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Case Report

An uncommon clinical presentation of relapsing dilated cardiomyopathy with identification of sequence variations in MYNPC3, KCNH2 and mitochondrial tRNA cysteine

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ABSTRACT

We describe a young girl with dilated cardiomyopathy, long QT syndrome, and possible energy deficiency. Two major sequence changes were identified by whole exome sequencing (WES) and mitochondrial DNA analysis that were interpreted as potentially causative. Changes were identified in the KCNH2 gene and mitochondrial tRNA for cysteine. A variation was also seen in MYPBC3. Since the launch of WES as a clinically available technology in 2010, there has been concern regarding the identification of variants unrelated to the patient's phenotype. However, in cases where targeted sequencing fails to explain the clinical presentation, the underlying etiology could be more complex than anticipated. In this situation, the extensive reach of this tool helped explain both her phenotype and family history.

1. Introduction

Whole exome sequencing (WES) is a powerful tool that can be utilized for the identification of pathogenic mutations. However it can also identify variants unrelated to phenotype. Here, we present a patient identified to have multiple mutations by WES that more effectively describe their complex phenotype than a single change.

Our patient initially came to attention for dilated cardiomyopathy (DCM) but also had a history of sensorineural hearing loss. Her clinical course was complicated as she had required extracorporeal membrane oxygenation (ECMO) on several occasions without a clear precipitating event. Her cardiac and family history prompted concern that there may be more than one cause for her findings. However extensive previous testing had been non-diagnostic, so WES was performed during a particularly serious and protracted hospital admission. Initial WES interpretation implicated genes associated with DCM, long QT syndrome (LQTS) in addition to multiple variants. Mitochondrial DNA sequencing identified a transfer RNA variant.

Typically, DCM can present with heart failure, cardiac arrhythmias or sudden cardiac death in an otherwise seemingly healthy individual. It has an estimated prevalence of 36 per 100,000 individuals and 25–30% of those cases are familial [1–3]. Inheritance patterns may be autosomal dominant, autosomal recessive, X-linked or mitochondrial. Massive parallel sequencing technologies have allowed the identification of the responsible gene in up to 40% of cases of familial DCM, making possible the screening of asymptomatic at-risk individuals [4–6].

LQTS is another leading cause of sudden cardiac death in children and its prevalence has been estimated to be as high as 1 in 2000 [7]. Gene sequencing panels currently available can identify mutations in 75% of patients with congenital LQTS [4].

Although the prevalence of congenital LQTS in families with DCM has not been studied, both conditions are most commonly inherited in an autosomal dominant manner. The contribution of a change in mitochondrial transfer RNA and LQTS in the context of a DCM variant of unknown significance could have potentiated a fatal scenario.

2. Case presentation

A 4 year old girl with sensorineural hearing loss and speech delay initially presented to the emergency room due to breathing difficulty. Physical exam revealed a non-dysmorphic appearance with evidence of cardiovascular compromise and generalized hypotonia. Dilated eye exam was normal. Family history was significant for an older sister

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with speech delay and hearing loss who passed suddenly at age 2 years. The autopsy interpreted her death secondary to myocarditis, presumed to be of viral etiology. Both parents and two younger sisters were reportedly healthy although none had been evaluated formally for hearing or cardiac concerns. Two older paternal half-sisters were also reportedly healthy.

Upon admission, an echocardiogram revealed dilated cardiomyopathy (DCM). Endomyocardial biopsy showed no signs of myocarditis, negative viral DNA/RNA (adenovirus, CMV, EBV, enterovirus, parvovirus) and mild to moderate subendothelial fibrosis. Skeletal muscle biopsy was normal and included histochemical stains for mitochondrial oxidative phosphorylation defects (cytochrome C oxidase and succinate dehydrogenase), and analysis for ragged red fibers. Biochemical analyses to include plasma amino acids, urine organic acids, an acylcarnitine profile, and total and free carnitine were also normal.

During this initial presentation and hospitalization, the patient required extracorporeal membrane oxygenation (ECMO) with a left ventricular assist device (LVAD) and was evaluated for heart transplantation, but her cardiac function recovered prior to the anticipated surgery (Fig. 1). During the next four years, she was hospitalized five more times with acute heart failure and decompensation. Additional molecular genetic testing completed during these hospitalizations included chromosomal oligoarray (GeneDx, 2011), dilated cardiomyopathy sequencing panel (GeneDx, 2011, 27 genes), connexin 26 and connexin 30, Otoscope

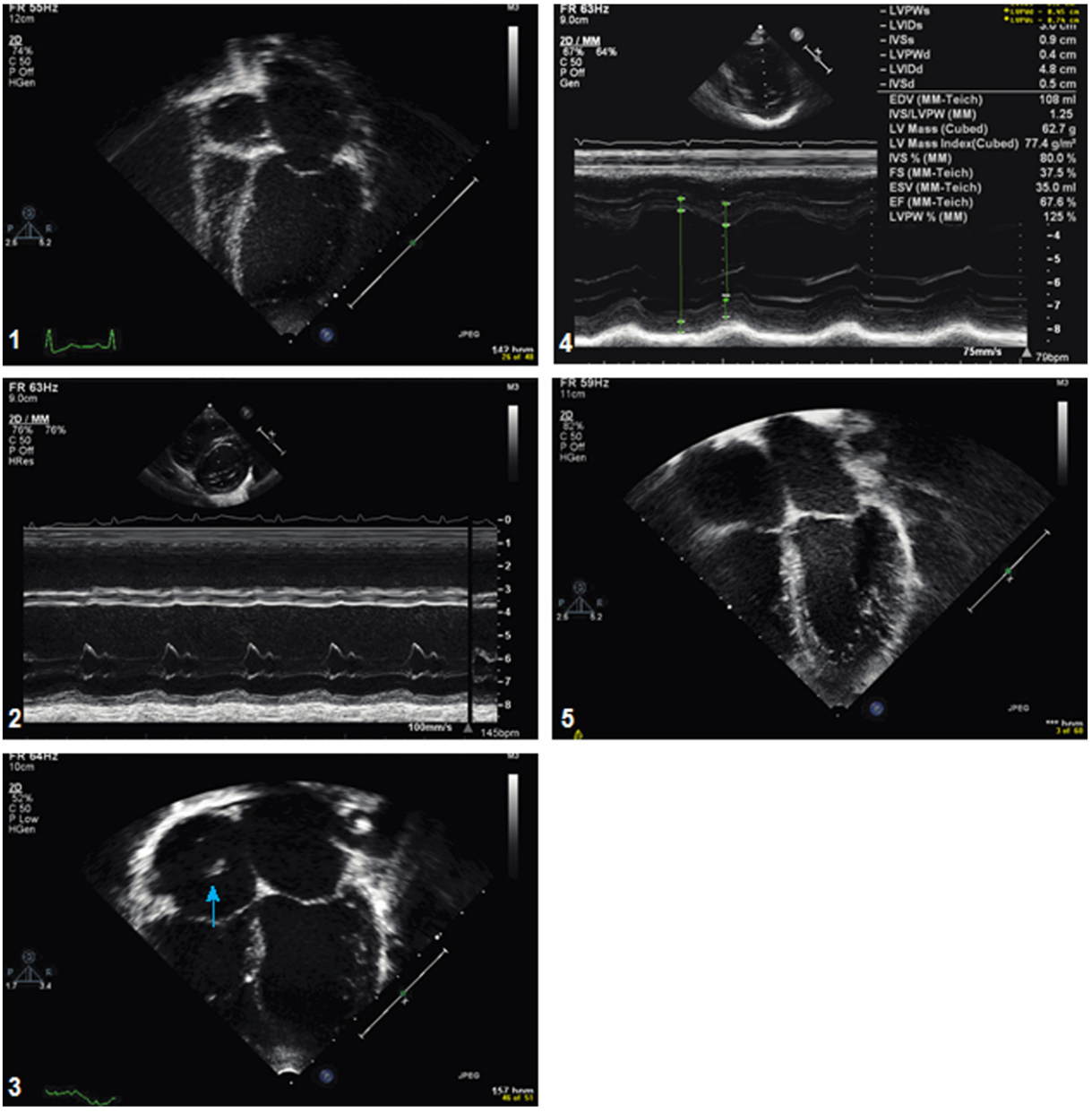

Fig. 1. 1–3: Initial presentation in congestive heart failure. (2) and (3) were obtained prior to placement on ECMO after rapidly worsening cardiac function. (1) Mildly dilated left atrium and ventricle. (2) parasternal short axis image showing minimal motion of the interventricular septum and excursion of the posterior wall, suggesting severely decreased left ventricular function. The calculated shortening fraction (SF) was 10% (normal range 28–40%). (3) Apical 4 chamber view showing generalized dilatation with thin left ventricular walls, consistent with dilated cardiomyopathy (DCM). The left ventricle also shows mild hypertrabeculation of the posterior wall which can represent non-compaction of the left ventricle. There is a thrombus in the right atrium (shown with the arrow). Images 4 and 5 were obtained between hospitalizations and show complete echocardiographic resolution of her failed systolic function. (4) Parasternal short axis view showing a thicker ventricular septum and posterior walls more consistent with non-compaction/hypertrophic cardiomyopathy (HCM) when compared with (2). Note the normal excursion of both walls. SF was 37%. (5) Apical 4 chamber view showing normal systolic function and significant hypertrabeculation.

Table 1
Results of WES clinical testing (Baylor, Molecular Diagnostics Laboratory) in the initial proband.

Gene	Protein	Function	Position	Isoform	Location	Variant (amino acid)	Variant (protein)	Genbank accession numbers	Parent of origin	Pathogenicity	Predicted phenotype	Polyphen/SiFT	Polymorphism or ESP5400 status
Mutations per initial clinical reports													
MYBPC3	Myosin binding protein C	Binds myosin to modulate contraction	Chr11:47367777	NM_000256	Exon 11	c. 1071C>T	p.Arg358X	ENSG00000134571	Mother	Likely pathogenic	HCM/DCM	NA/NA	Not reported
KCNH2	Membrane potassium channel	Potassium flow during repolarization	Chr7:150647150	NM_172058	Exon 9	c.2503del C	p.Leu835fs	ENSG0000055118	Father	Likely pathogenic	LQTS2	NA/NA	Not reported
MT-TC	tRNA Cys	Mitochondrial cysteine transport				m.5814T>C		HGNC:7477	Mother	Pathogenic	Mitochondrial myopathy MELAS asymptomatic		
Variants													
MYPN	Myopalladin	Interacts with nebullete in cardiac muscle and nebulin in skeletal muscle in Z-lines	Chr10:69934085	NM_032578	Exon 11	c.2236A>G	p.Thr746Ala		Mother	VUS	DCM/HCM		rs147287437
TTN	Titin	Major component in striated muscle	Chr2:179455631	NM_133378	Exon 253	c.53117C>T	p.Pro177706Leu	ENSG00000155657	Father	VUS	CM, MD, myopathy		ESP5400
TTN	Titin	Major component in striated muscle	Chr2:179449188	NM_133378	Exon 260	c.57388C>T	p.Arg19130Cys	ENSG00000155657	Father	VUS	CM, MD, myopathy		ESP5400
TTN	Titin	Major component in striated muscle	Chr2:179603991	NM_003319	Exon 45	c.12880A>C	p.Asn4294HIs	ENSG00000155657	Father	VUS	CM, MD, myopathy		ESP5400
TTN	Titin	Major component in striated muscle	Chr2:179585257	NM_133378	Exon 77	c.19500C>G	p.Asn6500Lys	ENSG00000155657	Father	VUS	CM, MD, myopathy		ESP5400
TTN	Titin	Major component in striated muscle	Chr2: 179612873	NM_133379	Exon 46	c.14254A>C	p.Ser4752Arg	ENSG00000155657	Mother	VUS	CM, MD, myopathy		rs146504870
COG6	Component of the oligomeric Golgi complex 6	Component of the conserve oligomeric Golgi complex	Chr13:40235007	NM_020751	Exon 3	c.358A>G	p.Ser120Gly	ENSG00000133103		VUS	CDG III		rs139313781
GIPC3	GIPC PDZ domain containing family	Role in hair bundle survival	Chr19:3590081	NM_133261	Exon 6	c.832G>A	p.Glu278Lys	ENSG00000179855	Novel	VUS	Deafness AR15		Novel
MED23	Mediator complex subunit 23	Role in identification of enhancer sites in DNA for transcription	Chr6:131908846	NM_004830	Exon 29	c.4080G>T	p.Val1360Val	ENSG00000112282		VUS	Intellectual disability (AR 18)		rs138742804
LAMA2	Laminin	Component of basement membrane	Chr6:129759787	NM_000426	Intronic	c.5969-4G>A		ENSG00000196569	Novel	VUS	MD (Merosin)		Novel
UPF3B	UPF3 regulator of nonsense transcripts homolog B	Regulates post-splicing multiprotein complex	ChrX:118971901	NM_080632	Exon 10	c.1121G>A	p.Arg374His	ENSG00000125351	Father	VUS	Intellectual disability (X-linked 14)		rs143538947

panel (University of Iowa 2012, 66 genes), were all non-diagnostic. The contents of each of these studies are listed in Appendix A.

Her average length of hospital stay was 41 days and after prolonged periods of cardiac and nutritional support she would fully recover to cardiac baseline. One prolonged hospitalization with apparent end organ failure required over three months of ECMO therapy. The chronicity and severity of these episodes were unusual particularly with the family history of sudden death and sensorineural hearing loss, and more aggressive molecular analysis was pursued.

3. Molecular diagnostics

Whole exome sequencing (WES) inclusive of mitochondrial DNA testing targeting 162 nuclear and 37 mitochondrial genes (Baylor College of Medicine/MitomeNGSSM) was requested and revealed a maternally inherited "pathogenic" mutation in MYBPC3 and a likely pathogenic mutation in KCNH2 that was paternally inherited. Pathogenicity was determined by Mercury 1.0 (Baylor) [8]. All reported mutations and variants are listed in Table 1 and Appendix A. The MYBPC3 mutation was later reclassified as a variant of unknown significance (VUS).

Our patient also had an apparently homoplasmic mutation affecting the mitochondrial transfer RNA Cysteine (tRNA Cys) that was interpreted as pathogenic (Table 1 and Appendix A).

Neither one of the parents nor other older relatives had a known history of cardiac disease (Pedigree in Appendix B). The family was informed of the testing results and extensive genetic counseling was provided. The patient eventually died at 8 years of age after decompensation following a sudden illness. One of the patient's younger sisters was subsequently diagnosed with sensorineural hearing loss and developmental delay. Serial echocardiogram and EKG analyses have been normal, and she has never been hospitalized. Recent molecular testing showed that she has the same change in mitochondrial tRNA Cys in addition to the MYBPC3 variant. Testing of her deceased older sister was not able to be completed.

4. Discussion

The combination of hearing loss and cardiomyopathy, in our patient and her deceased sister, suggested an underlying genetic etiology. However the initially available tools for genetic testing failed to provide a diagnosis until massive parallel sequencing of the entire exome became available.

Common causes of dilated cardiomyopathy in children include myocarditis, infiltrative disease and drugs. Approximately 50% of cases are considered idiopathic of which 20–50% are thought to be familial, depending on the screening methods used [3,9]. Our patient was found

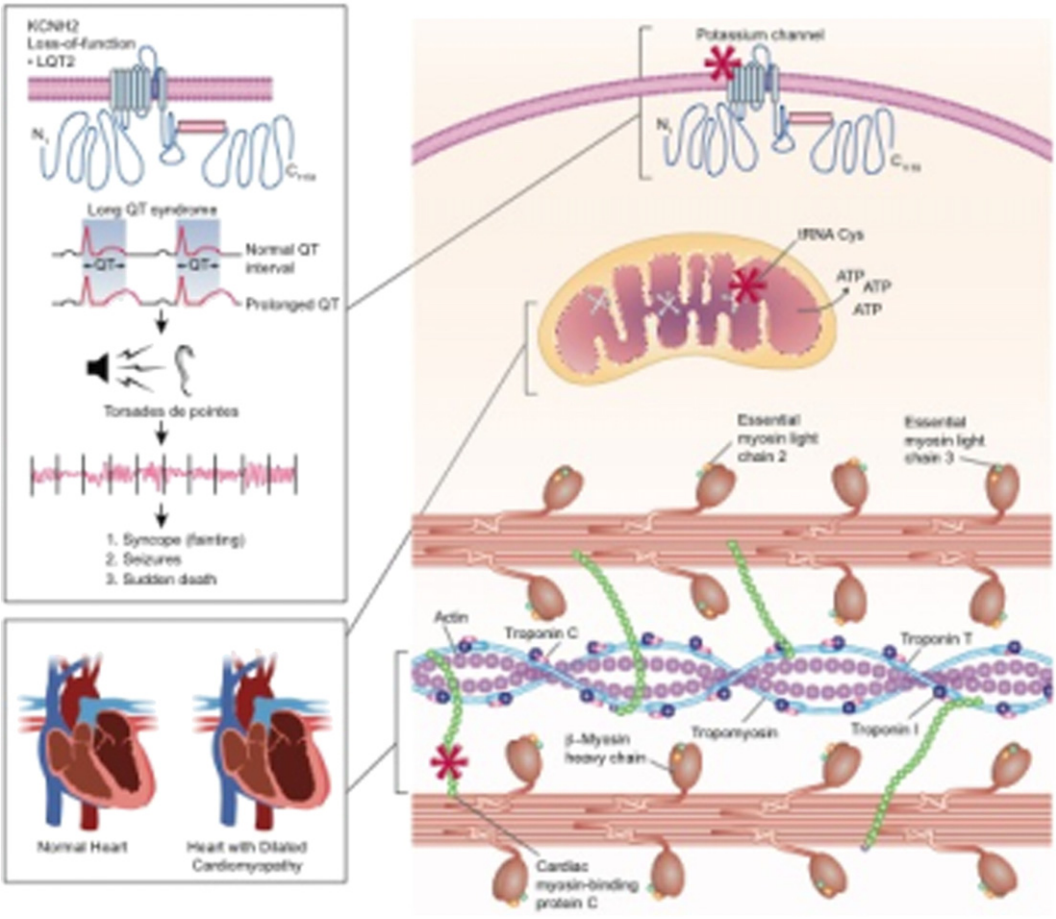

Fig. 2. The 3 pathogenic mutations and their interaction in the heart are depicted. Loss of function mutations in KCNH2 and a membrane potassium channel are associated with long QT syndrome type 2 (LQTS2). In LQTS2 loud noises can trigger torsades de pointes, ultimately leading to syncope, seizures or sudden cardiac death. Cardiac myosin-binding protein C, encoded by MYBPC3, binds myosin and when phosphorylated mediates contraction. The mytochondrial transfer RNA-cysteine (tRNACys) localizes within the mitochondria and abnormal synthesis of mitochondrial proteins and/or oxidative stress imbalances have been associated with DCM [20]. We postulate that abnormalities in cardiac myosin-binding protein C were responsible for the dilated cardiomyopathy present in our patient and the mitochondrial dysfunction secondary to the mutation in the tRNACys had an additive effect on the severity of the phenotype.

to have a likely pathogenic mutation in the MYBPC3 gene, usually associated with hypertrophic cardiomyopathy (40%), but also reported in 4% of patients with familial or idiopathic dilated cardiomyopathy [10]. It was not reported abnormal in the initial cardiomyopathy panel ordered for this patient although included.

Interestingly, WES also revealed a mutation in KCNH2 associated with LQTS type 2 [11]. Although, we have no evidence of long QT in our patient, individuals with mutations in KCNH2 are at increased risk of sudden cardiac death, even in the absence of electrocardiographic abnormalities [12,13].

Mitochondrial genome sequencing was ordered concurrently to consider an explanation to the patient's hearing loss, initial presentation of hypotonia, and severe recurrent episodes of heart failure. Mitochondrial disease can be secondary to alterations in mitochondrial proteins, which in turn can be encoded by nuclear or mtDNA [14]. Many mitochondrial mutations also affect the tRNA genes. Pathogenic mutations have been reported in 1 in 200 live births, however the prevalence of mitochondrial disorders is about 1 in 10,000 [15]. In general, mitochondrial disease refers to disorders of the respiratory chain, which tend to effect in organs with high energy demand, like the myocardium, and mitochondrial cardiomyopathy is a well-recognized entity [16,17]. Not surprisingly, mitochondrial dysfunction has been associated with cardiomyopathy [18,19] and mutations in the mitochondrial genome affecting tRNA have been identified in individuals with DCM [20,21].

Mitochondrial DNA is solely maternally inherited in most instances [22], and in this family, as two of four children have been identified with homoplasmic mutations, the laboratory interpretation (personal discussion with Baylor Miraca Genetics Laboratories) is that there is a probability of maternal homoplasmy as well. The mutation in the tRNA Cys, found in our patients has been reported in other patients with encephalomyopathy and mitochondrial myopathy, Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes (MELAS), hearing loss as well as asymptomatic family members [23–25]. As SNHL was present in both our patient and her sister who did not have the long QT mutation, we feel that the mitochondrial tRNA Cys change is the underlying etiology.

Additionally, we feel that the mitochondrial mutation may have contributed to or even potentiated the clinical presentation of cardiomyopathy and the seemingly complete remission after prolonged and intensive cardiac support (Fig. 1). There are reports of a child with both long QT and hypertrophic cardiomyopathy mutations as well as a child with same tRNA Cys mutation who hypertrophic cardiomyopathy and mitochondrial myopathy [26,27], but none of a patient or family similar to ours.

WES also allows the determination of the parent of origin in the case of inherited mutations. All family members carrying either mutation have been recommended to undergo routine clinical screening along with genetic testing. Screening offered to family members included echocardiography and EKGs.

The exact cause of the sudden cardiac death in the older sister is unclear. It is quite possible that she also carried the same mutations or variants in mitochondrial tRNA Cys, MYBPC3, KCNH2, or a combination of more than one. Post-mortem genetic testing could have potential benefit for the family [26], though was not possible in this case. Nevertheless, information regarding both the mechanisms and related risks to all surviving family members may prove to be invaluable for their health.

5. Conclusions

As we continue to accumulate information on variants found by whole exome sequencing, it is likely that we will be able to better classify them as benign or pathogenic. While mutations in any one of these three genes can convey pathogenicity in a variable manner, it is clear that in combination, initial cardiac stress also became a risk for both rhythm disturbances and dilated cardiomyopathy, ultimately leading to functional compromise. The identification of the two individual gene mutations via clinical testing may have provided an initial clue, but not the full physiologic phenotype for this child's cardiac risks and intermingled pathology (Fig. 2). Multiple episodes of full cardiac support via ECMO allowed the myocardium to rest but the underlying genetic risks to metabolic stress may have ultimately led to this child's passing. We also feel that it is important to consider the possible contribution of the sequence variation in MYBPC3, as may also have potentiated pathogenicity under the unique circumstance of mitochondrial compromise and arrhythmia.

This case demonstrates that multiple underlying genetic mechanisms should be considered in extraordinary clinical presentations. We offer that multiple genetic mutations and/or variants of unclear significance may be acting synergistically to compound phenotype. Thoughtful identification can have a profound effect upon both the patient's care and counseling to other family members regarding their own health risks.

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Appendix A

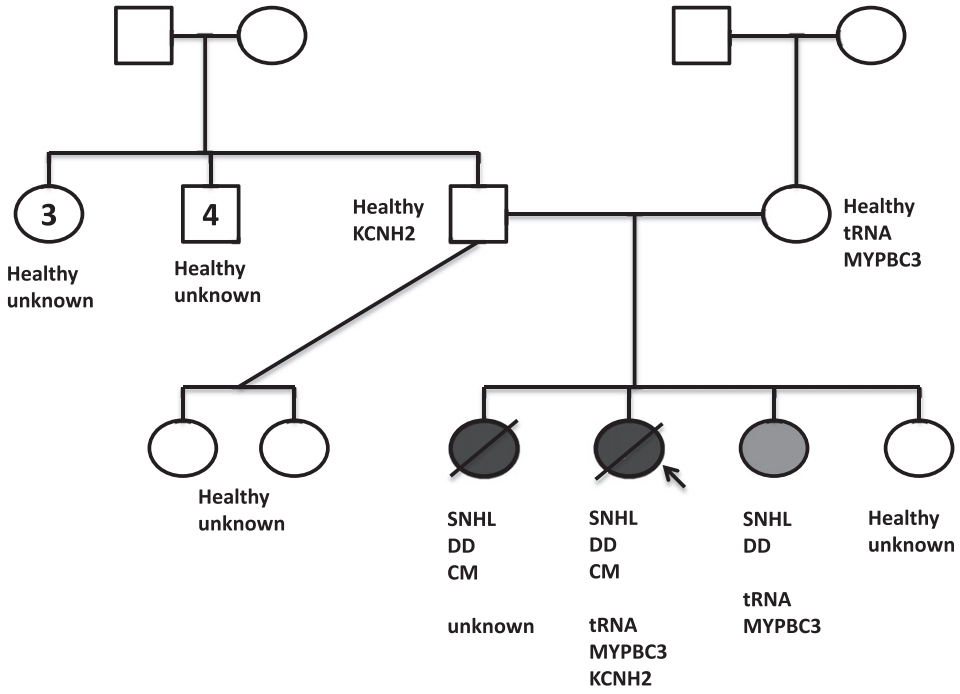
Gene test	Gene Dx Microarray 2011	GeneDX dilated cardiomyopathy panel 2011	Otoscope	Saint Francis	Whole exome	Mitochondrial DNA
Results	No deletions duplication	No mutations identified	No mutations identified	No mutations identified	Mutations and variations within	Mutations
Genes	180,000 oligonucleotide probes	LMNA LDB3/ZASP TTNT2 DES SGCD ACTC1 PLN MYH7 TPM1 TNNI3 TAZ	ATCG1 CCDC50 CDH23 CLDN14 CLRN1 COCH COL11A2 CRYM DRNA5 DIAPH1 DSPP	Cx26/GJB2 CX30/GJB6	Per publshed protocol Reid et al. Mutations KCNH2 (c.2503delC) Variations MYBPC3 (c.1071C>T) MYPN (c.2236A>G) TTN (c.53117C>T) TTN (c. 57388C>T) TTN (c. 12880A>C) TTN (c.19500C>G)	MT-TC (m.5814T>C)

(continued on next page)

Appendix A (*continued*)

Gene test	Gene Dx Microarray 2011	GeneDX dilated cardiomyopathy panel 2011	Otoscope	Saint Francis	Whole exome	Mitochondrial DNA
Results	No deletions duplication	No mutations identified	No mutations identified	No mutations identified	Mutations and variations within	Mutations
		TTR	ESPN		TTN (c. 14254A>C)	
		MYBPC3	ESSRB		COG6 (c. 358A>G)	
		LAMP2	EYA4		GIPC3 (c. 832G>A)	
		MTTK	GIPC3		MED23 (c.4080G>T)	
		MTTL1	CX26/GJB2		LAMA2 (c. 5969-4G>A)	
		MTTL2	GJB3		UPF3B (c. 1121G>A)	
		MTTQ	CX30/GJB6			
		MTTH	GPR96			
		MTTD	GPSM2			
		MTTI	GRHL2			
		MTTV	GRXCR1			
		MTTS1	HGF			
		MTTS2	ILDR1			
		MTND1	KCNQ4			
		MTND5	LHFPL5			
		MTND6	LOXHD1			
			LRTOMT			
			MARVELD2			
			miR-96			
			miR-182			
			miR-183			
			MTRNR1			
			MTTS1			
			MYH14			
			MYH9			
			MYO1A			
			MYO15A			
			MYO3A			
			MYO6			
			MYO7A			
			OTOA			
			OTOF			
			PCDH15			
			PJVK			
			POU3F4			
			POU4F3			
			PRPS1			
			PTPRQ			
			RDX			
			SLC17A3			
			SLC26A4			
			SLC26A5			
			STRC			
			TECTA			
			TJP2			
			TMC1			
			TMIE			
			TMPRSS3			
			TPRN			
			TRIOBP			
			USH1C			
			USH1G			
			USH2A			
			WFS1			
			WHRN			

Appendix B



Healthy = reported healthy
Unknown = unknown molecular status as has not been either tested or reported tested
SNHL = sensorineural hearing loss
CM = cardiomyopathy

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