Scapuloperoneal syndrome type Kaeser and a wide phenotypic spectrum of adult-onset, dominant myopathies are associated with the desmin mutation R350P

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In 1965, an adult-onset, autosomal dominant disorder with a peculiar scapuloperoneal distribution of weakness and atrophy was described in a large, multi-generation kindred and named ‘scapuloperoneal syndrome type Kaeser’ (OMIM #181400). By genetic analysis of the original kindred, we discovered a heterozygous missense mutation of the desmin gene (R350P) cosegregating with the disorder. Moreover, we detected DES R350P in four unrelated German families allowing for genotype-phenotype correlations in a total of 15 patients carrying the same mutation. Large clinical variability was recognized, even within the same family, ranging from scapuloperoneal (n = 2, 12%), limb girdle (n = 10, 60%) and distal phenotypes (n = 3, 18%) with variable cardiac (n = 7, 41%) or respiratory involvement (n = 7, 41%). Facial weakness, dysphagia and gynaecomastia were frequent additional symptoms. Overall and within each family, affected men seemingly bear a higher risk of sudden, cardiac death as compared to affected women. Moreover, histological and immunohistochemical examination of muscle biopsy specimens revealed a wide spectrum of findings ranging from near normal or unspecific pathology to typical, myofibrillar changes with accumulation of desmin. This study reveals that the clinical and pathological variability generally observed in desminopathies may not be attributed to the nature of the DES mutation alone, but may be influenced by additional genetic and epigenetic factors such as gender. In addition, mutations of the desmin gene should be considered early in the diagnostic work-up of any adult-onset, dominant myopathy, even if specific myofibrillar pathology is absent.

Keywords: myofibrillar myopathy; scapuloperoneal syndrome; desminopathy; desmin-related myopathy

Abbreviations: EM = electron microscopy; EMG = electromyography; Gd-DTPA = gadolinium-diethyltriaminepentaacetic acid; LGMD = limb girdle muscular dystrophy; MRI = magnetic resonance imaging


Introduction

Mutations of the human desmin gene on chromosome 2q35 cause familial or sporadic forms of skeletal myopathy, characterized morphologically by abnormal accumulation of desmin within muscle fibres (Goebel, 1995). The majority of cases show autosomal-dominant inheritance, but rare autosomal-recessive cases as well as an increasing number of sporadic cases have been reported (Goldfarb et al., 2004). Several clinical presentations such as rare severe childhood-onset cardioskeletal myopathy (Goldfarb et al., 1998), adult-onset skeletal myopathy with cardiac involvement (Goldfarb et al., 1998; Park et al., 2000a, b; Kaminska et al., 2004), skeletal myopathy without cardiac involvement...
(Kaminska et al., 2004), severe generalized myopathy (Ariza et al., 1995), pure dilated cardiomyopathy (Li et al., 1999), cardiomyopathy with distal weakness (Sugawara et al., 2000; Goudeau et al., 2001; Schroder et al., 2003) and distal myopathy with cardiac, respiratory, bulbar and facial involve- ment (Horowitz and Schmalbruch, 1994; Sjoberg et al., 1999) were described (OMIM #125660). Most DES mutations were reported in one family or in a few patients, only. Therefore, it is difficult to assess whether a distinct clinical phenotype is closely correlated to a certain mutation or whether certain mutations cause various clinical presentations.

Recently, we identified a novel DES mutation (R350P) in a German family with distal myopathy. R350P was shown to exert a dominant negative effect on the ordered lateral arrangement of desmin subunits leading to abnormal protein aggregation. Here we present clinical findings in 15 patients from 5 unrelated families harbouring DES (R350P) and demonstrate a wide phenotypic spectrum associated with this mutation including scapuloperoneal syndrome type Kaeser (OMIM #181400) (Kaeser, 1965).

Material and methods

Patients

A total of 205 unrelated, adult patients with clinical evidence for a myopathy in scapuloperoneal, distal or limb girdle distribution were screened for mutations in the desmin gene (see later). DES (R350P) was detected in five families. All index patients and affected relatives described in this study were examined by one of the coauthors. Consanguinity was not reported. Pedigrees were compatible with autosomal dominant traits. All patients described are of German descent.

Magnetic resonance imaging

A recently introduced 1.5 tesla scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) combines 76 coil elements (‘matrix coils’) and 32 receiver channels. It allows whole body MRI in all three dimensions with free table movement. The protocol used for musculoskeletal system on this scanner incorporates T1-weighted SE (TR 540, TE 13) before and after intravenous application of Gad-DTPA as contrast-material and STIR-sequences (TR 2680, TE 101 and TI 150).

Muscle biopsy

An open muscle biopsy was taken from the right vastus lateralis muscle of patient 9 and from the left gastrocnemius muscle of patient 13 in family 4 and analysed by standard histological and immunohistological methods. Protein aggregates were visualized using antibodies against desmin (Dako M0760, clone D33, Glostrup, Denmark; dilution 1 : 100), αB-crystallin (Novocastra, Newcastle Upon Tyne, UK, dilution 1 : 100) and filamin c (clone RR90; dilution 1 : 3 (van der Ven et al., 2000) and appropriate secondary antibodies for immunohistochemistry.

Haplotype analysis

Venous blood samples for genomic DNA extraction were collected with informed consent. Haplotype analysis was performed using polymorphic microsatellite markers for the chromosomal loci of LGMD1A–F, MYH2A, CRYAB and DES as recently described (von der Hagen et al., 2006). For each gene locus, four to six microsatellite markers flanking the gene on either side were investigated. The order of markers was based on published human linkage maps and physical mapping data.

Mutation analysis of the desmin gene (DES)

A PCR fragment encompassing the mutation R350P was amplified by PCR using primers D6f [5’-ATGGCCAGGACCTGACCATT CTG-3’] and D350r [5’-TGCCATCTCCACATCAGGCCC-3’]. The resulting 293bp fragment was purified using the NucleoSpin Extract kit (Macherey–Nagel, Düren, Germany), digested with the restriction endonuclease HpaII (New England Biolabs, Frankfurt, Germany), and the resulting fragments separated on 2% agarose gels by electrophoresis. The mutant fragment (R350P) digested into three fragments of 131, 88 and 74 bp, whereas wild-type DNA is cleaved into two fragments of 205 and 88 bp length. To confirm the presence of DES R350P the same PCR product was sequenced using an Applied Biosystems model 3100 Avant DNA sequencer and fluorescein-labelled dideoxy terminators (Perkin–Elmer, Foster City, CA, USA).

Results

Molecular genetics

Linkage analysis was performed in family 1 and 2, and suggested possible linkage to the DES gene, whereas loci for LGMD1A–F, MYH2A and CRYAB were excluded. Mutation screening of DES revealed a heterozygous R350P (1049 G>C) mutation in all affected family members, segregating with the disease phenotype. The mutation has been previously described by us in family 4 (Bar et al., 2005). By screening a cohort of 205 patients, the same mutation was identified in two additional, unrelated families (families 3 and 5), where it also segregates with the disease. Haplotype analysis using six microsatellite markers flanking the desmin gene revealed that the affected family members in families 1–5 share a common haplotype on one allele including the gene region which cosegregates with the R350P mutation (Table 1). In families 3, 4 and 5, recombination events occurred downstream from the DES gene region between markers D2S2359 and D2S126 and between D2S163 and D2S2359, respectively.

Interestingly, the disease allele in all five families shares a core region of at least 3 Mb with most distal common microsatellite marker D2S163 (Table 1). This may point towards a common origin of the mutation (founder allele).

Clinical observations

Family I—scapuloperoneal phenotype

We examined two affected descendants of the kindred originally described by Kaeser (1965) with 12 affected members in five generations following autosomal dominant inheritance, and a distinct scapuloperoneal distribution of weakness (Fig. 1). The 60-year-old male index patient (patient 1, Table 2, Figs 2, 3 and 4) experienced first
walking difficulties at age 39 years. At age 41 years, paresis of foot flexors and extensors was noted, and at age 43 years, shoulder girdle weakness occurred. Ten years after onset of the disease, the patient became wheelchair-bound; standing with support was possible up to age 58 years. At examination at age 60 years, the patient showed pronounced atrophy and weakness of the lower limb and shoulder girdle muscles as well as mild involvement of the facial muscles, dysphagia and gynaecomastia. Whole body MRI scan showed marked atrophy and fatty degeneration of proximal and distal muscles, only the biceps brachii muscle was relatively spared (Fig. 3). CK levels were elevated up to 700 U/l (normal value 580). There was subclinical cardiac involvement with mild arrhythmia. Genetically, facioscapulohumeral muscular dystrophy (FSHD) was excluded.

EMG showed myogenic findings in various muscles as well as subtle neurogenic changes in the distal lower extremities. Morphological and ultrastructural examination of the biceps brachii muscle revealed unsppecific signs of myopathy. Immunohistochemical staining for desmin and filamin c was normal except for a few, subsarcolemmal aggregates in single fibres (Fig. 5).

The 61-year-old sister of the index patient (patient 2, Table 2) observed mild abdominal weakness between age 40 and 50 years. At age 56 years, mild dysphagia and weakness of foot extensors occurred. Since age 60 years, she noticed marked problems in climbing stairs or in getting up from sitting position due to proximal leg weakness. Two years later, distal and proximal weakness of arm muscles developed, and dysphagia worsened. CK levels were only elevated at 215 U/l (normal value 5167). There is no cardiac or pulmonary involvement, and the patient is still able to walk without aids for up to 30 min.

Historical data of the family reveal mean onset of disease around 40 years of age with earlier onset in male as compared to female patients. Up to now, 20 persons (11 males, 9 females) from seven generations are reported to be affected, penetrance seems to be complete.

### Family 2—limb girdle phenotype

In this family, we examined five patients from two generations with an autosomal dominant myopathy. The female index patient (patient 3, Table 2, Fig. 4) showed first symptoms at age 50 years with slowly progressive proximal leg weakness and cardiac conduction problems. During the progression of the disease, distal involvement occurred in leg muscles. However, only mild proximal paresis was seen in the upper extremity, and no dysphagia. Since age 70 years, there is severe pulmonary involvement requiring non-invasive ventilation. CK levels were normal or mildly elevated. EMG showed a mixed myopathic–neurogenic pattern, muscle biopsy revealed a degenerative myopathy with additional neurogenic changes, fibre-size variations, rimmed vacuoles, whorled fibres, suggesting myofibrillar myopathy. Additional family
### Table 2 Clinical, morphological and genetic findings in R350P desminopathy patients

<table>
<thead>
<tr>
<th>Patient no./pedigree no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Age onset</th>
<th>Initial symptoms</th>
<th>Distribution of weakness</th>
<th>MRC grades (Arms proximal Legs proximal Legs distal)</th>
<th>Additional signs and symptoms</th>
<th>CK (U/l)</th>
<th>EMG</th>
<th>Histology</th>
<th>RV</th>
<th>Protein aggregates/desmin positive inclusions</th>
<th>Z-line disorganization</th>
<th>EM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family 1</strong></td>
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<tr>
<td>1/VI : 59</td>
<td>60</td>
<td>M</td>
<td>39</td>
<td>Climbing stairs impaired</td>
<td>Scapuloperoneal, wheel-chair bound</td>
<td>3–4/5, 4–2/5</td>
<td>Dysphagia, gynaecomastia, cardiac (mild arrhythmia), mild facial weakness</td>
<td>700</td>
<td>Mixed myopathic/neurogenic</td>
<td>Mild degenerative myopathy</td>
<td>–</td>
<td>(+-)</td>
<td>Z-line disorganization no protein aggregates</td>
<td></td>
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<tr>
<td><strong>Family 2</strong></td>
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<tr>
<td>3/V : 4</td>
<td>82</td>
<td>F</td>
<td>50</td>
<td>Climbing stairs impaired</td>
<td>LGMD, bed-confined</td>
<td>3–4/5, 4–2/5</td>
<td>Cardiac (conduction problems), pulmonary (requiring ventilation)</td>
<td>150</td>
<td>Mainly myopathic</td>
<td>Degenerative myopathy with neurogenic-like changes</td>
<td>–</td>
<td>n.d.</td>
<td>n.d.</td>
<td></td>
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<tr>
<td>7/VII : 25</td>
<td>52</td>
<td>M</td>
<td>40</td>
<td>Standing on heels and toes impaired</td>
<td>Distal/LGMD, walks with support</td>
<td>4–5/5, 4–5</td>
<td>None</td>
<td>500</td>
<td>Myopathic</td>
<td>Degenerative myopathy</td>
<td>++</td>
<td>n.d.</td>
<td>n.d.</td>
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<tr>
<td><strong>Family 3</strong></td>
<td></td>
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<tr>
<td>8/IV : 2</td>
<td>48</td>
<td>M</td>
<td>31</td>
<td>Walking impaired due to foot drop</td>
<td>Distal, walks independently</td>
<td>4–5/5, 4–3/5</td>
<td>Mild dysphagia, gynaecomastia</td>
<td>900</td>
<td>Myopathic</td>
<td>Degenerative myopathy with neurogenic-like changes</td>
<td>+</td>
<td>Normal</td>
<td>Z-line disorganization autophagic vacuoles no protein aggregates</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Patient no./ pedigree no.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Initial symptoms</th>
<th>Distribution of weakness</th>
<th>MRC grades (Arms proximal, Arms distal, Legs proximal, Legs distal)</th>
<th>Additional signs and symptoms</th>
<th>CK (U/l)</th>
<th>EMG</th>
<th>Histology</th>
<th>RV</th>
<th>Protein aggregates/ desmin positive inclusions</th>
<th>EM</th>
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<tr>
<td><strong>Family 4</strong></td>
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<tr>
<td>9/II : 3</td>
<td>56</td>
<td>M</td>
<td>Dyspnoea on exertion</td>
<td>LGMD, proximal and distal weakness in upper and lower extremities, walks independently</td>
<td>4/5 5/5 3/5 4/5</td>
<td>Respiratory insufficiency (requiring ventilation), cardiac (arrrhythmia), deafness, gynaecomastia</td>
<td>2580</td>
<td>Myopathic</td>
<td>Degenerative myopathy +</td>
<td>+</td>
<td>Z-line streaming massive granulofilamentous material</td>
<td></td>
</tr>
<tr>
<td>11/II : 5</td>
<td>50</td>
<td>F</td>
<td>Dyspnoea on exertion, proximal leg weakness</td>
<td>LGMD, proximal and distal weakness in lower extremities, walks independently</td>
<td>5/5 5/5 4/5 4/5</td>
<td>Intermittent palpitations, exertional dyspnoea</td>
<td>370</td>
<td>n.d.</td>
<td>n.d.</td>
<td></td>
<td></td>
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<tr>
<td>13/III : 1</td>
<td>26</td>
<td>M</td>
<td>No complaints</td>
<td>Distant weakness in lower extremities, walks independently</td>
<td>5/5 5/5 5/5 4/5</td>
<td>Deafness</td>
<td>540</td>
<td>Mixed myopathic/ neurogenic</td>
<td>Degenerative myopathy with neurogenic-like changes +</td>
<td>+</td>
<td>n.d</td>
<td></td>
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<tr>
<td><strong>Family 5</strong></td>
<td></td>
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<tr>
<td>14/IV : 3</td>
<td>33</td>
<td>F</td>
<td>Myalgia, climbing stairs impaired</td>
<td>LGMD, proximal and distal weakness in lower extremities, walks independently</td>
<td>5/5 5/5 4/5 3/5</td>
<td>Beginning respiratory involvement</td>
<td>452</td>
<td>Myopathic</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>15/III 0 : 2</td>
<td>64</td>
<td>F</td>
<td>Proximal leg weakness, foot drop</td>
<td>LGMD, wheelchair-bound</td>
<td>3/5 4/5 2–3/5 2/5</td>
<td>Respiratory insufficiency (requiring ventilation), cardiac (arrrhythmia)</td>
<td>108</td>
<td>Myopathic</td>
<td>Degenerative myopathy +</td>
<td>n.d.</td>
<td>n.d.</td>
<td></td>
</tr>
</tbody>
</table>

n.d. = not done; + = some; ++ = many; − = none; CK = creatine kinase; LGMD = limb girdle muscular dystrophy; EMG = electromyography; EM = electron microscopy; RV = rimmed vacuoles; † = deceased.
members (patients 4–7, Table 2) were examined and found to be similarly affected with a limb girdle distribution of weakness. Similar to family 1, male patients experienced an earlier onset and a more severe course of the disease.

Historical data on the family revealed, that 18 patients (13 males, 7 females) in seven generations were known to be affected. Assignment (affected/unaffected) for generations II, III and IV (date of birth around 1780–1900) may be imperfect, given that a mild clinical presentation at a higher age may have been missed. Overall, patients show a limb girdle phenotype, frequently with pronounced cardiac involvement, and four affected males died from sudden cardiac events. Furthermore, two affected family members (one male, one female) show marked pulmonary involvement requiring non-invasive ventilation.

**Family 3—distal myopathy phenotype**

First symptoms occurred at age 31 years in the now 50-year-old male index patient (patient 8, Table 2, Fig. 4) as distal leg weakness predominantly in foot extensors. Ten years later, abdominal weakness, mildly progressive proximal leg weakness and gynaecomastia were noted. Since age 46 years, dysphagia and proximal arm weakness additionally occurred, but up to now we observed no signs of cardiac or pulmonary impairment. CK levels were elevated between 300 and 1000 U/l (normal value <180). Histologically, a myopathy with rimmed vacuoles was diagnosed; Z-line disorganization and autophagic vacuoles were observed by electron microscopy. Whole body MRI scan showed symmetric atrophy and degeneration of deltoideus muscles, while biceps brachii, supra- and infraspinatus muscles are relatively spared (Fig. 3). Furthermore, there was marked involvement of trunk muscles, proximal and distal lower-limb muscles with predominance of fatty degeneration in tibialis anterior muscles. Six individuals (three males, three females) from four generations are known to be affected.

**Family 4—mixed distal myopathy/limb girdle phenotype**

This family harbouring the R350P mutation has been recently described by us (Bar et al., 2005) and re-examined for the purpose of this study. The index patient is a 56-year-old male presenting with a history of increasing dyspnoea on exertion starting in his mid-forties (patient 9, Table 2, Fig. 4). Neuromuscular symptoms with difficulty in lifting his arms over shoulder level were first noted at age 48 years. Neurological examination showed mild bilateral weakness of proximal arm and shoulder girdle muscles and moderate weakness of both pelvic and proximal leg muscles. In addition, he exhibited mild weakness of distal leg muscles and showed mild gynaecomastia. Respiratory and cardiac work-up showed a restrictive ventilation disorder and a cardiomyopathy with conduction disorder. EMG showed a myopathic pattern, nerve conduction velocity was normal. Biopsy of his vastus lateralis muscle revealed myopathic findings including increased fibre-size variation, internalized myonuclei, rare angulated atrophic fibres, multiple fibres with cytoplasmic and subsarcolemmal basophilic inclusions and conspicuous cytoplasmatic protein aggregates in a large number of myofibres. These aggregates were immunoreactive for desmin and zB-crystallin (Fig. 5).

Several other family members were similarly affected (patients 10–13, Table 2). His mother suffered from slowly progressive leg weakness and died at age 44 years because of acute cardiac failure (patient 10, Table 2). His 50-year-old sister reported progressive muscle weakness and dyspnoea on exertion, starting at age 44 years. Her neurological examination demonstrated moderate weakness of distal and proximal leg muscles (patient 11, Table 2). His brother suffered from proximal leg weakness starting at age 31 years and died at age 46 years because of progressive cardio-respiratory insufficiency (patient 12, Table 2). One out of four offspring of patient 12 showed mild weakness of foot extensor muscles (patient 13 in Table 2). Muscle biopsy taken from the gastrocnemius muscle revealed a myopathic...
Fig. 3 Whole body MRI scans (T1-weighted images) and transverse sections of upper and lower-limb muscles. Patient 8: (left) symmetric atrophy and degeneration of deltoideus muscles, while biceps brachii, supra- and infraspinatus muscles are relatively spared. Note the marked involvement of trunk muscles, proximal and distal lower-limb muscles with predominance of fatty degeneration in tibialis anterior muscles. Patient 14: (middle) marked atrophy and fatty degeneration of proximal and distal leg muscles, predominantly in the dorsal leg compartment, while in the upper extremities only deltoideus muscles are mildly affected. Patient 1: (right) marked atrophy and fatty degeneration of proximal and distal muscles, only the biceps brachii muscle is relatively spared.
Fig. 4 Pedigrees of families. Families 1–5, index patients are described in Table 1.
Scapuloperoneal syndrome type Kaeser and desmin mutation R350P

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Fig. 4 Continued.
pattern with rounding of muscle fibres, increased fibre-size variability with diameters ranging from 16 to 153 μm (normal 40–80 μm), some necrotic and regenerating fibres, internalization of nuclei in 40% of the fibres and many fibres with basophilic inclusions which showed intense labelling with antibodies against desmin and αB-crystallin (Fig. 5).

Family 5—limb girdle phenotype
The 33-year-old female index patient (patient 14, Table 2, Fig. 4) noticed myalgia after exercise since age 16 years. At age 30 years, she noted first problems in climbing stairs. Around the same time she noticed an inability to walk on heels. Neurological examination at age 33 years revealed paresis of proximal leg muscles (MRC 4/5) and foot extensors (3/5), but full strength of foot flexors, arm and hand muscles. Lung function tests showed beginning respiratory involvement, cardiac function was normal. Whole body MRI scan showed marked atrophy and fatty degeneration of proximal and distal leg muscles, predominantly in the dorsal leg compartment, while in the upper extremities only deltoid muscles are mildly affected (Fig. 3).

The 64-year-old mother (patient 15, Table 2) of the index patient noted first symptoms at age 40 years in form of proximal leg weakness, foot drop and cardiac arrhythmia. At age 45 years additional weakness in shoulder girdle and arm muscles occurred, at age 55 years, finger flexors were also affected. From age 58 years, she used a walking frame, and is now wheelchair-bound. Meanwhile, her lung function deteriorated requiring non-invasive ventilation. A muscle biopsy was obtained 25 years ago and showed a vacuolar myopathy, suggestive of inclusion body myopathy. Ultrastructural and immunohistochemical analysis was not carried out.

Her father and a male paternal cousin both died from sudden cardiac death at age 53 and 56 years, respectively, the cousin was further reported to have suffered from muscle weakness.

Discussion
We report clinical, electrophysiological, histopathological and molecular data of 15 patients from five independent families affected with a dominant myopathy due to DES (R350P), presenting with a highly variable clinical and morphological phenotype. Up to now, more than 30 mutations in DES have been reported and some tentative genotype-phenotype correlations have been proposed based on the mutation site, inheritance pattern and clinical manifestations (Goldfarb et al., 2004; Paulin and Li, 2004). However, no distinct clinical phenotype was found to be closely associated with a certain mutation, since most mutations were limited to a single or few families. Clinical manifestations in the autosomal dominant syndrome included distal or proximal progressive skeletal myopathy, cardiomyopathy and respiratory dysfunction alone or their combination (Goldfarb et al., 2004). For the first time we describe a larger cohort of patients harbouring the same DES mutation (R350P). Large variability was recognized (Table 3) even within the same family, ranging from scapuloperoneal (n = 2, 12%), limb girdle (n = 10, 60%) and distal phenotypes (n = 3, 18%) with variable cardiac (n = 7, 41%) or respiratory involvement (n = 7, 41%). In advanced stages of the disease, all muscles are affected, but the biceps brachii is relatively spared in patients...
with scapuloperoneal distribution. In addition, facial weakness, dysphagia and gynaecomastia were frequently observed.

Desminopathy (R350P) is inherited with an autosomal dominant pattern and shows full penetrance. Mean onset of disease of male patients was at age 37 years. In female patients, disease onset occurred later (mean at age 46 years), and progression seemed less severe. While males do not have a higher overall incidence of cardiac or pulmonary involvement compared to females, risk for sudden death or fatal respiratory failure seems to be higher in males: 2 males versus 1 female in the patients investigated for this study, and 12 males versus 2 females from families’ historical data. Therefore, gender-related factors or modifier genes may be involved in determining disease onset and severity. Recently, similar gender-related phenotypic differences have been described in a Spanish desminopathy family due to a novel L370P mutation (Arias et al., 2006).

Furthermore, it would be important to identify genetic associations responsible for heart and respiratory problems, like mutations in other ‘neuromuscular’ genes modifying the clinical manifestation or synergistically contribute to disease severity of desminopathy, which was recently shown for dominant Emery–Dreifuss muscular dystrophy in a Spanish desminopathy family due to a novel L370P mutation (Arias et al., 2006).

Table 3 Clinical phenotype of DES R350P patients

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>All patients (n = 15)</th>
<th>Males (n = 9)</th>
<th>Females (n = 6)</th>
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<tr>
<td>Mean age of onset (years)</td>
<td>40 ± 10</td>
<td>37 ± 5</td>
<td>46 ± 13</td>
</tr>
<tr>
<td>Onset proximal</td>
<td>11</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Onset distal</td>
<td>4</td>
<td>3</td>
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<tr>
<td>Distal &gt; proximal weakness</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Proximal &gt; distal weakness</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Scapuloperoneal weakness</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Swallowing problems</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Facial weakness</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Gynaecomastia</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory involvement</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Death &lt; 60 years</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>CK level (normal &lt; 160)</td>
<td>557 ± 145</td>
<td>739 ± 213</td>
<td>256 ± 131</td>
</tr>
</tbody>
</table>

Usually, desminopathies are diagnosed through muscle histology. Pathological features in desminopathies consist of a myopathic pattern with variability of fibre-size, the presence of angulated atrophic fibres, internalized nuclei, rimmed and autophagic vacuoles, rarely cytoplasmic eosinophilic inclusions and accumulation of desmin in immunohistochemistry. Furthermore, in autophagic vacuoles myelin-like lamellae, aggregates, and IBM-like paired helical tubulofilaments were described (Vrabie et al., 2005). Selcen et al. (2004) reported in a cohort of patients with myofibrillar myopathy an abnormal fibre-size variation, with some fibre diameters as small as 5 μm or as large as 150 μm and type-grouping in 70% of the muscle specimens. In most cases, however, atrophic fibres accounted for only a small proportion of the total. Furthermore, neurogenic-like changes are described in other myofibrillar myopathies such as myotilinopathy (Selcen and Engel, 2004) and ZASPopathy (Selcen and Engel, 2005).

In 1965, Kaeser reported a kindred with atrophies and weakness in a scapuloperoneal distribution following an autosomal dominant trait. Histopathological examination at autopsy in one patient, the father of our index patient (patient 1, family 1), revealed fibre-size variation ranging from 12 to 54 μm, increase in muscle nuclei and small muscle fibres with varying shapes (some very small and round, others polyhedral) found in biceps, quadriceps, interosseus dorsalis and thenar muscles (Probst et al., 1977). However, clear myofibrillar changes are not reported. Ultrastructural findings were described as ‘a juxtanuclear inclusion which consisted of a crystal-like lattice of dense particles’, that may resemble protein aggregates. Retrospectively, there is considerable overlap with the myopathological changes described in myofibrillar myopathies. Kaeser suggested a neurogenic origin, but demonstrated significant differences from the cases reported by Davidenkow (1939). Neuropathic scapuloperoneal syndrome (Davidenkow’s syndrome) was recently found associated to chromosome 17p11.2 deletions (Verma, 2005). Interestingly, the current histopathological examination of the biceps brachii muscle of patient 1 showed very limited myofibrillar changes or protein aggregation which were only picked up by desmin and filamin c immunohistochemistry. Therefore, we suggest to proceed with genetic analysis in adult-onset, dominant myopathies even in the absence of typical, myofibrillar changes upon histological examination, once other causes of dominant myopathies have been excluded.

Our findings allow re-assigning the scapuloperoneal syndrome in the kindred originally described by Kaeser to the group of dominant myopathies, due to the R350P desmin mutation. Future studies will have to elucidate how other factors and modifier genes may influence the severity, penetrance and expression of the disease. Identification of these genes and pathways may lead to novel therapeutic strategies.
Acknowledgements
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References