potential genes causing or associated with myofibrillar pathology were analyzed. Fourth, although we did not identify definite cardiac involvement abnormalities for our patients, it is possible that more sensitive testing including cardiac MRI would have shown subclinical abnormalities, e.g., myocardial scarring. Despite these limitations, we believe that the clinicopathological evidence is supportively strong.

In summary, we report four patients with the DES R415W mutation. This tail domain mutation causes a late-onset myopathy primarily affecting the lower extremities. Respiratory muscle weakness, mild hyperCKemia, and sensory neuropathy – but not overt cardiac involvement – are associated features.

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