Desmin-related myopathy:
a review and meta-analysis

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ABSTRACT

Desmin-related myopathy (DRM) is an autosomally inherited skeletal and cardiac myopathy, mainly caused by dominant mutations in the desmin gene (DES). We provide (1) a literature review on DRM, including clinical manifestations, inheritance, molecular genetics, myopathology and management, and (2) a meta-analysis of reported DES mutation carriers, focusing on their clinical characteristics and potential genotype-phenotype correlations.

Meta-analysis: DES mutation carriers (n=159) with 40 different mutations were included. Neurological signs were present in 74% and cardiological signs in 74% of carriers (both neurological and cardiological signs in 49%, isolated neurological signs in 22%, and isolated cardiological signs in 22%). More than 70% of carriers exhibited myopathy or muscular weakness, with normal creatine kinase levels present in one-third of them. Up to 50% of carriers had cardiomyopathy and around 60% had cardiac conduction disease or arrhythmias, with atrioventricular block as an important hallmark. Symptoms generally started during the thirties; a quarter of carriers died at a mean age of 49 years. Sudden cardiac death occurred in two patients with a pacemaker, suggesting a ventricular tachyarrhythmia as cause of death. The majority of DES mutations were missense mutations, mostly located in the 2B domain. Mutations in the 2B domain were predominant in patients with an isolated neurological phenotype, whereas head and tail domain mutations were predominant in patients with an isolated cardiological phenotype.
**INTRODUCTION**

Myofibrillar myopathy (MFM) refers to a group of morphologically homogeneous, but genetically heterogeneous neuromuscular disorders. The morphologic changes in skeletal muscle in MFM include abnormal ectopic accumulation of multiple proteins, including desmin, alpha-B-crystallin, dystrophin, and myotilin. One of these disorders is desmin-related myopathy (DRM, OMIM#601419) with intrasarcoplasmic aggregates of desmin and usually also other proteins. DRM is an autosomally inherited skeletal and cardiac muscular myopathy mainly caused by mutations in the desmin gene (DES)\(^2,3\), or infrequently by mutations in the alpha-B-crystallin gene (CRYAB).\(^4,5\) For DES mutations this disorder is also referred to as desminopathy. Desmin is the main intermediate filament protein expressed in skeletal, cardiac, and smooth muscle.\(^6\) It 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, thus providing maintenance of cellular integrity, force transmission, and mechanochemical signaling (Figure 1). Desmin is much more abundant in cardiac muscle than in skeletal muscle and is a major component of Purkinje fibers, the specialized myocardial conduction system that enables the heart to contract in a coordinated fashion.\(^7\) The small heat shock protein alpha-B-crystallin associates with desmin and serves as a chaperone for desmin and other proteins, preventing them from aggregating under various forms of stress.\(^8\) Since the recognition of the involvement of DES in human disease in 1998 by Goldfarb et al.,\(^3\) the number of publications on different DES mutations and associated phenotypes has increased steadily. However, a clear and reliable interpretation of the phenotypes of all the patients described is hampered by a great number of publications on a limited number of patients and by the fact that several patients have been described more than once in different studies. This latter aspect was not mentioned in earlier reviews on DRM.\(^9-11\) We therefore aimed to provide: (1) a review of the literature about DRM and (2) a meta-analysis of all reported heterozygous DES mutation carriers, focusing on clinical characteristics (especially the cardiac phenotype), potential genotype-phenotype relationships, and practical implications. We have ensured that the patients who were described in different studies were included only once in our meta-analysis.

**LITERATURE REVIEW: DESMIN-RELATED MYOPATHY**

Clinical manifestations: an outline

DRM is characterized by progressive skeletal muscle weakness, cardiomyopathy, and cardiac conduction disease (CCD), which can occur in any order in time.\(^2,11\) The first symptoms of DRM generally occur during the thirties, but age of disease onset and rate of progression are highly variable.

The progressive skeletal myopathy associated with DRM is highly variable, but typically presents with lower and later with upper limb muscle weakness, sometimes slowly spreading to involve truncal, neck flexor, facial and bulbar muscles. Generally the involvement of distal muscles
Figure 1: Schematic representation of proteins involved in the cytoarchitecture of cardiomyocytes. Adapted with modifications from Capetanaki et al.29
Chapter 3

exceeds that of proximal muscles. Muscle imaging studies performed in DRM patients led to the identification of a recognizable pattern of muscle involvement.\textsuperscript{12,13} The cardiac phenotype of DRM includes different types of cardiomyopathy. Besides, CCD is a frequent feature of DRM attributed to the fact that the cardiac conduction system is rich in desmin.\textsuperscript{7} CCD occurs mostly in patients with cardiomyopathy. CCD without demonstrated cardiomyopathy is also seen, but this is probably an initial manifestation with cardiomyopathy developing at a later age.\textsuperscript{14}

Respiratory muscle weakness is a major complication in DRM patients, sometimes leading to respiratory failure and death.\textsuperscript{15} The critical role of desmin in respiratory function could reflect the fact that the content of desmin in the diaphragm is significantly higher than in muscles of the lower extremities.\textsuperscript{16}

Smooth muscle involvement is not reported as the main manifestation in DRM. However, some manifestations that indicate smooth muscle involvement have been reported, like swallowing difficulties,\textsuperscript{3} repetitive episodes of diarrhea and constipation,\textsuperscript{17} and intestinal pseudo-obstruction (with characteristic DRM muscle pathology in intestinal smooth muscle cells).\textsuperscript{18} Cataracts were initially thought to be a specific feature in DRM caused by \textit{CRYAB} mutations. However, cataracts have also been reported in two \textit{DES} mutation carriers,\textsuperscript{19} and, vice versa, cataracts were not present in all \textit{CRYAB} mutation carriers.\textsuperscript{5,20}

\textbf{Inheritance}

The inheritance pattern of DRM is mainly autosomal dominant.\textsuperscript{10} But many sporadic cases have been reported; in several cases \textit{de novo} mutations have been identified.\textsuperscript{21-23} Three families with autosomal recessive inheritance with either homozygous or compound heterozygous \textit{DES} mutations are known.\textsuperscript{3,18,24,25} DRM in these cases manifested at earlier age and with faster progression than DRM in patients with a single \textit{DES} mutation. Heterozygous carriers in these families were unaffected.

\textbf{Molecular genetics}

Desmin is encoded by the \textit{DES} gene located on chromosome 2q35. \textit{DES} encompasses 9 exons within an 8.4 kb region and codes for 476 amino acids.\textsuperscript{26} The desmin molecule is organized into three domains: a highly conserved alpha-helical core of 308 amino acid residues flanked by globular N- and C-terminal (“head” and “tail”) structures. The gene is highly conserved among vertebrate species.\textsuperscript{27} The alpha-helical core maintains a seven-residue (heptad) repeat pattern with a typical sequence of hydrophobic and hydrophilic amino acids. This heptad repeat structure guides two polypeptides into formation of a homopolymeric coiled-coil dimer, the elementary unit of the filament. The heptad periodicity within the helical rod is interrupted at several places resulting in four consecutive helical segments (domain 1A, 1B, 2A, and 2B) connected by short non-helical linkers.

Desmin normally interacts with other structural proteins, such as the well studied cytolinker plectin, which facilitates linking of desmin filaments to an extending network and to other
cytoskeletal elements of the muscle cells. This entire network seems to associate to cellular organelles and integrate their functions (Figure 1). The inability of mutated desmin to interact with different cellular structures may trigger disease development. The pathophysiological mechanism resulting from part of the DES mutations seems to be impairment of the desmin filament assembly and thus loss of function. On the other hand, at least half of the DES mutations actually allow desmin filament formation; these mutations are now believed to impact on desmin function at a higher order level, either by altering the intrinsic biophysical properties of the filament itself or by changing binding properties towards associated proteins (extrinsic filament properties). Studies with desmin-deficient mice, which develop dilated cardiomyopathy and heart failure, revealed the importance of desmin filaments in mitochondrial behavior and function. In these studies mitochondrial abnormalities could be detected very early, before other structural defects became obvious. Similar mitochondrial abnormalities have also been identified in a muscle biopsy from a patient with a DES mutation. In addition to mitochondrial abnormalities, recent observations demonstrated that DES mutations have an effect at the myocardial intercalated disk. Importantly, such abnormalities in both mitochondria and intercalated discs are also the hallmark of the classical transgenic heart failure mouse model where disruption and aggregate formation of desmin is due to its cleavage at the linker region, between 2A and 2B helical domains, by the tumor necrosis factor-alpha induced caspase-6.

Fifty-three DES mutations have been reported (Figure 2); the majority are inherited missense mutations, mostly located in the 2B domain. Genotype-phenotype correlations are emerging, but they are not yet useful for guiding clinical decisions. Alpha-B-crystallin is encoded by the CRYAB gene located on chromosome 11q22.3-23.1. CRYAB consists of three exons and is highly conserved in a variety of species. Although alpha-B-crystallin was originally discovered and classified as a lens protein, this small heat shock protein is abundant in cardiac and skeletal muscle. Only five CRYAB mutations associated with DRM have been reported. Mutations in CRYAB can also be associated with autosomally dominant inherited, isolated congenital cataract.

**Myopathology**

Desmin-immunoreactive deposits in skeletal and cardiac muscles and granulofilamentous material at the ultrastructural level are considered morphological hallmarks of desminopathy (Figure 3). Although many of the myopathological features are not specific, the overall pattern is recognizable and is being used for diagnostic purposes. Skeletal muscular pathology has been described far more often than cardiac pathology, but the pathologic characteristics seem to be very similar. The diagnostic value of skeletal muscle biopsies equals that of endomyocardial biopsies, but has less associated health risk. Desmin-positive aggregates and other phenomena characteristic of DRM skeletal muscle pathology were also encountered in intestinal smooth muscle cells of a DRM patient.
Chapter 3

Treatment and management

There is no specific treatment for DRM. For skeletal myopathy, only supportive management is available, for example physical therapy and assistive devices. However, early detection and treatment of arrhythmias and CCD is essential, since inserting an implantable cardioverter defibrillator (ICD) or pacemaker can be life-saving. Other symptomatic treatment includes treatment of heart failure in accordance with guidelines. Based on our experience and the literature, we propose yearly cardiological evaluation of all DRM mutation carriers starting at the age of 10 years for early detection of cardiac abnormalities, even when there are no cardiological complaints. Risk of chest infection should also be considered. Respiratory support is indicated in patients with respiratory failure.

Studies on desmin deficient mice have suggested that improvement of mitochondrial structure and function and cell death prevention, for instance by overexpression of B-cell lymphoma-2 or other cytoprotective molecules, might be good targets for development of future treatments for DRM.

**Figure 2:** Overview of reported DES mutations. Mutations above the schematic representation of desmin were included in the meta-analysis (n=40). Mutations below the schematic representation of desmin are reported in the literature but were not included in the meta-analysis because (1) no clinical characteristics of carriers of these mutations were reported, or (2) the mutation was associated with autosomal recessive inheritance, or (3) the mutation was not considered pathogenic (Ala213Val and Val459Ile), or (4) the mutation was reported in a patient with an additional mutation in a different gene which probably influences the phenotype (Arg454Trp and Val469Met).
META-ANALYSIS OF DES MUTATION CARRIERS

Methods
We performed a PubMed search for publications issued between 1998 and April 2010 with the keywords “desmin”, “desmin related myopathy”, “desminopathy”, “cardiomyopathy”, “myopathy”, and “dilated cardiomyopathy” in order to collect all reported DES mutation carriers. Clinical characteristics, family characteristics, and results from DNA analysis of mutation carriers and obligate DES mutation carriers were included. Cases with suggested autosomal recessive inheritance\(^3,18,24,25\) or those with an additional mutation in a different gene which probably influences the phenotype\(^17,49\) were excluded. Several clinical features such as gender, age of onset of neurological or cardiological complaints,
results from neurological and cardiological investigations, information regarding respiratory function, and age and mode of death were studied. The earliest neurological sign was defined as the age at which the first sign of neurological disease presented. This could be muscular weakness noticed by the patient or a neurological diagnosis confirmed by a physician. The following information on cardiological signs and investigations was included in detail: information on type of cardiomyopathy, cardiac conduction disease (CCD), arrhythmias, pacemaker therapy, ICD therapy, and heart transplantation. The earliest cardiological sign was defined as the age at which the first sign of cardiological disease appeared. This could either be a complaint (syncope, palpitations or dyspnoea) or a cardiological diagnosis confirmed by a physician. Information on respiratory function was often lacking or insufficient, but we included this feature where possible. If no clear index patient was indicated (n=5), the person most likely to be the index patient was assigned as such. In five cases reported in one publication we could not assign an index patient, because it was not stated whether they were sporadic patients or related to each other.\textsuperscript{12} Finally, details on the mutation, including the localization of the mutation within the protein, were included.

Statistical analysis was performed by SPSS 17.0. (SPSS Inc., Chicago, USA). We used the Chi-square test to compare discrete variables, and the independent Student’s t test for continuous data.

\section*{Results}

\subsection*{Patient inclusion and basic characteristics}

We found 39 publications (and one corrigendum) describing DES mutation carriers,\textsuperscript{2, 3, 12-15, 17, 19, 21, 23, 38, 45, 46, 50-76} including two publications containing additional clinical details of patients. In total, 195 DES mutation carriers were described. Of these, 36 patients were described more than once in different publications. All the different publications on a single patient were included, because additional clinical data could be obtained, but each patient was included only once in our meta-analysis. Two patients with the Ala213Val mutation and two patients with the Val459Ile mutation were excluded, because these mutations are not considered to be pathogenic, although a modifying effect cannot be excluded (both are reported in the NCBI SNP database).\textsuperscript{77} We finally included 159 patients (154 patients from 68 families and 5 patients for whom information about familial relationship is unknown) with 40 different DES mutations: 97 males, 58 females, and 4 patients with unreported gender. For 37 index patients (54\%) it was certain that the DRM was familial, for 6 index patients (9\%) this was likely, for 3 index patients (4\%) this was unlikely, and familial disease was excluded in 15 index patients (22\%). No information regarding the familial character of the disease was available for 7 index patients (10\%).

\subsection*{Clinical characteristics}

The clinical characteristics of DES mutation carriers are summarized in Table 1. Neurological signs were reported in 74\% of carriers, with a mean age of 35 years at earliest neurological sign; 22\% had an isolated neurological phenotype. Myopathy or muscular weakness was present in
74% of carriers. The majority (67%) presented with distal and proximal muscular weakness at the same time. Increased creatine kinase (CK) levels were noticed in 57% of carriers. The CK level was normal in 30% of carriers with myopathy or muscular weakness. Cardiological signs were reported in 74% of carriers, with a mean age of 35 years at earliest cardiological sign; 22% had an isolated cardiological phenotype. Almost 50% of carriers had cardiomyopathy. The distribution of the different types of cardiomyopathy with mean age at diagnosis is represented in Table 2. Dilated cardiomyopathy (DCM) was the most prevalent type of cardiomyopathy. Restrictive cardiomyopathy (RCM) and hypertrophic cardiomyopathy (HCM) were diagnosed at significantly earlier ages than DCM (RCM 33 years versus DCM 46 years, p=0.007; HCM 28 years versus DCM 46 years, p=0.002). Heart transplantations were reported in 4 patients with RCM (4/16), in 2 patients with unspecified cardiomyopathy (2/13), and in 1 patient with arrhythmogenic right ventricular cardiomyopathy (ARVC) (1/2). CCD and/or arrhythmias were reported in 62% of carriers, in two-thirds of cases this was combined with cardiomyopathy. The different types of CCD and arrhythmias are represented in Table 3. Figure 4 shows an example of a 12-lead electrocardiogram with sinus rhythm and trifascicular block and a rhythm strip with high-grade atrioventricular block. Atrioventricular block was the most prevalent type of CCD. Both neurological and cardiological signs were present in 49% of carriers. Respiratory insufficiency was suggested in 26% of carriers. Death was reported in 26% of carriers at a mean age of 49 years. Sudden cardiac death (SCD) was reported in 7 patients, while 15 patients died from other disease-related causes (13 heart failure, 1 respiratory insufficiency, 1 chest infection), and for five patients the cause of death was not reported. Cardiomyopathy was reported in 89% (16
### Table 1: Overview of occurrence of clinical characteristics with mean age at earliest sign or diagnosis or therapy of DES mutation carriers

<table>
<thead>
<tr>
<th>Mean age at earliest sign/diagnosis/therapy</th>
<th>Carriers (%)</th>
<th>Age (years)</th>
<th>SD</th>
<th>Range (years)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological signs</td>
<td>74 (113/152)</td>
<td>35</td>
<td>10.0</td>
<td>14–70</td>
<td>Isolated: 22% (31/141)</td>
</tr>
<tr>
<td>Cardiological signs</td>
<td>74 (105/141)</td>
<td>35</td>
<td>13.0</td>
<td>11–72</td>
<td>Isolated: 22% (34/152)</td>
</tr>
<tr>
<td>Neurological and cardiological signs</td>
<td>49 (67/137)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Myopathy or muscular weakness</td>
<td>74 (110/148)</td>
<td>35</td>
<td>10.1</td>
<td>14–70</td>
<td>Presentation: distal 27% (29/106), proximal 6% (6/106), distal and proximal 67% (71/106) CK level: normal: 30% (25/83), increased ≤4 times: 59% (49/83), increased &gt;4 times: 11% (9/83),</td>
</tr>
<tr>
<td>CK level increased</td>
<td>57 (62/109)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Increased &gt;4 times: 9% (10/109)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>49 (67/138)</td>
<td>37</td>
<td>14.5</td>
<td>11–65</td>
<td>See Table 2 for types of cardiomyopathy</td>
</tr>
<tr>
<td>Heart transplantation</td>
<td>4 (7/159)</td>
<td>36</td>
<td>15.2</td>
<td>15–56</td>
<td>RCM 4/16, unspecified CM 2/13, ARVC 1/2</td>
</tr>
<tr>
<td>CCD and/or arrhythmias</td>
<td>62 (83/133)</td>
<td>34</td>
<td>13</td>
<td>11–72</td>
<td>CCD 39% (52/133), arrhythmias 5% (6/133), CCD and arrhythmias 19% (25/133) See Table 3 for types of CCD/arrhythmias Occurrence of cardiomyopathy: 63% (43/68) in cases with CCD, 67% (20/30) in cases with arrhythmias</td>
</tr>
<tr>
<td>PM</td>
<td>36 (46/127)</td>
<td>35</td>
<td>11.0</td>
<td>15–63</td>
<td>All had CCD</td>
</tr>
<tr>
<td>ICD</td>
<td>4 (7/159)</td>
<td>35</td>
<td>16.0</td>
<td>15–62</td>
<td>—</td>
</tr>
<tr>
<td>Respiratory insufficiency</td>
<td>26 (29/110)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Death</td>
<td>26 (27/104)</td>
<td>49</td>
<td>9.3</td>
<td>28–62</td>
<td>26% (7/27) SCD, 56% (15/27) other causes, 19% (5/27) unknown cause Cardiomyopathy: 89% (16/18) in deceased patients; death in DCM: 50% (9/18), mean age 54 years; death in RCM: 20% (2/10), mean age 32 years; HCM (0/6) and ARVC (0/2); no death Pacemaker (PM): death with PM 30%(10/33)* (2/10 SCD); death without PM 11% (5/47)*</td>
</tr>
</tbody>
</table>

ARVC=arrhythmogenic right ventricular cardiomyopathy; CCD=cardiac conduction disease; CK=creatine kinase; CM=cardiomyopathy; DCM=dilated cardiomyopathy; ICD=implantable cardioverter defibrillator; HCM=hypertrophic cardiomyopathy; PM=pacemaker; RCM=restrictive cardiomyopathy; SCD=sudden cardiac death. *p = 0.027.
Table 2: Distribution of different types of cardiomyopathy with mean age at diagnosis of DES mutation carriers

<table>
<thead>
<tr>
<th>Carriers</th>
<th>Carriers % (n)</th>
<th>Mean age at diagnosis</th>
<th>Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n)</td>
<td>Age (years)</td>
<td>SD</td>
</tr>
<tr>
<td>DCM</td>
<td>17 (23)</td>
<td>46*†</td>
<td>11.0</td>
</tr>
<tr>
<td>RCM</td>
<td>12 (16)</td>
<td>33*</td>
<td>14.9</td>
</tr>
<tr>
<td>HCM</td>
<td>6 (8)</td>
<td>28†</td>
<td>11.3</td>
</tr>
<tr>
<td>ARVC</td>
<td>1 (2)</td>
<td>29</td>
<td>11.3</td>
</tr>
<tr>
<td>Unspecified CM</td>
<td>13 (18)</td>
<td>37</td>
<td>15.3</td>
</tr>
<tr>
<td>Total CM</td>
<td>49 (67)</td>
<td>37</td>
<td>14.5</td>
</tr>
<tr>
<td>No CM</td>
<td>51 (71)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

ARVC=arrhythmogenic right ventricular cardiomyopathy; CM=cardiomyopathy; DCM=dilated cardiomyopathy; F=female; HCM=hypertrophic cardiomyopathy; M=male; RCM=restrictive cardiomyopathy; U=unknown.

* p = 0.007.
† p = 0.002.
‡ p = 0.035.

Table 3: Distribution of different types of cardiac conduction disease (CCD) and arrhythmias of DES mutation carriers

<table>
<thead>
<tr>
<th>CCD (n = 77)</th>
<th>Arrhythmias (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrioventricular block (AVB)*</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Right bundle branch block (RBBB)</td>
<td>47</td>
</tr>
<tr>
<td>Left bundle branch block (LBBB)</td>
<td>14</td>
</tr>
<tr>
<td>RBBB/LBBB alternating</td>
<td>14</td>
</tr>
<tr>
<td>Left anterior fascicular block</td>
<td>2</td>
</tr>
<tr>
<td>Bifascicular block</td>
<td>3</td>
</tr>
<tr>
<td>Trifascicular block</td>
<td>1</td>
</tr>
<tr>
<td>Unspecified cardiac conduction disease</td>
<td>6</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>9</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2</td>
</tr>
<tr>
<td>Atrial tachycardia</td>
<td>8</td>
</tr>
<tr>
<td>Ventricular premature beats</td>
<td>7</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>1</td>
</tr>
<tr>
<td>Ventricular tachycardia and atrial fibrillation</td>
<td>3</td>
</tr>
<tr>
<td>Unspecified tachycardia</td>
<td>3</td>
</tr>
<tr>
<td>Unspecified arrhythmia</td>
<td>1</td>
</tr>
</tbody>
</table>

*AVB: first-, second-, third-degree, or unspecified.
of 18) of deceased patients. In the DCM group, 9/18 patients (50%) had died with a mean age of 54 years, in the RCM group 2/10 patients (20%) had died at a mean age of 32 years, and no deaths were reported in the HCM group (n=6) and in the ARVC patients (n=2). More patients had died in the group with a pacemaker compared to the non-pacemaker group (10/33 (30%) versus 5/47 (11%); p=0.027). SCD occurred in two patients with a pacemaker. Neurological signs and cardiological signs occurred in any order in time (Table 4). Five DES mutation carriers (three women (between the ages 39 and 54) and two children (age 5)) showed no phenotype at time of evaluation (Table 4). The only evident difference between the genders is that cardiomyopathy is reported more often in male mutation carriers than in females (Table 2).

**DNA analysis and genotype-phenotype relationships**

We identified 40 different DES mutations in the 68 families and five patients for whom information about familial relationship was unknown. The majority of mutations identified were missense mutations (32/40 mutations; 137/159 carriers). More than half of the mutations (22/40 mutations; 73/159 carriers) were located in the 2B domain (Figure 3).

Most of the patients with isolated neurological signs had a mutation in the 2B domain (28/31; 90%), whereas most of the patients with isolated cardiological signs had a mutation in the head or the tail domain (22/34; 65%) (Table 4). Myopathy (with or without cardiological signs) was also more prevalent in patients with a mutation in the 2B domain (65/72; 90%) than in patients with mutations in the other regions of the gene (45/76; 59%) (p<0.001).

### Table 4: Order of presentation of neurological and cardiological signs compared to the locations of the mutations in different domains of DES

<table>
<thead>
<tr>
<th></th>
<th>n patients</th>
<th>Head</th>
<th>1A</th>
<th>1B</th>
<th>2A</th>
<th>2B</th>
<th>Tail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological signs</td>
<td>31</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>28*</td>
<td>3</td>
</tr>
<tr>
<td>Neurological followed by cardiological signs</td>
<td>27</td>
<td>5</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Cardiological and neurological signs</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Cardiological followed by neurological signs</td>
<td>20</td>
<td>7</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Cardiological signs</td>
<td>34</td>
<td>15†</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>7†</td>
</tr>
<tr>
<td>No phenotype at time of evaluation</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>130</td>
<td>27</td>
<td>4</td>
<td>22</td>
<td>0</td>
<td>59</td>
<td>18</td>
</tr>
</tbody>
</table>

*90% of patients with isolated neurological signs have a mutation in 2B domain
†65% of patients with isolated cardiological signs have a mutation in head or tail domain
Discussion

Desmin-related myopathy (DRM) is a predominantly autosomal dominantly inherited progressive skeletal and cardiac myopathy mainly caused by mutations in the desmin gene (DES). In recent years, there have been several publications on individual or small series of patients and families with DES mutations. This series of reports and the fact that a substantial number of patients (n=36) has been described more than once, make it difficult to interpret all this information. We therefore performed a meta-analysis to better interpret these reports.

Our meta-analysis of 159 heterozygous DES mutation carriers shows that DRM caused by heterozygous DES mutations, also referred to as desminopathy, is a serious disorder with variable involvement of myopathy and a malignant cardiological phenotype, including cardiomyopathy, CCD, and arrhythmias. Both neurological and cardiological signs were present in 49% of carriers, whereas isolated neurological and isolated cardiological signs were both present in 22%. These isolated forms with either neurologic or cardiolical manifestations of DRM might reflect an early stage of disease, as DRM is progressive.

More than 70% of DES mutation carriers exhibited myopathy or muscular weakness. CK levels were normal in one-third of them. This underscores that normal CK levels do not exclude a myopathy, as has also been demonstrated in LMNA-related disorders. Cardiomyopathy was reported in up to 50% of DES mutation carriers, with DCM being the most prevalent type of cardiomyopathy. The actual frequency of cardiomyopathy in carriers might well be higher, because subclinical or mild forms of cardiomyopathy would probably be detected if imaging studies were systemically performed in all carriers, for example by MRI.

The course of disease in patients with RCM is worse than in those with DCM with regards to a younger age at diagnosis, more frequent heart transplantation and earlier age at death. This is reflected in the fact that RCM generally has a poor outcome. However, the observation that RCM and HCM are diagnosed at significantly earlier ages than DCM might be partially explained by the fact that asymptomatic RCM or HCM can evolve towards symptomatic DCM in a later stage. Approximately 60% of carriers had CCD or arrhythmias, with atrioventricular block as an important hallmark. Right bundle branch block, the second most common type of CCD, underscores the right ventricular involvement in DES mutation carriers. Right ventricular involvement was also reflected by the fact that some observed tachycardias originate from the right ventricle and by the occurrence of right ventricular heart failure in several patients, including two patients who fulfilled the criteria for ARVC. Cardiomyopathy was only reported in two-thirds of the cases with CCD and/or arrhythmias, but these features are probably an initial manifestation of cardiomyopathy, with signs of cardiomyopathy on echocardiogram developing at a later age.

Symptoms generally started during the thirties and DRM due to DES mutations can have a poor prognosis, as death was reported in a quarter of DES mutation carriers at a mean age of 49 years. Most deceased patients were pacemaker carriers who also had signs of a cardiomyopathy. The combination of cardiomyopathy (DCM in particular) and CCD shows similarities...
to inherited cardiac diseases caused by mutations in other genes that can also be associated with generalized muscular disease, such as LMNA. Specific electrocardiographic signs that can be identified in a subset of LMNA mutation carriers have not been described as such in DES mutation carriers. A high percentage of SCD is evident in LMNA-related disorders, even in patients carrying a pacemaker. Although the prevalence of death is high and at a young age in DES mutation carriers, SCD is not the major cause of death in this group. However, the fact that SCD occurred in two patients carrying a pacemaker may suggest a ventricular tachyarrhythmia. As with LMNA mutation carriers, we recommend considering ICD therapy rather than pacemaker therapy in DES mutations carriers who need a pacemaker. This is in accordance with Luethje et al.’s recommendation, who reported on ICD therapy in a DES mutation carrier with sustained ventricular tachycardia. Further studies are required to validate this recommendation. Respiratory insufficiency seems to be present in a quarter of cases. However, information was often lacking or insufficient, thus its occurrence is probably underestimated and its severity in the reported cases cannot be estimated.

One possible explanation for the variability of phenotypes associated with different mutations (i.e. combined neurological and cardiological phenotype versus isolated neurological or cardiological phenotype) is the location of the mutation. This study demonstrates a predominance of 2B domain mutations in patients with isolated neurological phenotype, in contrast to a predominance of head and tail domain mutations in patients with an isolated cardiological phenotype. This is the most extensive overview of the clinical characteristics of DES mutation carriers. Importantly, we found that a substantial number of patients were described more than once in different studies. We included these patients only once in our meta-analysis, whereas other publications about DES mutation carriers did not report this aspect. Unfortunately this type of study implies that follow-up data are lacking, so no information on the progression of disease in these patients is available.

Although the article by Kostera-Pruszczyk et al. does not report a correction for “double inclusion” of DES mutation carriers, it is interesting to compare their results with ours. They mainly report on the cardiological characteristics of 92 published DES mutation carriers, whereas we also provide detailed information about the neurological phenotype. Even though they do not summarize the exact mutations included in their study, we concluded that they had not included head domain or 1A domain mutations. Their frequency of cardiac involvement and distribution of different types of cardiomyopathy is similar to our results. However, Kostera-Pruszczyk et al. do not report on cases with unspecified cardiomyopathy, whereas we frequently encountered this diagnosis (18 carriers). Besides that we included two recently published ARVC cases. They too noted that 2B domain carriers have primarily neurological signs and that the location of the mutation exerts a significant influence on phenotypic characteristics.
CONCLUDING REMARKS
Recognition of DRM can be difficult because of the variability of clinical features and non-specificity of histopathology. DNA analysis may help in confirming a diagnosis and should be considered in patients with a combination of skeletal myopathy and cardiac phenotype (cardiomyopathy or CCD), but also in patients with an isolated neurological or cardiological phenotype. Cascade genetic testing in family members can then help to identify other individuals at risk and those who do not carry the disease-causing mutation. This enables timely diagnosis, with the possibility of preventing complications and reducing morbidity and mortality. It also means that family members who do not carry the mutation can be dismissed from regular monitoring. We propose yearly cardiological evaluation of all DES mutation carriers starting at the age of 10 years for early detection of cardiac abnormalities, even if there are no cardiological complaints. Further studies are necessary to evaluate whether ICD therapy is better than pacemaker therapy for DES mutation carriers in need of a pacemaker. Although genotype-phenotype correlations are emerging, these findings do not yet lead to specific clinical decisions.

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REFERENCES


Chapter 3


