LAMP2 shines a light on cardiomyopathy in an athlete

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Introduction

Inherited cardiomyopathies are an important cause of life-threatening arrhythmias, heart failure, and sudden death.[1] These inherited cardiomyopathies include hypertrophic, dilated, and restrictive forms, as well as arrhythmogenic right ventricular cardiomyopathy and left ventricular noncompaction. Common features that underpin these cardiomyopathies include earlier age of onset, the presence of a family history of disease, and a specific genetic cause in up to 50%.[2]

For clinicians, the diagnosis of inherited cardiomyopathies can be challenging despite each of the cardiomyopathies having specific diagnostic criteria. The emergence of "overlap syndromes" within families, where 2 or more phenotypes may exist, such as dilated cardiomyopathy and left ventricular noncompaction, provides additional challenges to the clinician. Specific to hypertrophic cardiomyopathy (HCM), the finding of significant left ventricular hypertrophy must be considered in the absence of other loading conditions such as hypertension.[3,4] In addition, consideration must be given to phenocopies of HCM, such as glycogen storage diseases (PRKAG2), Fabry disease, and other infiltrative diseases that may mimic HCM.[4–7] Accurate diagnosis in such cases is critical as it may lead to important changes in clinical management of both the patient and family, owing to differences in natural history, inheritance patterns, response to therapy, and prognosis.

Rapid advances in next-generation sequencing platforms have allowed the screening of thousands of genes involved in human diseases. This includes genetic applications in the inherited arrhythmia and cardiomyopathy syndromes, including sudden cardiac death.[8–10] Here we report the clinical and genetic evaluation of a young athlete who presented after a blow to the chest, whereby the genetic findings have more precisely defined both the underlying diagnosis and modification of the clinical management plan.

KEYWORDS Cardiomyopathy; Arrhythmia; Genetics; ICD therapy; Sudden death (Heart Rhythm Case Reports 2017;3:172–176)

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Methods

Clinical assessment

Clinical evaluation of the patient and family members was performed in the Department of Cardiology at Royal Prince Alfred Hospital, Sydney, Australia. Clinical assessment of the index case included detailed family history, physical examination, 12-lead electrocardiogram (ECG), transthoracic echocardiography, 24-hour Holter monitoring, cardiac magnetic resonance (CMR) imaging, and endomyocardial biopsy. All family members provided written informed consent, including parental consent for children.

Genetic analysis

Following genomic DNA extraction from blood, whole exome sequencing was performed as previously reported by our group.[8,10] Variants were excluded if they had a minor allele frequency of $>0.1\%$ in the 1000 Genomes Project (1KG) data (http://www.1000genomes.org/) or Exome Sequencing Project data (Seattle, WA; http://evs.gs.washington.edu/EVS/). The frequency of the variant in the Exome Aggregation Consortium (ExAC; http://exac.broadinstitute.org) was reviewed. The analysis focused on 46 cardiac genes (Supplemental Table 1, available online). The *in silico* predicted effect of variants on protein function and conservation across species were assessed using a number of tools, as previously described.[8]

All studies were carried out under strict approval and in accordance with the Sydney Local Health District Ethics Review Committee, Australia.

Case report

Clinical features

We present a 16-year-old male state-level athlete (index case II:1, Figure 1A) who was struck on the left side of his chest

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KEY TEACHING POINTS

- Danon disease is a rare, X-linked dominant disorder that is characterized by cardiomyopathy, cardiac conduction abnormalities, skeletal muscle weakness, and mild intellectual disability, and is caused by mutations in the LAMP2 gene.
- Severe left ventricular hypertrophy and cardiac conduction abnormalities are common in Danon disease, with a Wolff-Parkinson-White syndrome pattern the most common electrocardiography finding in up to 70% of affected male subjects. Implantable cardioverter-defibrillator therapy does not always prevent sudden death in Danon disease.
- Genetic testing has a direct impact on clinical diagnosis, treatment, and prognosis in a range of inherited arrhythmia syndromes and cardiomyopathies, and should be considered in such cases.

with a high-speed cricket ball during a cricket match. He developed a chest wall hematoma from the incident. After he experienced several weeks of persistent pain, a general practitioner arranged further investigations, including an ECG for ongoing "chest pain." The ECG was very abnormal, showing sinus rhythm with intraventricular conduction delay, tall QRS complexes meeting voltage criteria for hypertrophy, and very deep (giant) T-wave inversion consistent with a cardiomyopathic process (Figure 1B). On further questioning, the patient described occasional light-headedness but no syncope. There was no significant past medical history or any relevant family history of cardiovascular disease.

Physical examination showed a blood pressure of 120/80 mm Hg, heart rate of 70 beats per minute, and weight of 91 kg. There was a systolic murmur with no exaggeration after Valsalva maneuver and no features of left or right ventricular failure. Echocardiography showed massive hypertrophy with a maximal thickness of up to 35 mm in the septum and 21 mm in the posterior wall. The basal posterior wall was spared, and there was no systolic anterior motion of the mitral valve leaflet, mitral regurgitation, or left ventricular outflow tract obstruction (Figure 2A and B). Subsequent CMR imaging confirmed severe asymmetric and diffuse hypertrophy with hyperintense myocardial T2 signal and patchy, diffuse scar (Figure 2C–F).

Although the initial pattern was thought to be consistent with a severe form of apical HCM, some features on the CMR imaging raised suspicion of an infiltrative pathology and a likely HCM phenocopy. Specifically, extensive hyperintense myocardial signal noted on T2 imaging throughout the left ventricle, beyond the distribution of the described patchy delayed enhancement, raised suspicion of left ventricular infiltration. Further biochemistry and a myocardial biopsy were performed. Routine hematology, autoimmune screen, serum angiotensin-converting enzyme level, serum electrophoretogram, and alpha-galactosidase levels were normal. Endomyocardial biopsy revealed nonspecific mild myocyte hypertrophy with no infiltration or disarray, and no evidence of an inflammatory infiltrate, glycogen accumulation, granulomas, amyloid, or vacuolization.

Genetic analysis

Genetic analysis was performed for 46 major cardiomyopathy genes. No pathogenic mutations were identified in the known HCM genes, or in other HCM phenocopy genes such as *PRKAG2* (glycogen storage) or *GLA* (Fabry disease). A novel pathogenic mutation was identified in the

Table 1 Clinical features comparing Danon disease vs hypertrophic cardiomyopathy

	Danon disease	Hypertrophic cardiomyopathy
Inheritance pattern	X-linked dominant	Autosomal dominant
Main causative genes	*LAMP2* (lysosomal storage)	*MYBPC3*, *MYH7* (sarcomere function)
Symptom onset	Male: second decade of life Female: third decade of life	All age groups
Clinical features	Cardiomyopathy (syndromic) (eg, skeletal muscle weakness, cognitive impairment)	Cardiomyopathy (nonsyndromic)
Electrocardiogram	Prexcitation common, increased lead voltages, deep T-wave inversion	Increased lead voltages, ST-T wave changes Q waves
Echocardiography	Marked cardiac hypertrophy usually involving both right and left ventricles	Predominantly LV hypertrophy, often asymmetric
Endomyocardial biopsy	Myocyte hypertrophy, cytoplasmic vacuolization, lysosomal glycogen accumulation	Myocyte hypertrophy, myofibre disarray, interstitial fibrosis
CMR findings	Evidence of LV infiltration on T2 imaging	Asymmetric LV hypertrophy with scar
Efficacy of ICD therapy	Generally poor	ICD therapy prevents sudden death
Need for heart transplantation	Common (>50%)	Uncommon (<5%)
Prognosis	Without transplantation, mean age of death 19 years in male patients, 36 years in female patients	Most have normal life expectancy

CMR = cardiac magnetic resonance; ICD = implantable cardioverter-defibrillator; LV = left ventricular.

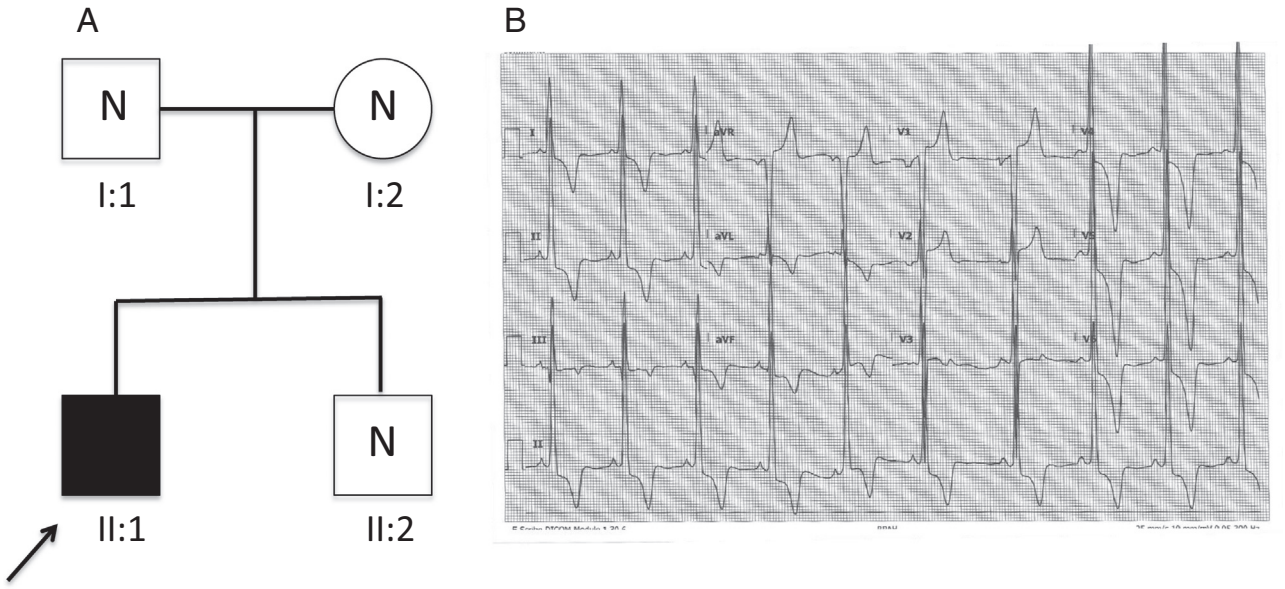

Figure 1 Clinical features. **A:** Family pedigree (arrow for index case, "N" = normal clinical screening). **B:** The 12-lead electrocardiogram of index case (II:1) showing sinus rhythm, severe left ventricular hypertrophy, and deep T-wave inversion.

lysosome-associated membrane protein 2 (*LAMP2*) gene responsible for X-linked Danon disease (LAMP2 cardiomyopathy),[11,12] that is, an intronic splice donor variant in intron 2 of the *LAMP2* gene (c.183+2T>C, Figure 3). Results were confirmed with Sanger sequencing.

Follow-up

The initial management of the index case included implantable cardioverter-defibrillator (ICD) insertion, given the increased risk of sudden cardiac death. Following confirmation of a diagnosis of Danon disease, and the more severe clinical outcome data suggesting a poor prognosis, the patient was referred for assessment regarding cardiac transplantation.

Because Danon disease is an X-linked disorder, clinical and genetic evaluation of the family was an important aspect of clinical management. To date, the father (age 50 years, I:1), mother (age 49 years, I:2), and only sibling (age 11 years, II:2) have no clinical evidence of cardiomyopathy (Figure 1A). Cascade genetic testing of the parents identified the mother (I:2) as a carrier of the *LAMP2* mutation, consistent with X-linked inheritance.

Discussion

This report describes a young athlete, incidentally diagnosed initially with HCM after a blow to the chest with a cricket ball. Following comprehensive clinical investigation, genetic testing revealed a novel mutation in the *LAMP2* gene, confirming a diagnosis of Danon disease. Both the diagnosis and subsequent clinical management were guided by this genetic finding, because male subjects with Danon disease have a more severe and progressive phenotype, including arrhythmias, heart failure, sudden death, and the need for cardiac transplantation. The case highlights both the importance of considering HCM phenocopies in clinical assessment and the key role of genetic testing in clarifying diagnosis, guiding management, and assessing prognosis.

The identification of a *LAMP2* mutation in this case prompted more aggressive clinical management with a view to early cardiac transplantation. Danon disease is a rare, X-linked dominant disorder that is characterized by cardiomyopathy, cardiac conduction abnormalities, skeletal muscle weakness, and mild intellectual disability. Overall prognosis in male subjects is poor, with a low chance of survival beyond the mid-20s without cardiac transplantation, although some patients do survive into the fifth and sixth decades, reflecting disease heterogeneity. Female subjects tend to be less severely affected. The mean age of male patients at diagnosis is 12 years, with transplantation at 18 years and death at 19 years when transplantation is not performed.[13] Mutations in the *LAMP2* gene lead to accumulation of autophagic material and glycogen in myocytes, leading to a hypertrophic phenotype that mimics HCM (also referred to as "LAMP2 cardiomyopathy").[11,14] Biopsy specimens showing a deficiency of LAMP2 protein on immunohistochemistry testing can also suggest Danon disease in the context of a typical clinical morphology.

Cardiac conduction abnormalities are common in Danon disease. Pre-excitation with a Wolff-Parkinson-White (WPW) syndrome pattern is the most common ECG finding in up to 70% of affected male subjects.[13] This makes it a distinguishing feature when compared with HCM, where WPW syndrome occurs in 1%–2%. Furthermore, the ECG findings in Danon disease are often difficult to distinguish from other HCM phenocopies, such as Fabry disease and glycogen storage diseases, where the ECG can typically show pre-excitation, tall QRS complexes, left ventricular hypertrophy, and T-wave inversion. This brings Fabry disease and glycogen storage diseases into diagnostic consideration along with Danon disease.

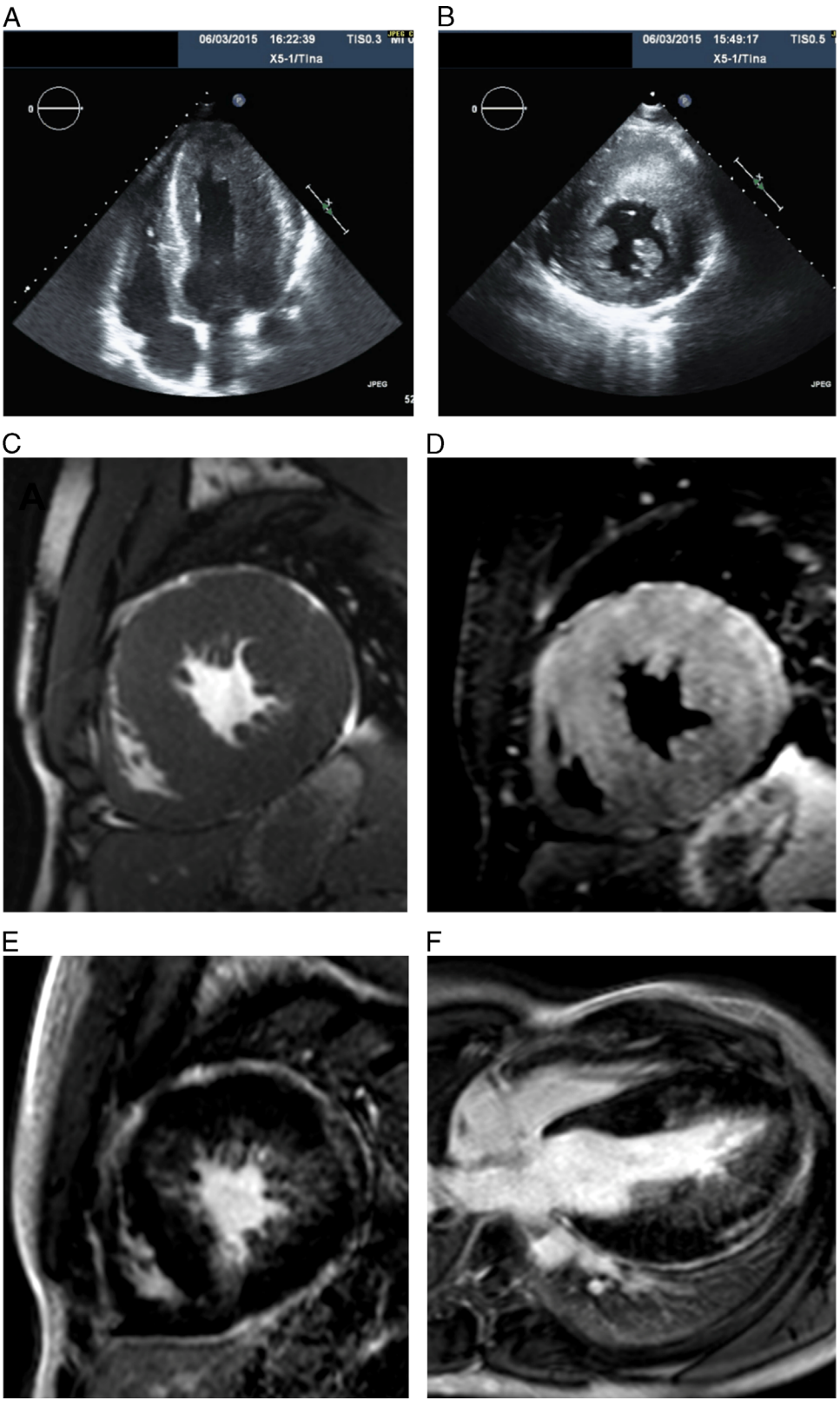

Figure 2 Echocardiographic imaging. **A:** Apical 4-chamber view and **B:** parasternal short axis view of the index case showing diffuse myocardial hypertrophy. Cardiac magnetic resonance imaging. **C:** Severe concentric left ventricular wall thickening in a representative midventricular short-axis cine-slice in end-diastole. **D:** Increased myocardial signal in the basal anteroseptal, anterolateral, and lateral walls on T2-weighted imaging. **E, F:** Late gadolinium enhancement images in short axis (**E**) and 4-chamber (**F**) orientation showed a patchy pattern of enhancement in the mid-distal anteroseptal, inferoseptal, and lateral walls.

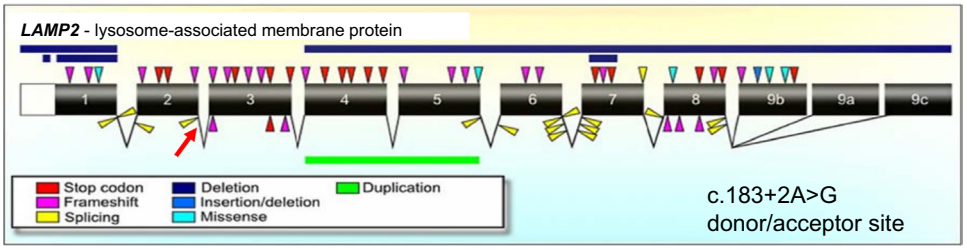

Figure 3 Schematic diagram of the *LAMP2* gene. Red arrow indicates location of the intronic splice variant in intron 2 (c.183+2T>C). Diagram modified from D'souza et al.[14]

Arrhythmias and cardiac ablation procedures are common in 53% and 41% of Danon disease patients, respectively, and management approaches are similar to those in patients with WPW alone.[13] Importantly, ICD therapy and antiarrhythmic therapy do not always revert ventricular arrhythmias and prevent sudden death in Danon disease, highlighting further the need for early transplantation.[11] Though our case had an ICD implanted early following diagnosis, the unreliability in preventing sudden death, coupled with the mean age of death of 19 years in male subjects,[13] were important considerations in advising early cardiac transplantation.

Our case highlights the growing influence of genetic testing in a range of inherited arrhythmia syndromes and cardiomyopathies, impacting directly on clinical diagnosis, treatment, and prognosis.[2] The clinical diagnosis and management of traditional HCM caused by sarcomere mutations is very different from HCM phenocopies such as Danon disease caused by *LAMP2* mutations (Table 1). Recent Heart Rhythm Society USA guidelines illustrate further how several cardiac disorders, such as long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia, can be diagnosed solely on the presence of a pathogenic gene mutation.[15] Moreover, a recent study in LQTS type 3 patients (caused by mutations in the sodium channel gene *SCN5A*) suggests that gene-specific therapies should be initiated in LQTS gene subgroups.[16] Therapy with the sodium channel blocker mexiletine in LQTS type 3 patients resulted in a reduction in both the QT interval and adverse arrhythmic events.[16] These examples, coupled with our case, illustrate the utility of genetic testing in guiding clinical management.

Conclusion

Danon disease represents a rare cause of severe left ventricular hypertrophy, which may be clinically indistinguishable from HCM. Cardiomyopathy, cardiac conduction abnormalities, skeletal myopathy, and cognitive disabilities are common features in Danon disease. The case demonstrates the important role of genetic testing in confirming the diagnosis, which is essential for appropriate management and prognostication, with early cardiac transplantation critical in male patients with Danon disease.

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Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrcr.2016.11.005.

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