

## Danon Disease as an Underrecognized Cause of Hypertrophic Cardiomyopathy in Children

Zhao Yang, MD; Colin J. McMahon, MB; Liana R. Smith, BS; Jeathrina Bersola, MS; Adekunle M. Adesina, MD, PhD; John P. Breinholt, MD; Debra L. Kearney, MD; William J. Dreyer, MD; Susan W. Denfield, MD; Jack F. Price, MD; Michelle Grenier, MD; Naomi J. Kertesz, MD; Sarah K. Clunie, RN; Susan D. Fernbach, BSN; James F. Southern, MD, PhD; Stuart Berger, MD; Jeffrey A. Towbin, MD; Karla R. Bowles, PhD; Neil E. Bowles, PhD

**Background**—Some patients with hypertrophic cardiomyopathy (HCM) or left ventricular hypertrophy also present with skeletal myopathy and Wolff-Parkinson-White (WPW) syndrome; mutations in the gene encoding the lysosome-associated protein-2 (LAMP-2) have been identified in these patients, suggesting that some of these patients have Danon disease. In this study we investigated the frequency of *LAMP2* mutations in an unselected pediatric HCM population.

**Methods and Results**—*LAMP2* was amplified from genomic DNA isolated from peripheral lymphocytes of 50 patients diagnosed with HCM and analyzed by direct DNA sequencing. In 2 of the 50 probands (4%), nonsense mutations were identified. In 1 family the proband initially presented with HCM as a teenager, which progressed to dilated cardiomyopathy (DCM) and heart failure. Skeletal myopathy and WPW were also noted. The teenage sister of the proband is a carrier of the same *LAMP2* mutation and has HCM without skeletal myopathy or WPW. The other proband presented with HCM, WPW, and skeletal myopathy as a teenager, whereas his carrier mother developed DCM during her 40s. Skeletal and cardiac muscle sections revealed the absence of LAMP-2 on immunohistochemical staining.

**Conclusions**—*LAMP2* mutations may account for a significant proportion of cases of HCM in children, especially when skeletal myopathy and/or WPW is present, suggesting that Danon disease is an underrecognized entity in the pediatric cardiology community. (*Circulation*. 2005;112:1612-1617.)

**Key Words:** cardiomyopathy ■ genetics ■ heart failure ■ Wolff-Parkinson-White syndrome

Hypertrophic cardiomyopathy (HCM) is a complex cardiac disease with unique pathophysiological characteristics and a wide spectrum of morphological, functional, and clinical features.<sup>1</sup> Although sporadic cases are common, familial disease predominates,<sup>1</sup> and mutations in genes encoding proteins of the sarcomere are most commonly identified.<sup>2</sup> However, other genes have been identified in a proportion of patients, including the gene encoding the  $\gamma$ 2 subunit of AMP-activated protein kinase (*PRKAG2*),<sup>3,4</sup> and some patients with Fabry disease also develop HCM.<sup>5,6</sup> Recently, mutations in the *LAMP2* gene were identified in patients with HCM with evidence of skeletal myopathy.<sup>7</sup> This is an X-linked gene that encodes lysosome-associated protein-2 (LAMP-2). This gene was identified as causing Danon disease,<sup>8</sup> a lysosomal glycogen storage disease,<sup>9</sup> which is characterized clinically by cardiomyopathy, myop-

athy, and variable mental retardation with intracytoplasmic vacuoles containing autophagic material and glycogen in skeletal and cardiac muscle cells. Female carriers manifest cardiomyopathy during adulthood, whereas affected males usually develop symptoms before the age of 20 years.<sup>10</sup> Female carriers also have skeletal myopathy and mental retardation less commonly than affected males.<sup>10</sup> Other manifestations of Danon disease can include Wolff-Parkinson-White (WPW) syndrome,<sup>11</sup> increased serum creatine kinase (CK),<sup>10,12</sup> and ophthalmic abnormalities.<sup>7,13</sup> A recent study by Arad and colleagues<sup>14</sup> identified *LAMP2* mutations in 2 of 35 patients with HCM and in 4 of 24 patients with increased left ventricular wall thickness and ECGs suggesting ventricular preexcitation. On the basis of these observations, we screened probands diagnosed with pediatric- or juvenile-onset HCM for mutations in *LAMP2*.

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From the Departments of Medicine (Cardiovascular Sciences Program) (Z.Y., J.A.T.), Pediatrics (Section of Cardiology) (C.J.M., L.R.S., J.B., J.P.B., W.J.D., S.W.D., J.F.P., M.G., N.J.K., S.K.C., J.A.T., K.R.B., N.E.B.), Pathology (A.M.A., D.L.K.), and Molecular and Human Genetics (S.D.F., J.A.T.), Baylor College of Medicine, Houston, Tex; and Departments of Pathology (J.F.S.) and Cardiology (S.B.), Children's Hospital of Wisconsin, Milwaukee.

The online-only Data Supplement, which contains additional information about Methods, can be found at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.105.546481/DC1>.

Correspondence to Neil E. Bowles, PhD, Department of Pediatrics (Cardiology), Baylor College of Medicine, 6621 Fannin, FC.430.09, Houston, TX 77030. E-mail [nbowles@bcm.tmc.edu](mailto:nbowles@bcm.tmc.edu)

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## Methods

### Patient Samples

Patients were enrolled and blood and tissue samples were obtained after informed consent was provided, as approved by the Baylor College of Medicine institutional review board. Genomic DNA was extracted from blood with the use of a Roche MagnaPure Compact Robot.

### Analysis of the *LAMP2* Gene

The *LAMP2* gene, including intron-exon boundaries, was analyzed by direct DNA sequence analysis. See the online-only Data Supplement for technical details.

### Histological Assessment of Muscle

Specimens of skeletal muscle were snap-frozen or fixed in formalin and paraffin embedded before they were sectioned. Sections were evaluated by routine histological methods as described in the online-only Data Supplement. In addition, a portion of skeletal muscle was fixed in glutaraldehyde and processed for electron microscopy (EM).

### Immunofluorescent Analysis of Muscle Sections

Sections of frozen skeletal muscle biopsy samples and formalin-fixed cardiac samples were stained with monoclonal antibodies against LAMP-2, lysosomal integral membrane protein-1 (LIMP-1), LAMP-1, and dystrophin. See the online-only Data Supplement for technical details.

## Results

### *LAMP2* Mutation Analysis

The patient cohort consisted of 50 probands (33 male and 17 female) with pediatric- or juvenile-onset HCM (age at diagnosis ranged from 1 day to 15 years; mean age, 6 years 11 months) and was composed of 31 white, 4 black, and 9 Hispanic individuals (the ethnicities of 6 were unreported). Nonsense mutations were identified in 2 white males (4%): No other genetic variants or polymorphisms were identified in *LAMP2*. After the initial identification of these mutations, other family members were screened. The results are described below.

#### *Family HCM-3873*

The proband of this family had moderate left ventricular hypertrophy, identified by echocardiography at 13 years of age, associated with WPW, requiring radiofrequency ablation because of frequent episodes of supraventricular tachycardia. At the age of 14 years, echocardiography revealed development of an unusual form of HCM with moderate to severe apical and midcavitary hypertrophy. By the age of 15 years he had severe obstruction and subsequently developed DCM with heart failure requiring transplantation. The patient complained of muscle weakness and underwent muscle biopsy. Just before his transplantation, his CK level was 1825 U/L; the MM isoform was 96.9 ng/mL, and the MB isoform was 56.6 ng/mL. Several liver enzymes were elevated (aspartate aminotransferase [AST] 303 U/L; alanine aminotransferase [ALT] 386 U/L; lactate dehydrogenase 1260 U/L), as previously reported,<sup>10</sup> although serum alkaline phosphatase (106 U/L) was normal. Mild developmental delay and attention deficit disorder were also noted.

We identified a hemizygous 1075C→T substitution in exon 8, resulting in the nonsense mutation Q359X codon

(Figure 1). His sister was heterozygous for the same mutation, which was not carried by their unaffected father; DNA was not available from their deceased mother or maternal uncle, but the inheritance is consistent with X-linked dominant disease (Figure 1).

The sister of the proband had mild concentric left ventricular hypertrophy on echocardiography at the age of 14 years, which has worsened slightly over the past 5 years. She has not developed any symptoms of skeletal muscle disease or WPW, and developmental delay has not been noted. Serum chemistries for muscle and liver function were normal (CK 83 U/L; AST 54 U/L; alkaline phosphatase 92 U/L) or borderline abnormal (troponin I 0.3 ng/mL). Similarly, their mother developed HCM at the age of 31 years and underwent transplantation at the age of 42 years but died 3 months later. She had no skeletal muscle symptoms or history of arrhythmias. The maternal uncle died at the age of 22 years with a diagnosis of HCM with muscular dystrophy, as well as evidence of attention deficit disorder.

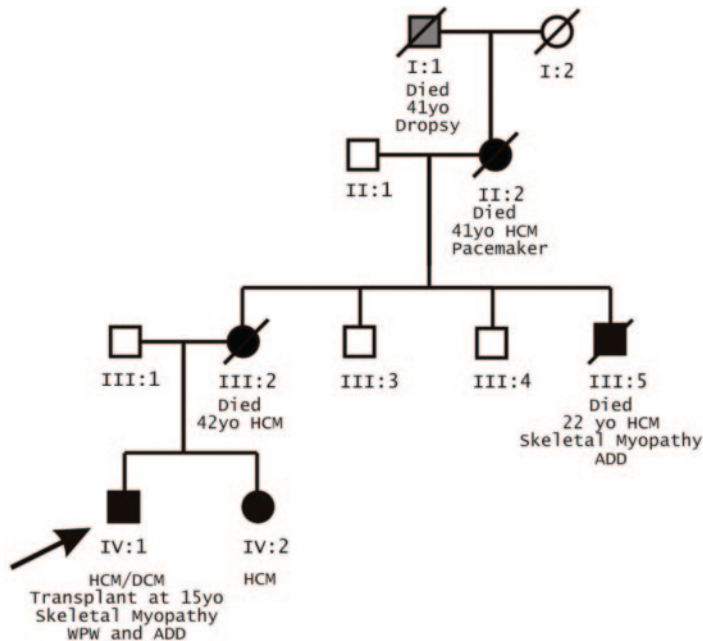
#### *Family HCM-5937*

This male patient presented at 13 years of age complaining of palpitations and several near syncopal episodes. An echocardiogram demonstrated HCM with moderate concentric hypertrophy and no left ventricular outflow tract obstruction at the time of diagnosis. The initial ECG demonstrated WPW syndrome, and Holter monitoring demonstrated runs of supraventricular tachycardia. In addition, he developed chronic atrial fibrillation, which was refractory to medical management. He subsequently developed nonsustained ventricular tachycardia as well as decreasing left ventricular systolic function and underwent implantation of a biventricular implantable cardiac defibrillator. He also underwent skeletal muscle biopsy, which was consistent with myofibrillar myopathy. Creatine kinase levels ranged from 516 to 895 U/L, and levels of the MB isoform of 5.8 to 10.0 ng/mL and troponin I levels were somewhat elevated (0.46 ng/mL). Like the other proband, several liver enzymes were elevated (AST 137 to 257 U/L; ALT 90 to 173 U/L; lactate dehydrogenase 2307 U/L), although to a lesser degree, and alkaline phosphatase levels were normal. However, this patient has not yet progressed to cardiac failure. No learning difficulties were reported, but he has some ophthalmological problems, and an ophthalmic examination revealed "salt and pepper" changes in the fundus and depigmentation of the peripheral retina with some small yellowish depigmented spots in the fovea of both eyes.

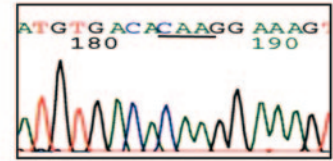
We identified a hemizygous 467T→G substitution in exon 4, resulting in a premature stop codon (L156X; Figure 1), which was inherited from his mother. No mutations were detected in the phenotypically normal brother, father, uncle, and grandfather (Figure 1: III:1, II:1, II:3, and I:1, respectively).

The 51-year-old mother of the proband was diagnosed with idiopathic dilated cardiomyopathy at 47 years of age and had an implantable cardiac defibrillator placed the year after diagnosis. In addition, she has a history of atrial fibrillation. She had a mildly dilated left ventricle and left atrium, concentric left ventricular hypertrophy, and depressed systol-

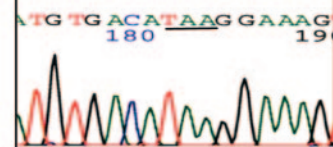
## HCM-3873



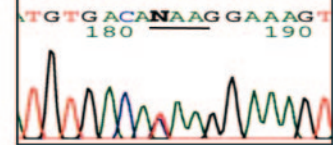
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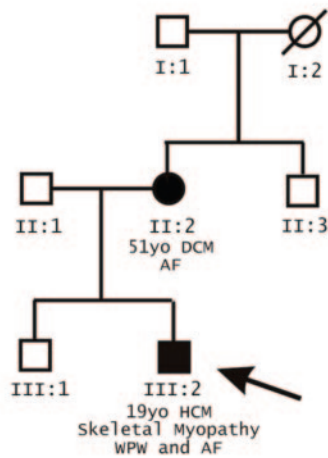
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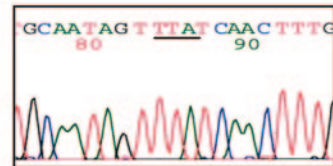
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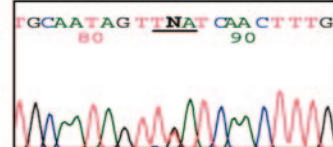
## HCM-5937



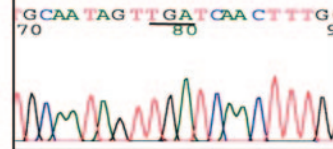
II.1



II.2



III.2



**Figure 1.** Left, Pedigrees of the families with *LAMP2* mutations. Open symbols indicate unaffected; black symbols, affected; and shaded symbols, uncertain or unknown status. The probands are indicated by arrows. Right, Sequence analysis of the *LAMP2* gene. The sequencing chromatograms for exon 8 (HCM-3873) and exon 4 (HCM-5937) are shown for the unaffected fathers, the symptomatic carrier females (sister and mother, respectively), and proband of each family. ADD indicates attention deficit disorder; AF, atrial fibrillation.

ic function, and she is listed for transplantation. Neither of her parents had evidence of cardiomyopathy; DNA was not available from her deceased mother.

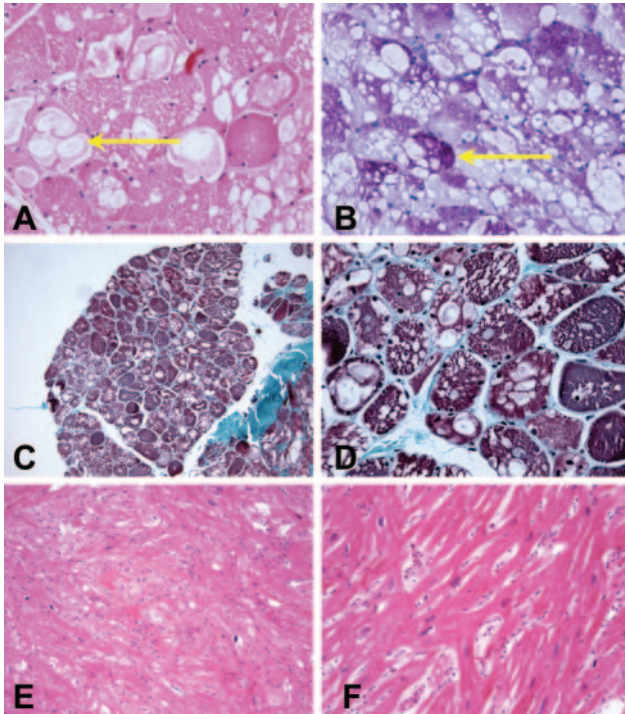
### Skeletal Muscle Pathology

#### *HCM-3873*

Sections of biopsy samples showed significant variations in fiber size, with diameters ranging from 15 to 60  $\mu\text{m}$ , with scattered necrotic fibers. Many fibers exhibited vacuolar changes, whereas some showed features of acute myophagia,

but there was no inflammation or fibrosis (Figure 2). There was no increase in internalized nuclei or in perimysial connective tissue and no ragged red fibers, although endomy-sial connective tissue was mildly increased.

Oxidative stains showed significant disorganization of the myofibrillar staining pattern along with vacuolar changes. Periodic acid–Schiff (PAS) stains showed large areas of staining precipitate at the sarcolemma of the most degenerated cells, whereas oil red O staining showed significant increases in lipids in many myofibers. The muscle fibers



**Figure 2.** Histochemistry of skeletal muscle (A to D) and cardiac muscle samples (E and F) from the proband of HCM-3873 showing hematoxylin-eosin (A) and PAS (B) staining of skeletal muscle, with vacuoles and glycogen deposition indicated by arrows. C and D, Masson trichrome staining. E and F, Hematoxylin-eosin-stained section of cardiac muscle shows marked myocyte hypertrophy and disarray. Magnification  $\times 400$  (A, B, D);  $\times 100$  (C, E);  $\times 200$  (F).

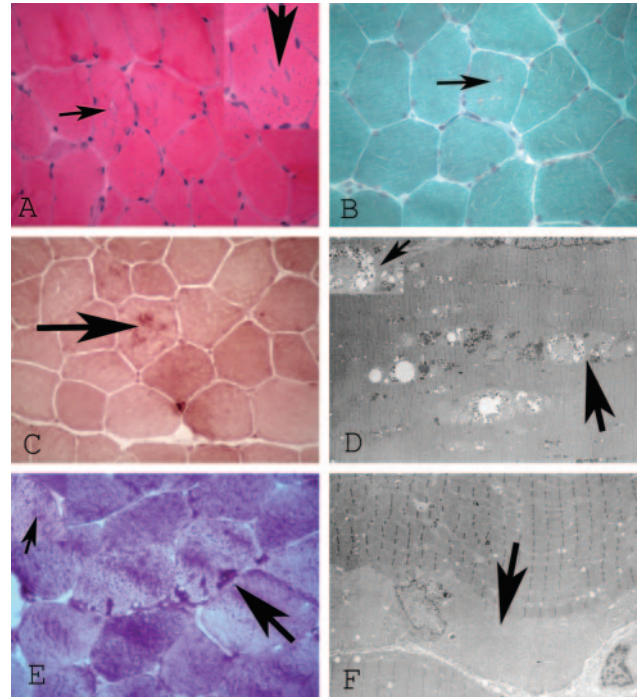
showed fair fiber type differentiation without fiber type grouping with the use of ATPase enzyme stain. The vacuoles were present in both type I and type II muscle fibers. Acid phosphatase was mildly increased in necrotic muscle fibers.

EM revealed marked vacuolar degeneration with 1 to multiple vacuoles in individual muscle fibers that were lipid filled, accompanied by increased numbers of lysosomes, significant loss of contractile elements, and focal basement membrane reduplication.

### HCM-5937

There was mild variation in fiber size and shape with occasional randomly distributed angulated atrophic fibers but no small or large group atrophy (Figure 3). Few randomly distributed fibers with basophilic microvacuoles and granules were seen (Figure 3A to 3D), and although an occasional degenerating fiber was present, no phagocytosis was seen. There was no increase in internalized nuclei or increase in endomysial or perimysial connective tissue and no ragged red fibers. Nonspecific esterase stain highlighted the sarcoplasmic granules and microvacuoles, whereas PAS with and without diastase showed slight increases in glycogen within the myofibers (Figure 3E).

EM showed normal sarcomeric banding patterns with only a focal Z-band irregularity detected. A significant increase in the number and distribution of lysosomal granules was observed, with a slight prominence of lipid vacuoles (Figure 3F). There was an increase in glycogen granules with sub-



**Figure 3.** Histochemistry and EM of skeletal muscle samples from the proband of HCM-5937 show hematoxylin-eosin-stained section of skeletal muscle biopsy with basophilic microvacuoles and granules (small arrow) and in inset (large arrow) (A), modified Gomori's trichrome stain (B), and nonspecific esterase showing esterase positivity in the basophilic microvacuoles and granules (C). EM shows that basophilic microvacuoles are composed of degenerating cellular material within lysosomal aggregates (large arrow) (D). Inset shows a higher magnification of the lysosomal material (small arrow). PAS stain shows subsarcolemmal glycogen lakes (large arrow) and positivity of the basophilic microvacuoles and granules (inset with small arrow) (E), and EM shows subsarcolemmal accumulation of glycogen granules (F). Magnification  $\times 400$  (A, B, C, E) (A inset  $\times 800$ );  $\times 3200$  (D) (inset  $\times 16\,000$ );  $\times 2400$  (F).

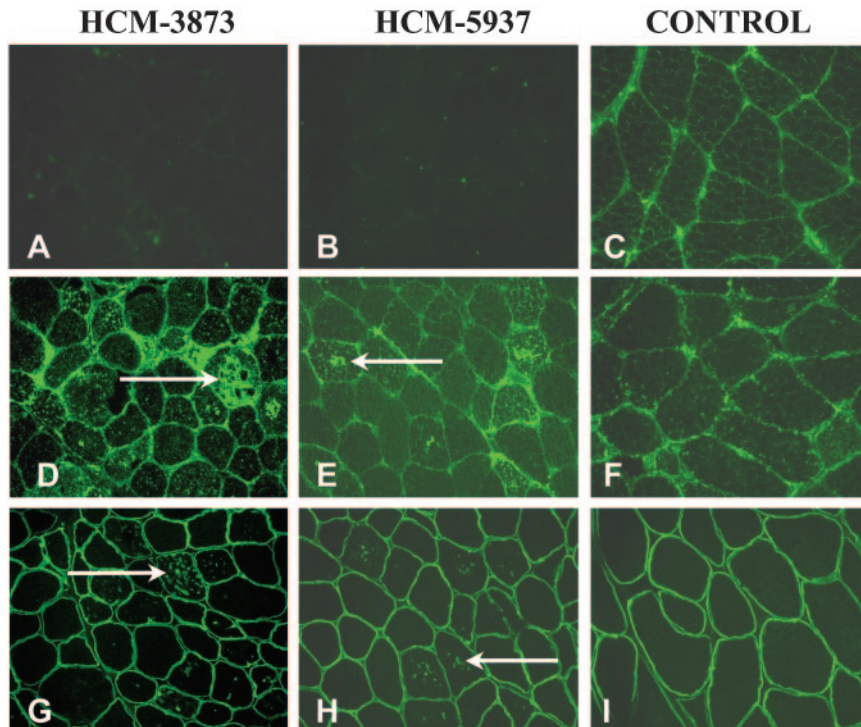
sarcolemmal accumulation. Mitochondria appeared to be of normal density with no demonstrable abnormal cristae pattern or intramitochondrial inclusions.

### Cardiac Muscle Pathology

The explanted heart of the proband of HCM-3873 had fibrosis beneath the epicardium in the posterior left ventricle. There was asymmetrical hypertrophy of the apical half of the interventricular septum up to 3.5 cm thick. Focal zones of fatty replacement fibrosis were present in all ventricular walls. Cardiac myocytes were markedly hypertrophic with distinct fiber disarray involving  $>80\%$  of the total ventricular wall thickness (Figure 2).

### Immunofluorescence Analysis of Muscle Samples

Staining of skeletal muscle sections revealed no detectable LAMP-2 in the samples from the probands (Figure 4A to 4C). Staining for other lysosomal membrane proteins (LAMP-1) (data not shown) and LIMP-1 (Figure 4D to 4F) and sarcolemmal protein (dystrophin) was similar to that in controls (Figure 4), although some staining of intracytoplasmic vacuoles could be detected, as previously reported, especially in patient HCM-3873.<sup>7,10</sup>



**Figure 4.** Immunohistochemical analysis of skeletal muscle samples from the probands of family HCM-3873 (A, D, and G) and family HCM-5937 (B, E, and H) and a normal control (C, F, and I) stained for LAMP-2 (A to C), LIMP-1 (D to F), and the N-terminus of dystrophin (G to I). The staining of intracytoplasmic vacuoles is indicated (arrows). Magnification  $\times 200$ .

Fixed samples were available from the explanted heart of the proband of HCM-3873 and were stained along with control sections from the heart of an age-matched trauma victim. Staining with the antibodies against LAMP-2 resulted in more diffuse signals in the fixed sections (Figure 5B) than those seen in the frozen skeletal muscle sections (Figure 4). However, the absence of staining in the myocardial sections from the patient (Figure 5A) shows the lack of expression of this protein in cardiomyocytes. LIMP-1 was also detected predominantly in the cytoplasm (Figure 5D); large intracytoplasmic aggregates were noted on staining of the patient sample (Figure 5C). Staining with the antibody against dystrophin clearly stained intracytoplasmic inclusions (indicated by the arrows in Figure 5E).

### Discussion

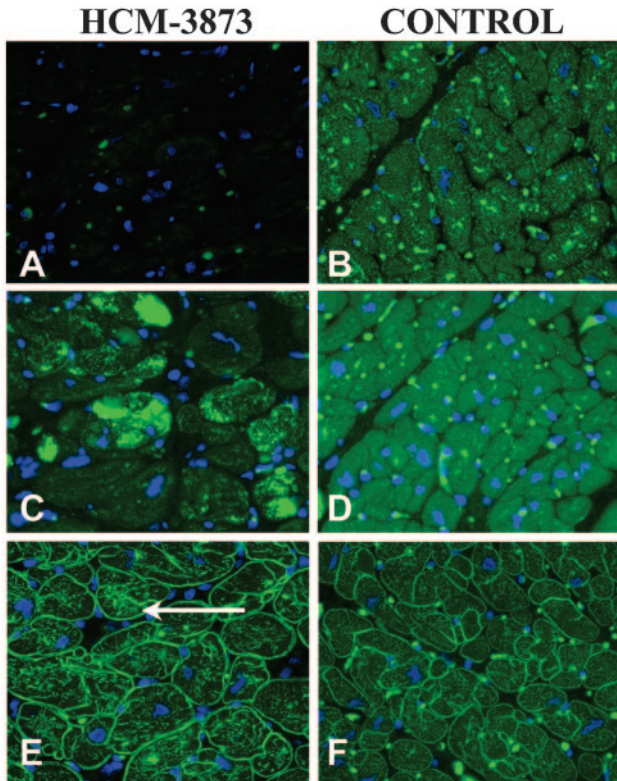
On the basis of a number of reports identifying *LAMP2* mutations in patients diagnosed with HCM with associated skeletal myopathy and WPW, we investigated the prevalence of *LAMP2* mutations in a population with pediatric- or juvenile-onset HCM and identified mutations in 2 of 50 (4%). This is similar to the frequency of *LAMP2* mutations reported by Arad and colleagues.<sup>14</sup> In both cases the patients presented with associated clinical skeletal myopathy and WPW syndrome; none of the other 51 patients had skeletal myopathy, but 1 had WPW and was negative for *LAMP2* mutations.

In the analysis of our families, a number of interesting findings related to phenotypic variability associated with *LAMP2* mutations are apparent. For example, in family 3878, each of the females was reported to have HCM rather than DCM, which is the more common phenotype in females.<sup>10</sup> The sister of the proband developed HCM at the age of 14 years and is now listed for transplantation, whereas their mother developed HCM at the age of 31 and died at the age of 42 years shortly after

undergoing transplantation. Manifestation of cardiac symptoms has been reported in female carriers previously, but these usually develop in the fourth or fifth decade.<sup>10,15</sup>

The recent study by Arad and colleagues<sup>14</sup> also suggests that Danon disease can present as a primary cardiomyopathy that is distinguishable from "sarcomeric HCM" by electrophysiological abnormalities, particularly ventricular preexcitation. However, in their study most of the female carriers did not develop a cardiac phenotype, and in several cases the mutations were de novo rather than inherited. Furthermore, 5 of the 6 mutations affected splice signals, whereas most previous mutations have been nonsense mutations. Skeletal muscle function was not characterized in this patient cohort, but in 4 of the 6 probands with mutations, serum CK and ALT levels were significantly elevated. In addition, age of onset was significantly younger than that in patients with sarcomeric protein or *PRKAG* gene mutations, and maximal wall thickness was significantly higher.<sup>14</sup> In this study, cardiac muscle samples were available from 1 of the patients with a splice site mutation, and LAMP-2 was detected in cardiomyocyte intracytoplasmic vacuoles. In contrast, in our patient no LAMP-2 was detected in cardiomyocytes, whereas the detection of LIMP-1 demonstrated highly abnormal lysosomal protein expression in the heart, similar to that observed for LAMP-1 and cathepsin D in atrophic or degenerative cardiomyocytes in patients with idiopathic DCM.<sup>16</sup> These findings suggested that autophagy is associated with progressive destruction of cardiomyocytes and that autophagic degeneration is one of the mechanisms of myocardial cell death. In our patient, vacuoles were observed in the cardiomyocytes, as has been noted in patients with *PRKAG* gene mutations and in transgenic mice expressing mutated forms of *PRKAG*.<sup>17</sup>

The cardiac phenotype of Danon disease is severe with early onset and poor prognosis, even in some manifesting



**Figure 5.** Immunohistochemical analysis of cardiac muscle samples from the proband of family HCM-3873 (A, C, and E) and a control (B, D, and F) stained for LAMP-2 (A and B), LIMP-1 (C and D), and dystrophin (E and F). The nuclei are stained blue with DAPI. The staining of intracytoplasmic vacuoles is indicated (arrows). Magnification  $\times 400$ .

female carriers. In a study of 20 male patients, the mean age at onset was 17 years (range, 10 months to 19 years), and all patients except 1 died before the age of 30 years.<sup>10</sup> Deaths were due to heart failure or sudden cardiac death in all cases.

On the basis of these findings, we recommend that patients diagnosed with HCM with evidence of skeletal myopathy and/or WPW be screened for mutations in *LAMP2*, except in familial cases in which X-linked inheritance can definitively be excluded (male-to-male transmission). In addition, the differential diagnosis between HCM and lysosomal storage diseases such as Danon disease may be achieved by clinical assessment that includes skeletal muscle testing, measurements of serum CK and troponins, liver enzyme chemistries, and evaluation for WPW. It should also be noted that ophthalmological abnormalities have been documented in some patients with Danon disease, and it was noted in the proband of family HCM-5937. Mental retardation was reported in 70% of cases<sup>10</sup>: Attention deficit disorder was reported in both the proband of HCM-3873 and his maternal uncle and should be considered part of the disorder. However, it should also be noted that manifesting females only present with symptoms of cardiac disease, complicating the differential diagnosis in families without affected males.

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### Disclosure

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