Prevalence of Desmin Mutations in Dilated Cardiomyopathy

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Background—Desmin-related myofibrillar myopathy (DRM) is a cardiac and skeletal muscle disease caused by mutations in the desmin (DES) gene. Mutations in the central 2B domain of DES cause skeletal muscle disease that typically precedes cardiac involvement. However, the prevalence of DES mutations in dilated cardiomyopathy (DCM) without skeletal muscle disease is not known.

Methods and Results—Denaturing high-performance liquid chromatography was used to screen DES for mutations in 116 DCM families from the Familial Dilated Cardiomyopathy Registry and in 309 subjects with DCM from the Beta-Blocker Evaluation of Survival Trial (BEST). DES mutations were transfected into SW13 and human smooth muscle cells and neonatal rat cardiac myocytes, and the effects on cytoskeletal desmin network architecture were analyzed with confocal microscopy. Five novel missense DES mutations, including the first localized to the highly conserved 1A domain, were detected in 6 subjects (1.4%). Transfection of DES mutations in the 2B domain severely disrupted the fine intracytoplasmic staining of desmin, causing clumping of the desmin protein. A tail domain mutation (Val459Ile) showed milder effects on desmin cytoplasmic network formation and appears to be a low-penetrant mutation restricted to black subjects.

Conclusions—The prevalence of DES mutations in DCM is between 1% and 2%, and mutations in the 1A helical domain, as well as the 2B rod domain, are capable of causing a DCM phenotype. The lack of severe disruption of cytoskeletal desmin network formation seen with mutations in the 1A and tail domains suggests that dysfunction of seemingly intact desmin networks is sufficient to cause DCM. (Circulation. 2007;115:1244-1251.)

Key Words: cardiomyopathy ■ desmin ■ genetics ■ heart failure

Desmin-related myofibrillar myopathy (DRM) is a rare heritable myopathy affecting skeletal and cardiac muscle (OMIM #601419),1 caused by mutations in the desmin (DES) gene. Skeletal muscle weakness starting in the lower limbs and progressing to involve truncal, neck flexor, bulbar, and respiratory muscles without cardiac involvement has been reported most commonly.2–5 Cardiac manifestations in other families include restrictive cardiomyopathy, dilated cardiomyopathy, conduction system diseases, arrhythmias, and sudden death.6–7 The majority of the >40 DES mutations reported cause DRM and are localized to the central rod domain of the desmin protein (Figure 1). Selected skeletal and cardiac muscle biopsies from affected patients have shown cytoplasmic aggregations of intermediate filaments, which are presumed to reflect a disruption of the assembly of desmin protein into a filamentous network.4,6–14 Mutations in α-B-crystallin (CRYAB), dystrophin (DMD), and myotilin (TTID) cause similar morphological changes to skeletal muscle. Transfection of various DES mutations into cellular models has largely confirmed in vitro aggregation of desmin protein and disruption of the cytoplasmic filamentous desmin network.4,5,8,9,11,13–15

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Only 1 reported mutation (Ile451Met), located in the tail domain of the desmin protein and found in a study of 44 subjects with dilated cardiomyopathy (DCM), has been linked to DCM without skeletal muscle disease.16 The Ile451Met mutation is either a recurrent or founder mutation because a screen of 265 unrelated Japanese DCM cases for this specific mutation detected 3 additional cases (1.1%).12 Ile451Met mutations were also found in a family with classic DRM4 and in another family with slowly progressive skeletal...
myopathy with no apparent cardiac involvement and incomplete penetrance evidenced by 3 adult healthy mutation carriers. Thus, the contribution of DES mutations to isolated DCM and whether mutations located outside the desmin tail region can cause DCM are incompletely understood. The largest previous population study of 63 cases of DCM did not identify any DES mutations. The aim of the present study was to comprehensively screen a large population of DCM cases for DES mutations with the use of 2 unique DCM cohorts: (1) subjects from 115 DCM families with familial and nonfamilial (sporadic) forms and (2) 309 DCM subjects from the Beta-Blocker Evaluation of Survival Trial (BEST).18,19

**Methods**

**Patient Cohorts**
The family-based cohort drew subjects from the Familial Cardiomyopathy Registry, a multicenter DCM study. Affected subjects from 116 DCM families were screened for DES mutations (1 subject from a recessive-appearing pedigree was unaffected). The diagnosis of DCM was made according to published criteria; probands and available relatives were evaluated by the investigators, an evaluation that included a detailed history, physical examination, 12-lead ECG, and echocardiography; medical records were also reviewed in the case of unavailable or deceased relatives. Informed consent was obtained from Familial Cardiomyopathy Registry subjects under the institutional review board policies of the participating institutions. The 148 subjects were predominantly white and comprised 90 men and 58 women with an average age at study entry of 44 years. A second group of DCM subjects was screened from the BEST cohort, which was cosponsored by the National Heart, Lung, and Blood Institute and the Department of Veterans Affairs Cooperative Studies Program. BEST was a multicenter study of moderate to severe congestive heart failure (New York Heart Association class III-IV and ejection fraction of ≤35% at entry) comparing bucindolol with placebo. A subset of BEST subjects participated in a DNA bank, and we were granted approval to study 309 anonymous samples from DCM subjects. This cohort had an average age of 56 years and was divided into 213 men and 96 women, with 240 and 69 nonblack and black (non-Hispanic) subjects, respectively.

**DES Mutation Screening**

Genetic screening was done with the use of denaturing high-performance liquid chromatography with a Transgenicome WAVE Fragment Analysis System (Transgenicome Inc, Omaha, Neb) followed by selective DNA sequencing of variants with abnormal denaturing high-performance liquid chromatography elution profiles on an ABI 377 DNA Sequencer (Applied Biosystems, Foster City, Calif). The 9 DES exons and intron boundaries and the 5' upstream enhancer sequence that modulates expression of the desmin protein28 were studied (primer sequences and conditions available on request). Wild-type control DNA was added to those samples from Familial Cardiomyopathy Registry families in which autosomal recessive inheritance or sporadic disease was suspected. This approach favors the formation of heteroduplexes in which homozygous mutations could potentially be present. This step was not done in the case of the BEST samples because inheritance data were not collected in that study. We used standard criteria for classification of a variant as a pathogenic mutation including the following: predicted alteration of amino acid sequence, location of the mutation at an evolutionarily conserved residue, predicted effects on protein secondary structure, segregation among affected family members, and absence of the variant in a collection of 300 predominantly white control chromosomes from healthy subjects.

**Expression Studies**

The majority of DES mutations studied previously led to in vivo (muscle biopsies) or in vitro (cellular models) abnormal aggregation of cytoplasmic desmin protein. Because cardiac tissue was not available from our subjects, we used the in vitro approach to determine whether the mutations found by genetic screening had cellular phenotypes. Accordingly, we developed constructs for cellular expression in (1) SW13 cells (ATCC, American Tissue Culture Collection, Manassas, Va), a human adrenal cortex carcinoma cell line, that does not express the intermediate filaments desmin, vimentin, or keratin; (2) human coronary artery smooth muscle cells (Cambrex Bio Science Walkersville, Inc, Rutherford, NJ), which express desmin and vimentin; and (3) neonatal rat cardiac ventricular myocytes cultured as previously described. Expression studies were performed in (1) HEK293 (American Type Culture Collection, Rockville, Md), a human embryonic kidney cell line, that does not express desmin, vimentin, or keratin; and (2) human foreskin fibroblasts (American Type Culture Collection, Rockville, Md), that do not express desmin, vimentin, or keratin. Desmin-deficient cell lines were transfected with 2 μg total DNA (1 μg GFP construct and 1 μg of each desmin construct) with the use of a Nucleofector device (Amaxa, Inc) according to the manufacturer’s instructions and with Lipofectamine–Neonatal Nucleofector transfection kits (Amaxa Inc). Briefly, cells were pelleted and suspended in 100 μL of the appropriate buffer. DNA was added to the solution, and cells were electroporated with the neonatal rat ventricular myocyte–specific program. Cells were plated in a 10-cm2 slide coated with 1% gelatin. Media solutions were supplemented with HEPEs (pH 7.5) to a final concentration of 20 mmol/L to buffer the media pH. Putative mutations were created in DES cDNA with a modified overlap extension approach,24 with the use of oligonucleotides containing the DES mutations. Polymerase chain reaction (PCR) fragments containing full-length desmin cDNA were inserted into pcDNA3.1/V5-His-Topo T/A cloning vector (Invitrogen, Carlsbad, Calif). Oligonucleotides with single-nucleotide mutations in combination with flanking primers (primers available on request) were used to generate PCR fragments from desmin cDNA clone (Gene Bank accession No. BC032116). PCR fragments without a mutation that overlapped mutagenized PCR products (overlap range, 243 to 613 nucleotides) were amplified with separate primers, and then

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**Figure 1.** Desmin protein represented with precoil domain (PCD) and rod domains separated by linkers and flanked by nonhelical head and tail domains. Mutations showing abnormal desmin aggregation in cellular studies are underlined. Mutations reported are identified by wild-type amino acid code/position/mutant amino acid; (mutations identified in current study in boldface italics). Arrows indicate phenotype reported for each mutation (up arrows—skeletal muscle only; down arrows—cardiomyopathy only; bi-directional arrows—both skeletal and cardiac muscle disease; *indicates restrictive cardiomyopathy; the R350P mutation causes skeletal and cardiac myopathy and occurs at the same site as our R350W mutation). Δ indicates deletion.
full-length desmin cDNA was generated by extension of overlapping PCR fragments. All mutations were confirmed by sequencing. Plasmid DNA constructs were transfected into *Escherichia coli* (top10; Invitrogen Inc), isolated, and sequenced from single colonies to confirm the presence of the mutations. Transfection was performed with the FuGene 6 transfection reagent (Roche Diagnostics Corp, Indianapolis, Ind) according to the manufacturer’s instructions (3 μL FuGene was diluted in 97 μL Opti-MEM (Invitrogen), and 1 μg plasmid DNA was added; DNA-FuGene complex was formed at room temperature for 30 minutes and added to cell culture). Cells (SW13 and coronary artery smooth muscle cells) were grown on 8-cm² slides to ~50% confluence and then transfected with 1 μg of plasmid DNA. After incubation for 48 hours, the slides were washed 3 times, for 10 minutes each, with PBS, and cells were fixed with an ice-cold mixture of 70% methyl alcohol and 30% acetone for 10 minutes. Slides were washed 3 times, for 10 minutes each, with PBS.

Immunostaining with primary monoclonal mouse anti-desmin antibody (D1033; Sigma Inc, St Louis, Mo) at 1:1000 dilution in PBS overnight (16 hours) at 4°C was followed by washing 3 times with PBS and incubation with secondary anti-mouse antibody FITC conjugate (F5387; Sigma) at 1:1000 dilution in PBS overnight. *In situ* hybridization with a digoxigenin-labeled desmin antisense riboprobe (G3893; Sigma) was performed with the use of an Olympus IX81 inverted motorized spinning-disk confocal microscope (Olympus America Inc, Center Valley, Pa) was used to evaluate the transfected cells for expression of desmin protein and its abilities to form an intracellular filament network. The Gln389Pro mutation reported by Goudeau et al25 to cause severe desmin network disruption was used as a positive control for our experiments.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**Mutation Screening**

Mutation screening detected 4 novel variants in 4 DCM subjects that predicted missense changes and met criteria for pathogenic mutations (Glu108Lys:c.308,G→A; Ser298Leu:c.979,C→T; Asp312Asn:c.1020,G→A; Arg350Trp:c.1134,C→T; reference NM_001927.3) (Figure 1 and Table). The Glu108Lys mutation is the first pathogenic mutation reported in the highly conserved 1A rod domain. The mutations were absent in 300 control chromosomes and were unique among all the alleles screened in the study subjects. We also found a mutation in the tail domain (Val459Ile:c.1461,G→A) in 2 black BEST subjects of a total of 69 black subjects in the BEST cohort. This mutation is only 8 amino acids away from the only other mutation (Ile451Met) linked to isolated DCM, which is also a recurrent mutation in unrelated families.5,5,12,16 The Val459Ile mutation was also absent in our standard controls but was heterozygous in 2 of 100 samples (200 chromosomes) from a population of black controls (Coriell Institute; human variation panel HD100A; http://www.coriell.org/).

A sixth *DES* mutation of interest was found in our study at position 213. An alanine to valine (Ala213Val:c.730,T→C; reference NM_001927.3) substitution was detected in a large familial dilated cardiomyopathy pedigree and in 6 unrelated BEST subjects. Three other groups have reported finding Ala213Val mutations, which have been proposed as low-penetrant mutations.3,26,27 To determine whether this was a pathogenic mutation in our study, we analyzed DNA samples from 12 additional members of this pedigree. The 213Val mutation did not segregate with the disease phenotype because it was present in 4 healthy individuals and absent in 1 affected individual. We further analyzed 86 DNA samples from healthy controls without cardiomyopathy and detected the Arg213Val mutation in 2 samples. These data suggest that the Ala213Val is most likely a benign polymorphism (allele frequency ~1%), making it currently the only known amino acid polymorphism in the rod domain of desmin.

**Phenotype Analysis**

The carriers of *DES* mutations in our study all had a pure DCM without any detected involvement of skeletal muscle disease (Table). Elevated creatinine kinase levels have been reported in some DRM patients.5,15,25 The creatinine kinase level was normal in the 1 subject for whom that information was available (Arg350Trp mutation). In contrast to typical observations in DRM, severe conduction system disease and arrhythmias were absent. The single mutation from the Familial Cardiomyopathy Registry cohort occurred in a male DCM subject who developed DCM at age 55 years. He had no evidence of skeletal myopathy and was the only affected member of his family (left ventricular ejection fraction 19% at age 68 years in 2004). His 2 children were clinically evaluated and were found to be normal; no DNA was available from the children. In this patient, the following DCM genes had already been screened negative: *LMNA, MYH7, MYH6, TMPO, TNNI3, and SGCD.*

**Characteristics of DES Mutation Carriers**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Age at Diagnosis, y</th>
<th>Race</th>
<th>Gender</th>
<th>NYHA Class</th>
<th>Conduction System Disease</th>
<th>Muscle Disease</th>
<th>EF, %</th>
<th>LVEDD, cm</th>
<th>Status</th>
<th>(Comments)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu108Lys</td>
<td>60</td>
<td>White</td>
<td>M</td>
<td>3</td>
<td>LAFB</td>
<td>None</td>
<td>33</td>
<td>NA</td>
<td>Living</td>
<td></td>
</tr>
<tr>
<td>Ser298Leu</td>
<td>45</td>
<td>White</td>
<td>F</td>
<td>3</td>
<td>LBBB</td>
<td>None</td>
<td>27</td>
<td>NA</td>
<td>Living</td>
<td></td>
</tr>
<tr>
<td>Asp312Asn</td>
<td>35</td>
<td>Black</td>
<td>M</td>
<td>3</td>
<td>None</td>
<td>None</td>
<td>17</td>
<td>NA</td>
<td>Living</td>
<td></td>
</tr>
<tr>
<td>Arg350Trp</td>
<td>55</td>
<td>White</td>
<td>M</td>
<td>2</td>
<td>None</td>
<td>None</td>
<td>29</td>
<td>7.1</td>
<td>Living</td>
<td>(EF 19% at 68 y)</td>
</tr>
<tr>
<td>Val459Ile*</td>
<td>44</td>
<td>Black</td>
<td>M</td>
<td>3</td>
<td>None</td>
<td>None</td>
<td>34</td>
<td>7.6</td>
<td>Living</td>
<td></td>
</tr>
<tr>
<td>Val459Ile*</td>
<td>34</td>
<td>Black</td>
<td>F</td>
<td>3</td>
<td>1ª AVB</td>
<td>None</td>
<td>17</td>
<td>NA</td>
<td>Living</td>
<td></td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; LAFB, left anterior fascicular block; LBBB, left bundle-branch block; AVB, atrioventricular block; and NA, not available.

*Allele frequency of 1% of black (ethnically matched) controls.
Expression Studies

Immunofluorescence microscopy analysis of transfected SW13 and human coronary artery smooth muscle cells and neonatal rat cardiac myocytes expressing our desmin mutations revealed obvious cellular phenotypes for mutations in the 2B rod domain (Ser298Leu, Asp312Asn, and Arg350Trp) (Figures 2 and 3) that mirrored the desmin disruption seen in the Gln389Pro-positive control. For these mutations, severe disruption of the normal desmin cytoskeletal architecture occurred in the majority of studied cells with clumping and aggregation of antibody-positive staining cytoplasmic protein. The mutations had a dominant phenotype in the human coronary artery smooth muscle cell lines in which the constitutively expressed desmin was unable to compensate for the presence of the introduced desmin mutations. Interestingly, the Glu108Lys mutation, located in a highly conserved region of the 1A rod domain, did not disrupt the assembly of desmin in SW13 or human coronary artery smooth muscle cells. Mutations in the 1A domain have not been reported previously, even mutations in the neighboring head domain are rare, and the effects on desmin network assembly have not been studied.

Figure 2. Immunofluorescence microscopy of transfected SW13 (A) and human coronary artery smooth muscle cells (B). The consequences of transfected mutations are shown for SW13 (no background desmin expression) and human coronary artery smooth muscle cells (constitutive desmin expression). The top 2 panels show pattern of wild-type desmin filamentous networks (top left panel shows detail). The desmin cytoskeletal network for the Glu108Lys mutation did not appear different from the pattern seen in wild-type cells. The remaining 4 mutations all showed evidence for aggregation of intracytoplasmic desmin protein, although the phenotype of Val459Ile was less severe. The Gln389Pro mutation reported by Goudeau et al served as a positive control. Magnification ×60.
The Val459Ile mutation in the tail domain showed an intermediate phenotype with modest impairment of the desmin filamentous network affecting approximately half of the cells observed. This result is similar to another reported tail domain mutation (Ile451Met) in which only subtle in vitro effects on desmin assembly were noted. Our Val459Ile mutation was found in 2 unrelated black patients; similarly, the Ile451Met tail mutation has been reported in at least 6 unrelated families. The Val459Ile mutation was found in 2 apparently healthy black control subjects; likewise, the Ile451Met tail mutation has also been reported in clinically unaffected adults, suggesting that the penetrance is incomplete. Overall, cellular studies and clinical findings suggest that the Val459Ile and the neighboring Ile451Met tail domain mutations are low-penetrant mutations that exert more modest pathogenic effects than the rod-domain mutations found in DRM.

Discussion

Our screening of DES in 425 probands with DCM, the largest number to date, indicates that DES mutations account for 1% to 2% of DCM. Before our study, only 1 mutation linked to isolated DCM (tail domain, Ile451Met) had been reported. It had been suggested that the tail domain might be functionally important in cardiac tissue. Another study of 265 Japanese DCM cases in whom only exon 8 was studied found 3 instances (1.1%) of the Ile451Met mutation. The detection of DES mutations in DCM is not restricted to familial forms of DCM, as evidenced by the 4 different mutations found in the BEST cohort, which was not a family-based study. Our study further demonstrates that DCM due to DES mutations can present without clinically recognizable skeletal muscle involvement. In addition, our data show that mutations in the rod domain can result in a DCM phenotype. Finally, the Ala213Val variant reported previously is likely a rare nonpathogenic polymorphism.

Overall, DES mutations can cause a spectrum of phenotypes including skeletal myopathy, mixed skeletal-cardiac disease (“desmin-related myopathy”), and cardiomyopathy (DCM as well as hypertrophic or restrictive cardiomyopathies). Cardiac conduction disease may also be found in some cases. Of the 28 DES mutations we found in the literature in which cardiac status was clearly reported, only the Ile451Met mutation is described as causing an isolated DCM phenotype, although others have linked this mutation to DRM. The 5 novel mutations reported here had an apparently cardiac-restricted phenotype. Mild conduction disease was present in 2 of the 4 mutation carriers, and none of the carriers had evidence of clinical skeletal muscle disease, suggesting that the recognition of DES mutation carriers in the cardiology clinic setting on the basis of clinical data alone is a difficult task.

Desmin is expressed early in cardiac development, is the major muscle-specific intermediate filament protein, and is highly expressed in heart tissue, accounting for 2% of cellular protein in myocytes. Desmin filament assembly is a complex process that proceeds stepwise, with desmin monomers first associating into parallel coiled-coil homodimers. After this, antiparallel staggered tetramers form, leading next to laterally associating unit length filaments that ultimately interact end to end to form the final desmin filament. The process of filament assembly depends on the central rod domain, whereas the tail domain is believed to be important for interactions between tetramers and elongation of higher-order filament structures. The collection of morpholog-
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ically homogeneous disorders in which desmin architecture is perturbed is referred to as myofibrillar, desmin-related myopathies and is due to mutations in desmin as well as myotilin, dystrophin, and α-B-crystallin. Haploinsufficiency for desmin may potentially be less deleterious than single-point mutations (the bulk of reported mutations); this model is supported by observations in mice heterozygous for desmin-null mutations that have unremarkable skeletal and cardiac phenotypes.32

Three of the DCM-causing DES mutations we found (Ser298Leu, Asp312Asn, and Arg350Trp) are located in the 2B rod domain and caused severe disruption of desmin filament assembly. This domain of desmin is home to the majority of known DES mutations and is believed to be important for dimer-dimer interactions within the mature desmin filament as well as with correct filament assembly.4,33

The clustering of mutations in the 2B domain means that genetic analysis in suspected desmin-related myopathy could be initially targeted to this region as well as to the 1B rod region, where another clustering of mutations occurs. Cardiac conduction abnormalities are prominent features of mutations in the 2B domain, being reported in 7 of 10 previously described 2B mutations.4,6–9,11,14,15,34 A left bundle branch block was present in the Ser298Leu carrier in our study, and normal conduction was found for the Asp312N and Arg350Trp carriers.

In our cellular assay, all 3 2B domain mutations caused the same phenotype of the positive control, Gln389Pro.25 Notably, the introduction of a proline, not normally present in the desmin rod and able to cause kinks in protein structure, was the mutant residue in 8 of the 13 previously reported 2B rod domain mutations causing DRM.4,6–9,11,14,15,34 A left bundle branch block was present in the Ser298Leu carrier in our study, and normal conduction was found for the Asp312N and Arg350Trp carriers.

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The Glu108Lys mutation found in our study is unique for the majority of known DES mutations and is believed to be important for dimer-dimer interactions within the mature desmin filament as well as with correct filament assembly.4,33

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could not test whether our patients have desmin aggregation in myocytes, as has been demonstrated by others.\textsuperscript{5,12} Finally, an estimate of the penetrance of \textit{DES} mutations is also not apparent from the literature because data are currently available predominantly from affected individuals, although we and others have found evidence of probable mutations in healthy adults.\textsuperscript{3,5} The effects of mutation status on lifetime penetrance as well as age-dependent manifestations of the disease will need to be explored in future family studies.

In summary, we found that \textit{DES} mutations can be implicated in 1\% to 2\% of DCM without skeletal muscle disease involvement. We have shown that DCM-causing mutations occur outside the tail domain and have reported the first mutation in the highly conserved region of the 1A rod domain. Disruption of desmin cytoskeletal networks was not reproducibly shown in the 1 previous \textit{DES} mutation linked to DCM (Ile451Met). Three of our mutations located in the 2B helical rod domain clearly interfere with desmin network assembly, suggesting that similar pathogenic mechanisms exist between DCM and DRM. One of our mutations, Glu108Lys, occurred in the most conserved domain of desmin and did not visibly disrupt the pattern of intracytoplasmic desmin filaments. It is possible that this mutation exerts its effect by perturbing the desmin dimer-dimer interactions in the assembled network. Our finding of a second desmin tail mutation that is recurrent and low penetrant indicates that mutations in the less-conserved tail domain are perhaps better tolerated and may require interactions with other genetic or environmental factors to exert an effect. Finally, because clinical screening of DCM is now available, clinicians evaluating patients with cardiomyopathy/myopathies need to be selective in their utilization of \textit{DES} testing and critical in their evaluation of novel variants detected in such testing. Clinical mutation testing of DCM patients should initially focus on other genes in which the prevalence of mutations is higher, such as \textit{LMNA}.\textsuperscript{44–47} We believe that specific testing for \textit{DES} mutations should be included in a second-tier level of testing if mutations in more frequent DCM genes are not found.

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Disclosures

None.

References


Desmin Mutations in Dilated Cardiomyopathy

Desmin-related myofibrillar myopathy is a cardiac and skeletal muscle disease caused by mutations in the desmin gene. Mutations cluster near the center of the protein (2B domain) and typically cause skeletal muscle disease, which usually precedes any overt cardiomyopathy. Previously, only 1 desmin mutation leading to a pure cardiac phenotype had been reported, and the overall prevalence of desmin mutations in dilated cardiomyopathy was unknown. We screened the desmin gene for mutations using denaturing high-performance liquid chromatography in 425 unrelated patients and detected 5 novel mutations in 6 individuals for an overall prevalence of 1.4%. None of the individuals had any overt signs of skeletal disease. Missense mutations in desmin associated with familial cardiac and skeletal myopathy.

CLINICAL PERSPECTIVE

Desmin-related myofibrillar myopathy is a cardiac and skeletal muscle disease caused by mutations in the desmin gene. Mutations cluster near the center of the protein (2B domain) and typically cause skeletal muscle disease, which usually precedes any overt cardiomyopathy. Previously, only 1 desmin mutation leading to a pure cardiac phenotype had been reported, and the overall prevalence of desmin mutations in dilated cardiomyopathy was unknown. We screened the desmin gene for mutations using denaturing high-performance liquid chromatography in 425 unrelated patients and detected 5 novel mutations in 6 individuals for an overall prevalence of 1.4%. None of the individuals had any overt signs of skeletal muscle disease. The Glu108Lys mutation we detected is the first reported pathogenic mutation in the highly conserved 1A domain of the desmin protein. Expression of the 3 2B domain mutations in cell lines, including neonatal rat cardiomyocytes, severely disrupted the normal cytoplasmic desmin network. One mutation in the tail domain had a milder effect on desmin architecture, and the mutation in the 1A domain did not visibly affect desmin staining, suggesting that dysfunction of seemingly intact desmin networks is sufficient to cause dilated cardiomyopathy. Overall, the results show that desmin mutations are a relatively rare cause of dilated cardiomyopathy, can present in the absence of overt muscle disease, and mechanistically disrupt desmin cytoskeletal architecture in the majority of cases.
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