Inherited cardiomyopathies
Tintelen, Johannes Peter van

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Two Related Dutch Families With a Clinically Variable Presentation of Cardioskeletal Myopathy Caused by a Novel S13F Mutation in the Desmin Gene

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Abstract
Desmin-related myopathy is characterised by skeletal muscle weakness often combined with cardiac involvement. Mutations in the desmin gene have been described as a cause of desmin-related myopathy (OMIM 601419). We report here on two distantly related Dutch families with autosomal dominant inheritance of desmin-related myopathy affecting 15 family members. A highly heterogeneous clinical picture is apparent, varying from isolated dilated cardiomyopathy to a more generalised skeletal myopathy and mild respiratory problems. Morphological analysis of muscle biopsies revealed intracytoplasmic desmin aggregates (desmin and p62 staining). In both families we identified an identical novel pathogenic heterozygous missense mutation, S13F, in the ‘head’ domain of the desmin gene which cosegregates with the disease phenotype. This is the 5th reported missense mutation located at the ‘head’ domain of the desmin gene and the first reported Dutch family with desmin-related myopathy. This article illustrates the importance of analysing the desmin gene in patients with (familial) cardiac conduction disease, dilated cardiomyopathy and/or a progressive skeletal myopathy resembling limb-girdle muscular dystrophy.

Introduction
The heterogeneous group of myofibrillar myopathies (MFM) is clinically characterised by skeletal myopathy and/or cardiomyopathy and smooth muscle disease. Histopathological examination of affected muscles reveals abnormal accumulation of several proteins, including desmin (DES), αB-crystallin, myotilin, β-amyloid precursor protein and dystrophin. Desmin-related myopathy (DRM) is a subgroup within the wide spectrum of MFM with comparable clinical characteristics and histopathological abnormalities, caused by dysfunctional desmin or other proteins interacting with desmin. In approximately one-third of DRM patients, mutations have been identified in the DES or αB-crystallin gene. The cause of DRM in the other patients has not been elucidated, but might well be caused by mutations in genes encoding other intermediate filament proteins.1

We have identified a novel DES mutation in two distantly related Dutch families with autosomal dominant inheritance of cardioskeletal myopathy in four generations. The clinical features of 15 affected family members are described, including the results from muscle biopsy, serum creatine kinase (CK) activities, electromyography (EMG), CT scanning and sequence analysis of the DES gene.
Materials and methods

Patients and families
The two index patients were referred to our genetic department for evaluation of muscle complaints and cardiac conduction disease. Family history revealed that several family members had similar complaints and were studied in the past by neurologists and/or cardiologists (Figure 1). After obtaining informed consent we studied the medical records of affected family members (Table 1). Additional information was obtained by hetero-anamnesis.

Muscle biopsy analysis
Skeletal muscle biopsies were obtained by open procedure and endomyocardial biopsies by endovascular procedure. Studies were carried out on fresh-frozen and paraffin-embedded muscle biopsy tissue (standard procedure). Of the paraffin blocks 3-μm-thick sections were cut and routinely stained with Hematoxylin and Eosin (HE). Furthermore, immunohistochemical stains were applied using antibodies against desmin (1:50, clone DE-R-11, Monosan) and p62 (1:100, clone sc-28359, Santa Cruz). The frozen material was cut in 4 to 5μm-thick sections. These sections were stained according to standard procedure with HE, PAS, Oil Red O, Gomori trichrome and several enzyme-staining procedures (ATP-ases, NADH, SDH, cytochrome C oxidase). All sections were studied using light microscopy. Also several immunohistochemical procedures and multiplex Western blotting were performed (dystrophin 1, 2, 3, spectrin, dysferlin, α, β, γ-sarcoglycan, calpain-3 and actin).

Figure 1. Pedigrees of family A (left) and family B (right). The closed symbols depict the family members highly suspicious of DRM, while the half closed symbols depict patients with possible DRM. The arrows show the index patients. Both pedigrees were slightly adapted for anonymisation.
## Table 1. Clinical characteristics of patients clinically affected with desmin-related myopathy (DRM)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)/sex (cause of death)</th>
<th>Age at onset</th>
<th>Weakness distribution</th>
<th>Cardiac involvement</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>SM</td>
<td>CM</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Family A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index: III:6</td>
<td>49/F</td>
<td>30</td>
<td>43</td>
<td>Proximal&gt;distal (30), objectivated at age 45</td>
<td>Tachycardias (43), left anterior hemi block, PM (45), LBBB</td>
</tr>
<tr>
<td>III:5</td>
<td>51*/F (heart failure)</td>
<td>36</td>
<td>25</td>
<td>Distal&gt;proximal, periorcular weakness</td>
<td>HCM (25), complete AVB, PM (29), tachycardias (30), TI, right sided heart failure (51)</td>
</tr>
<tr>
<td>IV:1</td>
<td>36/M</td>
<td>(-)</td>
<td>31</td>
<td></td>
<td>Complete AVB, PM</td>
</tr>
<tr>
<td>II:4</td>
<td>60*/M (heart failure)</td>
<td>58</td>
<td>47</td>
<td>Distal and bulbar, footdrop</td>
<td>Complete AVB, PM (47), heart failure (58)</td>
</tr>
<tr>
<td>II:5</td>
<td>31*/F (SCD)</td>
<td>(-)</td>
<td>(&lt;31)</td>
<td></td>
<td>Several collapses, SCD</td>
</tr>
<tr>
<td>II:6</td>
<td>59*/F (myocardial infarction)</td>
<td>52</td>
<td>47</td>
<td>Proximal&gt;distal, pelvic, truncal and periorcular weakness, footdrop (52)</td>
<td>Complete AVB (47), PM (51), tachycardias, cardiomyopathy (47), coronary disease</td>
</tr>
<tr>
<td>I:1</td>
<td>53*/M (myocardial infarction)</td>
<td>(-)</td>
<td>(&lt;53)</td>
<td></td>
<td>Several collapses, RBBB, tachycardias</td>
</tr>
<tr>
<td><strong>Family B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index: III:7</td>
<td>62/M</td>
<td>52</td>
<td>31</td>
<td>Proximal&gt;distal, weakness of TA, EHL, adductors, iliopsoas, atrophy</td>
<td>Arrhythmias (31), AF, first degree AVB, RBBB, DCM (56)</td>
</tr>
<tr>
<td>III:3</td>
<td>55*/M (myocardial infarction)</td>
<td>(-)</td>
<td>54</td>
<td></td>
<td>Heart failure (54)</td>
</tr>
<tr>
<td>III:4</td>
<td>54*/M (U)</td>
<td>37</td>
<td>-</td>
<td>Distal&gt;proximal, weakness facial muscles, atrophy, progressive</td>
<td></td>
</tr>
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<td>---</td>
<td>----------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>III:5</td>
<td>37*/M (heart failure)</td>
<td>(-)</td>
<td>37</td>
<td>Heart failure</td>
<td></td>
</tr>
<tr>
<td>III:6</td>
<td>34*/M</td>
<td>(-)</td>
<td>34</td>
<td>Heart failure, DCM, first degree AVB, PM</td>
<td></td>
</tr>
<tr>
<td>II:3</td>
<td>76*/F (myocardial infarction?)</td>
<td>(-)</td>
<td>60</td>
<td>PM (60) (insulin dependent diabetes)</td>
<td></td>
</tr>
<tr>
<td>II:2</td>
<td>54*/M (myocardial infarction)</td>
<td>(-)</td>
<td>54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I:2</td>
<td>42*/F (myocardial infarction)</td>
<td>(-)</td>
<td>42</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibration; AVB, atrioventricular block; CM, cardiomyopathy; DCM, dilated cardiomyopathy; EHL, extensor hallucis longus; F, female; HCM, hypertrophic cardiomyopathy; LBBB, left bundle branch block; M, male; NIDDM, non insulin dependent diabetes mellitus; PM, pacemaker; PNP, polyneuropathy; RBBB, right bundle branch block; SCD, sudden cardiac death; SM, skeletal myopathy; TA, tibialis anterior; TI, tricuspid valve insufficiency; U, unknown; y: year.

* Age of death, Italics: presumably affected with DRM, {...}: information obtained by hetero-anamnesis
Chapter 6

Mutation analysis
Genomic DNA was extracted from whole blood by standard procedures using the Wizard genomic DNA purification kit (Promega, Leiden, the Netherlands). The coding exons of DES, including the splice-junctions, were amplified by PCR. PCR reactions (50μl) contained 1x Taq buffer (Invitrogen, Groningen, the Netherlands), 0.2 mM dNTPs, 100ng of each primer and 1.0 U Taq DNA polymerase (Invitrogen). PCR conditions were; 30s 94°C, 30s 62°C, 50s 72°C for 35 cycles, initiated by 90s at 94°C and terminated by 420s at 72°C. PCR products were purified in 50μl elution buffer (Tris 10mM, PH 8.0) with a MultiScreen-PCR filter plate (Millipore) or Qiagen PCR purification kit (Qiagen Benelux B.V.). Subsequently, 1μl was directly sequenced with the Big dye terminator V1.1 cycle sequencing kit (Applied Biosystems, Fostercity, CA, USA) using the PCR primers according to the specifications of the manufacturer (all primer sequences are available upon request). Sequence analysis was performed with Vector NTI software (Informax, Inc.). DES reference sequences used for mRNA and genomic sequence analysis were NM_001927.3 and AC053503.7 respectively.

Results
Clinical characteristics
First the index patients of both families will be described in detail, followed by more general information of both families. The features of all presumably affected family members are summarised in Tables 1 and 2. The pedigrees are shown in Figure 1.

Index family A
The (female) index patient of family A (III-6) presented at age 30 with difficulty climbing stairs and fibromyalgia-like complaints (muscle pain and tiredness). Mild proximal muscle weakness (grade 4/5) of the legs was apparent on neurological examination 15 years later. The weakness was progressive and started to involve the arms and hands as well. She was diagnosed as having limb-girdle muscular dystrophy (LGMD). At the age of 43 she suffered from palpitations caused by supraventricular tachycardias and ventricular extrasystoles. Two years later she collapsed and a left anterior hemiblock was apparent on cardiac examination, requiring a permanent pacemaker. Bronchial asthma (with a nearly normal respiratory function) was apparent. EMG showed normal results. Serum CK activities were elevated and a CT scan of the abdomen and lower extremities showed fatty degeneration of
<table>
<thead>
<tr>
<th>Case</th>
<th>CK levels (u/l)</th>
<th>EMG</th>
<th>CT scan</th>
<th>Muscle biopsy</th>
<th>Genetic analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index: III:6</td>
<td>59-350</td>
<td>Normal</td>
<td>Fatty degeneration abdominal wall, glutei and upper leg muscles</td>
<td>Variation in fibre size, resembles LGMD, fatty Degeneration. IHC: spectrin, dystrophin, dysferlin, calpain-3, α, β, γ sarcoglycan and actin: normal, desmin: irregular staining</td>
<td>DES: c.38C&gt;T</td>
</tr>
<tr>
<td>III:5</td>
<td>26-207</td>
<td>ND</td>
<td>Atrophy and fatty degeneration of leg and abdominal muscles</td>
<td>Post mortem: dystrophic muscle, variation in fibre size, fatty degeneration. Myocard: hypertrophy and interstitial fibrosis, dystrophic muscle. IHC: desmin: irregular staining</td>
<td>DES: c.38C&gt;T</td>
</tr>
<tr>
<td>II:4</td>
<td>ND</td>
<td>Severe PNP: n. peroneus (no response), n. medianus (51 m/sec)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>II:6</td>
<td>23-1096</td>
<td>Myopathic</td>
<td>ND</td>
<td>Variation in fibre size, fibrosis, dystrophic muscle, fatty degeneration</td>
<td>ND</td>
</tr>
<tr>
<td>Family B</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Index: III:7</td>
<td>300</td>
<td>Myopathic and neurogenic disturbance</td>
<td>ND</td>
<td>Myopathic muscle. IHC: α, β, γ sarcoglycan, dystrophin, dysferlin and calpain-3: normal. Gomori: normal</td>
<td>DES: c.38C&gt;T</td>
</tr>
<tr>
<td>III:4</td>
<td>Normal</td>
<td>Neurogenic disease and secondary myopathy</td>
<td>Hypodense affected muscles</td>
<td>Myopathy with signs of innervation problems</td>
<td>ND</td>
</tr>
<tr>
<td>III:6</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>Mild aspecific changes in right ventricle</td>
<td>ND</td>
</tr>
<tr>
<td>IV:1-3</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td>DES: c.38C&gt;T absent</td>
</tr>
</tbody>
</table>

Abbreviations: CK, creatine kinase activity (normal value < 50 u/l); DES, desmin gene; EMG, electromyogram; IHC, immunohistochemistry; LGMD, limb girdle muscular dystrophy; ND, not done; PNP, polyneuropathy.
the abdominal muscles and the proximal leg muscles.

**Index family B**
The (male) index patient of family B (III-7) presented with arrhythmias at age 31. From age 52 he experienced slowly progressive weakness of the proximal leg muscles. This was confirmed with neurological examination. Also muscle atrophy of proximal (and to a lesser extent distal) leg musculature was apparent. He was diagnosed with LGMD. Cardiac examination at age 56 showed a dilated cardiomyopathy (DCM), atrial fibrillation, a first degree atrioventricular block (AVB) and a complete right bundle branch block.

**Both families**
From Table 1 it can be derived that almost 90% (13/15) of the presumably affected family members presented with cardiac problems between the age of 25 to 60 years, consisting mainly of cardiac conduction defects. Skeletal muscle weakness was present in 40% (6/15) of the described DRM patients, with onset between 30 and 58 years of age. The weakness started evenly in the proximal or distal leg musculature. Mild respiratory function disturbance was found in a small subset of patients (2/15). The cause of death, occurring between 31 and 76 years of age, was presumably a heart attack in 6 patients, heart failure in 3 patients, sudden cardiac death in one patient and unknown in one patient.

**Morphological analysis**
Index patient of family A (III:6): HE staining of skeletal muscle biopsy tissue showed an increased variation in muscle fibre size and fatty degeneration. Furthermore, clumping of pyknotic nuclei, vacuolar changes and muscle fibre splitting were apparent (Figure 2A). The NADH-staining showed a “moth-eaten appearance” (Figure 2B), but the other enzymehistochemical stains were normal. Extra immunohistochemical staining, as well as multiplex Western blotting for spectrin, dystrophin, dysferlin, calpain-3, actin, α, β and γ sarcoglycan showed no abnormalities. Antibodies against desmin showed an irregular staining pattern of the myofibres (Figure 2C).

Index patient of family B (III:7): HE and NADH staining of skeletal muscle biopsy tissue were similar to the other index patient, but in addition endomysial fibrosis and central nuclei were observed. Immunohistochemical staining demonstrated irregular desmin accumulation.

Sister of index patient of family A (III:5): A skeletal muscle biopsy (at age
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46) showed less severe abnormalities (e.g. no vacuolar changes). The staining patterns for dystrophin and spectrin were normal. An endomyocardial biopsy (at age 51) showed both hypertrophic cardiomyocytes as well as degenerating cardiomyocytes with central vacuolar changes. Desmin staining showed dense aggregates of desmin (Figure 3A). Immunohistochemical staining with p62 demonstrated variable patterns, ranging from fine granular staining and small dense inclusions to muscle fibres that were almost completely filled (Figure 3B-C). A post-mortem skeletal muscle biopsy (at age 51) demonstrated severe muscle pathology with vacuolar changes. The staining for desmin showed pathological changes, ranging from small clumps in a background of a normal banding pattern to muscle fibres showing a complete and intense staining (Figure 3D).

Molecular genetic studies
Sequence analysis of the DES gene showed a heterozygous missense mutation in three patients (III:5 and III:6 of family A and III:7 of family B). The
mutation consists of a cytosine-to-thymine substitution at position 38 in exon 1 (c.38C>T), leading to a serine to phenylalanine substitution at codon 13 (p.S13F) in the ‘head’ domain of the desmin protein. Three unaffected family members of family B (IV:1-3) were tested negative for the DES mutation.

**Discussion**

Desmin is the main component of muscle intermediate filament (IF) and is expressed in cardiac, skeletal and smooth muscle fibres. It is located at the Z-lines where it connects IF to the sarcolemmal membrane and the nuclei (Figure 4). Desmin plays a pivotal role in maintaining muscle cell integrity and stability and also seems to be involved in mitochondrial function and positioning.\(^1\),\(^2\) It is hypothesised that absence of desmin causes increased susceptibility of muscle fibres for damage, which leads to degeneration of muscle fibres after repetitive strain injuries.\(^2\),\(^3\) Recently it was suggested that mutant desmin leads to aberrant protein aggregation in cardiomyocytes.

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**Figure 3.** Endomyocardial biopsy (A-C) and skeletal muscle biopsy (D) from III:5 of family A. (A) desmin-stain: dense aggregates. (B) p62-stain: fine granular staining and small dense inclusions. (C) p62 stain: muscle fibre completely filled with aggregates. (D) desmin-stain: aggregates of variable sizes and forms. Arrows show the histological abnormalities. (color image: page 268)
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which in turn impairs the proteolytic function of the ubiquitin-proteasome system.4

The DES gene is located at chromosome 2q35 and consists of 9 exons covering 8.4 kb. So far at least 32 pathogenic DES mutations have been described, including missense mutations, deletions, insertions and splice site mutations.1,5-16 The inheritance pattern in DRM is usually autosomal dominant (with a high percentage of de novo mutations), but occasionally follows an autosomal recessive pattern.1,5,7,9 An explanation for the different modes of inheritance is currently not available. The majority of the mutations are located in the 2B or 1B helix domain of the desmin gene. Only 3 mutations have been discovered in the ‘tail’ domain and 4 in the ‘head’ domain.5,17-19

We have detected a fifth missense mutation in the DES ‘head’ domain, where at position 13 a serine is replaced by a phenylalanine, which leads to a polarity change. The observed abnormality was absent in 216 ethnically matched control chromosomes and in 3 unaffected family members. The mutation is located in an evolutionary highly conserved nonapeptide motif (SSYRRTFGG at position 12-20) of the DES gene. The serine at position 13 serves as a phosphorylation site for protein kinase C and is required for appropriate

![Figure 4. Schematic picture of myocyte architecture. Desmin (dashed fibres) is located at the Z-discs and forms an elaborate network interconnecting myofibrils, mitochondria, the nucleus and desmosomes (in cardiac muscle) in order to maintain muscle cell integrity and stability. Reprinted with permission.20](image)

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dimer-dimer formation. The serine-residues seem to be crucial for desmin assembly and organisation.\textsuperscript{20,21} Combined with the immunohistochemistry (irregular desmin staining of the myofibers) and the typical clinical features we classified this mutation as being pathogenic. Since the same mutation was found in both families, which reside in nearby villages, we assumed that they were distantly related. This was confirmed by haplotype analysis (data not shown).

Typically, patients with DRM suffer from skeletal muscle weakness, starting in the legs and spreading to the hands, arms, truncal, neck-flexor and facial muscles. Late in the course of the disease bulbar and respiratory muscles can be affected, leading to impaired swallowing and respiratory insufficiency.\textsuperscript{22-26} In approximately 60% of the DRM families cardiac involvement is noted, consisting of arrhythmias, cardiac conduction disease, cardiomyopathy and/or heart failure. This can result in sudden cardiac death.\textsuperscript{1,22}

Two patients described in this report (III:6 and III:7) had DCM. The association between DRM and DCM has been described before.\textsuperscript{8,18,19,24} However, DES mutations were found in only a small proportion (1.6 to 2.2\%) of patients with ”isolated” DCM.\textsuperscript{18,27} Both restrictive cardiomyopathy and hypertrophic cardiomyopathy have also been reported in DRM patients.\textsuperscript{5,7,26-29}

Our families illustrate the broad intrafamilial variability of DRM. Some patients described in this report suffered from isolated cardiac conduction disease or heart failure, while others presented with skeletal muscle weakness as only feature. In some family members involvement of cardiac, skeletal and respiratory muscles was noted. Importantly, in one of the described family members the first disease manifestation was sudden cardiac death at age 31. This makes diagnosing DRM in an early stage essential, since timely and adequate treatment could prevent such a catastrophic event.\textsuperscript{5,14,18,28,30}

In unexplained cardiac conduction disorders or cardiomyopathy the family history may give a clue for diagnosis, but even with a negative family history DRM should still be considered because de novo DES mutations have been reported frequently.\textsuperscript{1} DNA analysis of the DES gene (and if negative the αB-crystallin gene) is indicated in patients with cardiac conduction disease and/or DCM when other frequent (genetic) causes have been excluded (such as lamin AC gene mutations), in patients with a progressive skeletal myopathy resembling LGMD and in patients with irregular desmin staining on muscle biopsy. On the other hand, in two-thirds of DRM patients no mutations in either the DES gene or αB-crystallin gene can be found. In those patients DRM can be diagnosed on clinical grounds in combination with the results of muscle or
endomyocardial biopsy. Unfortunately, the biopsy results can be misleading. The HE abnormalities are not specific and can also resemble LGMD or inclusion body myositis. Desmin staining is more specific, but could show very subtle abnormalities (Figure 2C), which could be mistaken for preparation or staining artefacts. Furthermore, desmin staining will always show a “background” of the normal banding pattern. Staining for p62 (an ubiquitin-binding protein) could be helpful, since it exclusively stains the aggregates and not the normal muscle proteins and structures (Figure 3B,C). Once DRM has been diagnosed, genetic counselling of the patient is important and clinical and/or genetic screening of family members can be offered.

In conclusion, we have presented evidence that the novel Ser13Phe mutation in the DES gene is the genetic basis for cardioskeletal myopathy in two distantly related Dutch families. We illustrated the clinical variability of DRM and addressed the importance of genetic analysis in combination with muscle or if possible endomyocardial biopsy in patients suspected of DRM.

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References


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