Clinical and Myopathological Characteristics of Desminopathy Caused by a Mutation in Desmin Tail Domain

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Key Words

Intermediate filaments · Desminopathy · Myofibrillar myopathy · Cardiomyopathy · Desmin gene mutations

Abstract

Background: Most of the previously described pathogenic mutations in desmin are located in highly conserved α -helical domains that play an important role in intermediate filament assembly. The role of the C-terminus non- α -helical 'tail' domain is much less investigated and until recently mutations in this domain have been implicated in only a few patients. The majority of reported desminopathy cases caused by the tail mutations were sporadic, creating a representation bias regarding the disease frequency and phenotypic characteristics. **Methods:** We performed detailed genotype-phenotype analysis of autosomal dominant desminopathy associated with tail domain mutations in a four-generation autosomal dominant family with 16 members affected by a progressive cardiac and/or skeletal myopathy

caused by a c.1346A>C (p.Lys449Thr) mutation located in the tail domain of desmin. **Results:** Phenotypic features in patients with tail domain mutations are similar to those in patients with mutations localized in the 1B and 2B α -helical domains. **Conclusion:** We recommend that the tail domain is searched for mutations as intensely as desmin coil domains which until recently were considered to be more 'functional'.

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Introduction

Myofibrillar myopathies (MFMs) are a genetically heterogeneous group of neuromuscular disorders associated with mutations in *DES*, *CRYAB*, *MYOT*, *ZASP*, *FLNC*, or *BAG3* genes, and characterized by disintegration of myofibrils with degradation products accumulating in abnormal intracellular inclusions [1]. One of the most common variants known as desminopathy is a neuromuscular dis-

order associated with mutations in *DES*. More than 200 cases of desminopathy have been reported [2]. The age of disease onset, clinical/myopathological features and the rate of progression vary significantly depending on the type of inheritance and the location of the causative mutation. Typically, patients with mutations in *DES* present with progressive bilateral skeletal muscle weakness that starts in distal leg muscles and spreads to the proximal limb muscles and is often combined with cardiomyopathy manifested by conduction blocks, arrhythmias and chronic heart failure [3, 4]. Some patients develop tachyarrhythmia requiring implantation of a cardioverter defibrillator [5]. Respiratory insufficiency can be a major cause of disability and death in desminopathy patients; it causes nocturnal hypoventilation with oxygen desaturation and, eventually, daytime respiratory failure [6]. Biopsies of affected skeletal and cardiac muscles show abnormal chimeric aggregates of desmin and other cytoskeletal proteins and granulofilamentous material at the ultrastructural level, among other less specific pathological features [7, 8].

In accordance with its function, the desmin molecule is organized into three domains: a highly conserved α -helical core of 308 amino acid residues flanked by globular N- and C-terminal ('head' and 'tail') structures [9]. The C-terminus non-helical ('tail') domain that starts from position 416 and extends to position 470 contains ~30% of β -sheet with the remainder of the domain having predominantly random structure and lacking the heptad repeat pattern. The tail is involved in the longitudinal head-to-tail tetramer assembly and control of lateral packing, stabilization and elongation of the higher order filament structures; however, the tail's major function seems to be interacting with other cytoskeletal proteins in establishing a cytoplasmic intermediate filament network [10].

Multiple *DES* mutations, point substitutions, an insertion, small in-frame deletions, and a larger exon-skipping deletion, have been identified in desminopathy patients. Recent filament and network assembly studies indicated that unlike the mutations located in the α -helical segments, some tail mutations do not affect filament assembly or disrupt the filamentous network in cell cultures [11]. Nevertheless, they cause severe cardiac and skeletal myopathy [12]. This discrepancy has not been addressed or even confirmed; in particular, there were limited observations of the desminopathy phenotype in large families with *DES* tail mutations. The latest review [13] emphasized biochemical and biophysical consequences while the clinical/pathological characteristics of patients

were sketchy: most have been published as case reports. We present here a comprehensive study of a large and clearly autosomal dominant family with a cardiac and skeletal myopathy caused by a tail domain p.Lys449Thr mutation in *DES* and discuss the pathological effects of previously reported tail domain mutations in light of recent experimental data.

Patients and Methods

Affected Kindred

We have identified a large family originating from Ireland and currently residing in the UK and Ireland with 16 members affected with a progressive skeletal muscle weakness and some with cardiomyopathy and respiratory failure (Pedigree, fig. 1). Clinical details on one possibly affected member (1:1) were sparse (death due to cardiac disease aged 30 years), and were therefore not included in this report. None of these patients has previously been reported. Patients were identified by local neurologists and referred to neuromuscular centres of the university hospitals of Leicester, Nottingham and Birmingham, UK, and at the Mater Misericordiae Hospital in Dublin, Ireland, for detailed studies. After obtaining informed consent, each affected family member had a neurological examination, including muscle strength assessment according to the Medical Research Council (MRC) grading scale, serum creatine kinase (CK) level assessment, electrophysiological studies that included nerve conduction tests and concentric needle electromyography (EMG), and when indicated respiratory function tests and cardiologic examination with electrocardiography and echocardiography. Fourteen patients underwent detailed cardiac investigations. Magnetic resonance images (MRI) of muscles were taken at mid-thigh and mid-calf levels in 5 patients. Time elapsed between the disease onset and the MRI examination varied from 4 to 15 years. Clinical, myopathological and molecular genetic studies were conducted under study protocols that conform to the ethical guidelines of the 1975 Declaration of Helsinki and approved by the institutional review boards of each participating institution. Informed consent was obtained in each case. Genetic testing was performed at the Clinical Neurogenetics Unit, National Institute of Neurological Disorders and Stroke, NIH, in Bethesda, Md., USA.

Muscle Biopsy

Diagnostic skeletal muscle biopsy was performed in 4 cases. Muscle was obtained from a clinically affected muscle, frozen in liquid nitrogen-cooled isopentane and processed for routine histochemical reactions and immunohistochemical analysis that included an antibody to Desmin (clone D33; Dako, Glostrup, Denmark, diluted 1:100) [14]. Samples for electron microscopy were fixed in glutaraldehyde and processed by routine methods [14].

Gene/Mutation Identification and Screening

Genomic DNA from the index case was simultaneously screened for mutations in genes known to be associated with MFM, *DES*, *CRYAB*, *MYOT*, *ZASP*, and *FLNC*, using previously described methodology [15]. Screening for the *DES* mutation in family members and unrelated controls was performed by amplification and direct sequencing of the PCR-amplified exon 8.

Fig. 1. Family tree of the UK-Ireland kindred segregating myopathy and cardiomyopathy associated with *DES* c.1346A>C (p.Lys449Thr) mutation. Filled symbols indicate affected family members; symbols with a line through indicate deceased individuals; symbols with a '+' indicate mutation carriers.

Results

Clinical Phenotypes and Disease Outcomes

Index Case (3:2; fig. 1)

A 38-year-old male presented with difficulty climbing stairs due to progressive proximal leg weakness. Needle EMG showed an 'irritative myopathy'; nerve conduction studies were normal, and CK was elevated at 1,044 U/l (normal <200 U/l). A muscle biopsy showed infrequent eosinophilic rounded inclusions (cytoplasmic bodies) and myofibrillar disruption. The patient was started on prednisolone 30 mg/day for suspected inflammatory myopathy, but with no positive effect. Ten years later he began to suffer intermittent dysrhythmia with atrial fibrillation and ventricular sustained polyfocal ectopic beats and was anticoagulated. Dilated cardiomyopathy was diagnosed. The patient became wheelchair bound by the age of 51, and on examination in a Muscle Disease Clinic at age 53 he had mild scapular weakness, bilateral weakness and wasting of the deltoid and triceps muscles (MRC grades 4 to 4-), with relative preservation of biceps; hip flexion was antigravity, adductors were MRC grade 4-, distal leg muscles 4+. Prednisolone was withdrawn and a second muscle biopsy was performed (fig. 2). The clinical course showed slow progression of muscle weakness. The patient developed heart failure with limb oedema, and he became breathless with forced vital capacity reduced to 2 litres and falling to 1.49 litres supine, indicative of diaphragmatic weakness. He died as a result of his cardiorespiratory complications at the age of 57 years.

Other Affected Family Members

Phenotypic features in other affected members of the PW family are summarized in table 1. Of 16 affected individuals, 10 were male and 6 female. The average age of disease onset was 41 within a range from 25 to 50 years. Myalgia was noted as the initial symptom in 8 patients. Progressive skeletal myopathy was present in 14 patients; muscle weakness typically started in proximal muscles of the lower or upper limbs, predominantly in the legs, and subsequently spread to distal muscles, although 2 patients developed distal lower limb weakness at onset, both in anterior and posterior compartment distal lower limb muscles. Significant facial or bulbar weakness was not observed, and spinal rigidity was not a feature in any of the kindred. In 8 patients all four limbs were eventually affected by weakness and muscle atrophy. Of 9 surviving patients, 3 are wheelchair bound. EMG studies showed motor unit potentials characteristic of myopathy and abnormal electric irritability. Muscle MRI studies performed in 5 patients revealed involvement of the calf muscle at an early stage (fig. 3a), with fatty degeneration of thigh muscles developing in a relatively selective pattern during the later course of the condition. Involvement of the semitendinosus, sartorius and gracilis muscles was prominent (fig. 3b). Ambulation with or without support was preserved for many years unless heart failure made walking impossible. Serum CK was moderately or slightly elevated in 6 of 7 tested patients.

Of 16 patients, 11 had cardiac disease, which in 6 was not disabling, but 4 developed severe cardiomyopathy (table 1). All severe phenotypes occurred in males. Of 8 males with cardiomyopathy studied by echocardiogra-

Fig. 2. Analysis of muscle biopsy samples from patients with *DES* c.1346A>C (p.Lys449Thr) mutation. Abnormal variation in fibre size, multiple internal nuclei, irregularly shaped eosinophilic areas with HE and stain (a) which are dark areas with the modified trichrome stain (b); large areas devoid of oxidative enzyme activity

(‘wiped out’) (c), and aggregates immunoreactive for desmin (d). At electron microscopy examination, patchy electron-dense coarse granulo-filamentous aggregates (e, 5- μ m resolution scale bar), most prominently near the Z-bands and beneath the sarcolemma, Z-bands streaming (f, inset of e at 1- μ m resolution scale bar).

phy, 1 had predominant involvement of the right ventricle, the left ventricle was affected in 3, and both ventricles in 4. One female had dilation of the right atrium but no ventricular dysfunction, and 1 male and 3 females had no abnormality on echocardiogram or cardiac MRI. Two patients (3:15 and 3:21) developed tachyarrhythmia requiring implantation of an ICD at the time when they already had severe cardiomyopathy and heart failure; both died within 2 years. Two patients died on the waiting list for cardiac transplantation. Cardiomyopathy progressed faster than skeletal myopathy and onset-to-death duration was on average shorter (9 years) than in cases with

no or mild signs of heart disease (12 years). One patient (3:21) had a cardiomyopathy without signs of skeletal muscle weakness, but interestingly he complained of myalgia at the initial phase of illness. Patients with rapidly progressive disease developed heart failure on the background of dilated cardiomyopathy. Heart failure was the main cause of death, occurring at an average age of 53 years (range 48–57). Respiratory muscle weakness was detected in 6 patients, including a patient (3:16) who had neither skeletal weakness nor cardiac symptoms. Respiratory insufficiency was initially observed as exercise-induced dyspnoea and later as nocturnal hypoventilation.

Fig. 3. Muscle MRI in patients with *DES* c.1346A>C (p.Lys449Thr) mutation of mid-calf (**a**) showing selective involvement of gastrocnemius, and of mid-thigh (**b**) showing selective involvement of semitendinosus, gracilis and sartorius.

Table 1. Clinical manifestations of desminopathy in the affected members of the *DES* p.Lys449Thr family

Pedigree ID	Age of onset/ current age or age at death [†]	Gender	Initial symptoms	Muscle weakness distribution	CK IU/l	Cardiac findings	Respiratory symptoms (FVC)
2:1	50/61 [†]	M	W	UL, LL		No data	Yes
2:4	?/78 [†]	F	My, W	UL, LL		Mild failure	Unknown
3:2	38/57 [†]	M	My, W (DLL)	PUL, LL	1,044	AF, RV-DCM (severe)	Yes (2.0 l)
3:5	41/58	F	W (PLL)	UL, LL		RA dilatation	No (2.77 l)
3:6	?/49 [†]	M	W	UL, LL		LV-HCM	Yes
3:9	50/55	F	My, W (PLL)	PLL	302	LV-HCM (mild)	No (1.88 l)
3:10	45/54	M	My, W (DLL)	UL, LL	358	LV-HCM (mild)	No (2.43 l)
3:14	45/55	M	W	PLL		Mild (ejection fraction 45%)	No
3:15	?/48 [†]	M	My, W	PLL		DCM (severe), ICD	Severe
3:16	40/48	F	My	None		Normal	Yes
3:17	38/42	F	My	PLL, DLL	157	Normal	No
3:19	?/52 [†] , *	M	C	PLL		DCM (severe)	Unknown
3:21	47/55 [†]	M	My	None	1,448	AF, DCM (severe), ICD	Yes
4:8	35/37	M	W (PLL)	PUL, PLL	319	RBBB, HCM (mild)	No (3.14 l)
4:9	34/35	M	W (PLL)	PUL, PLL	663	Normal	No
4:11	25/26	F	W	DLL mild		Normal	No

* Died of cancer; [†] deceased. W = Weakness; My = myalgia; C = cardiac symptoms; UL = upper limbs (both proximal and distal muscles); LL = lower limbs (both proximal and distal muscles); P = proximal; D = distal; AF = atrial fibrillation; RV-DCM = right ventricular dilated cardiomyopathy; RA = right atrium; LV-HCM = left ventricular hypertrophic cardiomyopathy; DCM = dilated cardiomyopathy (global); ICD = implanted defibrillator-cardioverter; RBBB = right bundle branch block; FVC = forced vital capacity (in litres).

Myopathology

Muscle biopsy performed in 4 affected family members at different stages of illness showed morphological hallmarks of desminopathy, including an abnormal variation in fibre size, vacuoles, increased internal nuclei that were often multiple, irregularly shaped eosinophilic areas

which were dark green with the modified trichrome stain (fig. 2a, b), large areas devoid of oxidative enzyme activity ('wiped out' areas) (fig. 2c) and aggregates immunoreactive for desmin (fig. 2d) and ubiquitin. With electron microscopy examination, patchy electron-dense coarse granulofilamentous aggregates were present most promi-

nently near the Z-bands and beneath the sarcolemma, there were notable areas of Z-band streaming and autophagic vacuoles (fig. 2e, f). A structure previously described as a cytoplasmic body was present in a single patient (not shown).

Analysis of Gene Sequences and Screening for Desmin Mutation

Analysis of *DES* sequences in patients 3:5, 3:9, 3:14, 3:15, 3:17, 3:19, 3:21, 4:8, 4:9, and 4:11 resulted in the identification of a heterozygous A-to-C missense mutation at mRNA position 1346 (c.1346A>C) predicted to replace threonine for lysine at amino acid position 449 (p.Lys449Thr). This substitution has previously been mentioned in one of the patients with MFM at the Mayo Clinic [16] and recently in a short communication describing a single patient [17], but no detailed phenotypic information was provided. The c.1346A>C (p.Lys449Thr) mutation is located in the tail domain of the desmin molecule. Lysine at this position is strongly conserved through evolution [12]. No other mutations or unknown variations have been encountered in *DES*, and sequencing of other MFM-associated genes, *CRYAB*, *MYOT*, *ZASP*, and *FLNC* tested as a panel in the index case did not show any significant alterations. The c.1346A>C (p.Lys449Thr) mutation was identified in each of the 9 molecularly analysed affected members of the PW family. The mutation has not been detected by direct sequencing in 100 control individuals from the UK or 177 additional controls from mixed populations in the USA or other countries (554 chromosomes).

Discussion

We investigated an extended kinship and identified 16 patients with skeletal and cardiac manifestations of desminopathy caused by a c.1346A>C (p.Lys449Thr) mutation in the tail domain of *DES*. Patients developed frank skeletal myopathy of predominantly limb-girdle distribution between the ages of 25 and 50 years, but this was frequently preceded by longstanding unspecific myalgia. Cardiomyopathy started later into the course of illness in 11 of 16 patients, except for one patient (3:19) with cardiomyopathy which was ultimately fatal at age 52, without his developing severe skeletal muscle weakness. Progressive reduction of respiratory muscle strength was seen in 6 patients, one (3:16) of whom had no signs of skeletal or cardiac myopathy. Cardiomyopathy rather than respiratory failure was shown to limit life expectancy in patients

with advanced disease in our pedigree. Comprehensive monitoring for cardiac disease should start early in patients with *DES* mutations, but we found no evidence to support prophylactic pacing or ICD implantation. These findings contrast with some of the published series of desminopathy. Significant conduction defects were less frequent in members of this family than in previously published affected families [18, 19].

Of 10 male patients of the PW family, 4 appeared to have earlier and more severe cardiac involvement. They were diagnosed with DCM and progressed to NYHA class 4 heart failure within 10 years. Only 3 of 6 female patients had cardiac involvement, and this was much milder than in men. This correlates with data on a 10-member family carrying *DES* p.Leu370Pro mutation in which the males had a higher incidence of cardiomyopathy and cardiac arrhythmia resulting in sudden death by the end of the fourth decade of life while the female patients had a slow progression of illness limited to skeletal muscles [20]. A frequently discussed controversy that the *DES* p.Ile451Met mutation causes DCM/no skeletal myopathy in one family [21], but this same mutation causes progressive skeletal myopathy/no cardiomyopathy in another family [22], can now be solved considering the fact that only male patients were represented in the first family and only females have been studied in the second. Further investigation needs to clarify whether this gender difference is a consistent feature of desminopathy and whether lifestyle differences play a role in its causation. Male patients with cardiomyopathy have a faster rate of progression and should be considered for cardiac transplantation earlier in the course of illness once cardiac failure develops. We have no evidence on whether medication prior to development of overt cardiomyopathy could be protective, comparable to other myopathies with predictable heart involvement [23].

Close phenotypic similarity to previously reported cases of desminopathy and the identification of a desmin mutation that was not present in 277 tested controls strengthens the diagnosis of desminopathy in the patients we studied. Nevertheless, muscle biopsy features varied significantly between the affected members of this family, and also between first and second biopsies. Desmin accumulation was not always obvious and this led to misinterpretation even in experienced laboratories. This may be due to selectivity of degenerative changes seen on muscle MRI which supports the argument for muscle imaging prior to selecting a muscle for biopsy. Nevertheless, some clinically affected muscles, such as anterior distal leg muscles, and selective thigh muscle involvement, were

not strikingly abnormal on MRI in some of our patients. This may have been due to the few (five) patients studied with MRI, and the differences in disease duration at image acquisition. No systematic follow-up MRI scans were performed. However, it has been previously noted that individual patients with Duchenne muscular dystrophy may show unexpected relative preservation of thigh muscles on MRI despite advanced disease, including loss of ambulation [24]. Electron microscopy is a useful adjunct that allows the identification of myofibrillar disruption when light microscopy features are felt to be non-specific. Molecular diagnostic screening should not be limited to desmin exon 6 or sequences encoding the 2B domain, and should always include the tail domain.

Comparative analysis of phenotypic features of the *DES* c.1346A>C (p.Lys449Thr) mutation with other tail domain mutations [11] indicates that the main phenotypic features are no different from the disease caused by desmin mutations occurring in the coil domains. The age of disease onset on average 33 years (range 25–50) is slightly younger than in patients with rod domain mutations; most patients with a tail mutation had a combination of cardiac and skeletal myopathy which is well known in the rod mutation-associated phenotypes. Myopathological characteristics of 4 patients in this study and previously reported patients are also identical to the findings reported in cases with mutations in coil domains, including the widespread desmin-reactive deposits and electron-dense granulofilamentous aggregates [4].

This similarity between phenotypic features of tail and non-tail mutations was difficult to explain because the tail lacks heptad repeats and the tail mutants form apparently normal filaments in transfected cells [22]. Moreover, direct assembly experiments indicated that tail mutants are able to form extended filamentous networks [11]. But lately, oscillatory shear experiments designed to characterize the mutants' mesh size of filament networks and their strain-stiffening properties revealed distinct reduction in strain stiffening due to several tail mutations, including c.1346A>C (p.Lys449Thr) [25]. Expressed in combination with wild-type desmin, the p.Lys449Thr mutant no longer assembled into extended filamentous networks and instead disturbed longitudinal annealing potential of heteropolymers [25]. These findings prove that tail domain mutations affect intrafilamentous architecture and exert a dominant-negative effect on desmin assembly.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

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