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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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 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 MYNPC3. 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.

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...
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.](image1.png)

**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.
| Gene         | Protein               | Function                                               | Isoform Location | Variant (amino acid) | Parent of origin | Pathogenicity Predicted phenotype | Polyphen/Sift Polymorphism or ESP5400 status |
|--------------|-----------------------|--------------------------------------------------------|-------------------|----------------------|------------------|------------------------------------|---------------------------------------------|
| MYBPC3       | Myosin binding protein C | Binds myosin to modulate contraction                   | NM_000256         | c.1071C>T p.Arg358X  | Mother           | Likely pathogenic                  | HCM/DCM NA/NA Not reported                  |
| KCNH2        | Membrane potassium channel | Potassium flow during repolarization                  | NM_172058         | c.2503del C p.Leu835fs | Father           | Likely pathogenic                  | LQTS2 NA/NA Not reported                    |
| MT-TC        | tRNA Cys               | Mitochondrial cysteine transport                       | m.5814T>C         | ENSG00000134571      | Mother           | Pathogenic                        | Mitochondrial myopathy MELAS asymptomatic  |
| MYPN         | Myopalladin            | Interacts with nebulette in cardiac muscle and nebulin in skeletal muscle in Z-lines | NM_032578         | c.2236A>G p.Thr746Ala | Mother           | VUS                               | DCM/HCM rs147287437                         |
| TTN          | Titin                 | Major component in striated muscle                    | NM_133378         | c.53117C>T p.Pro17706Leu | Father           | VUS                               | CM, MD, myopathy ESP5400                   |
| TTN          | Titin                 | Major component in striated muscle                    | NM_133378         | c.57388C>T p.Arg19130Cys | Father           | VUS                               | CM, MD, myopathy ESP5400                   |
| TTN          | Titin                 | Major component in striated muscle                    | NM_003319         | c.12880A>C p.Asn4294His | Father           | VUS                               | CM, MD, myopathy ESP5400                   |
| TTN          | Titin                 | Major component in striated muscle                    | NM_133378         | c.19500C>G p.Asn6500Lys | Father           | VUS                               | CM, MD, myopathy ESP5400                   |
| TTN          | Titin                 | Major component in striated muscle                    | NM_133379         | c.14254A>C p.Ser4752Arg | Mother           | VUS                               | CM, MD, myopathy CDG III rs146504870       |
| COG6         | Component of the oligomeric Golgi complex 6 | Component of the conserve oligomeric Golgi complex | NM_020751         | c.358A>G p.Ser120Gly | VUS               | Novel                             | Deafness AR15 rs139313781                   |
| GIPC3        | GIPC PDZ domain containing family | Role in hair bundle survival                     | NM_133261         | c.832G>A p.Glu278lys | Novel            | VUS                               | Novel                                       |
| MED23        | Mediator complex subunit 23 | Role in identification of enhancer sites in DNA for transcription | NM_004830         | c.4080G>T p.Val1360Val | VUS               | Novel                             | Intellectual disability (AR 18) rs138742804 |
| LAMA2        | Laminin               | Component of basement membrane                        | NM_000426         | c.5969-4G-A          | Novel            | VUS                               | MD (Merosin) Novel                          |
| UPF3B        | UPF3 regulator of nonsense transcripts homolog B | Regulates post-splicing multiprotein complex           | NM_080632         | c.1121G>A p.Arg374His | VUS               | VUS                               | Intellectual disability (X-linked 14) rs143538047 |
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).

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.](image-url)

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 mitochondrial transfer RNA-cysteine (tRNA Cys) 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 tRNA Cys 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 homoplasy 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

| Genes | 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 | No mutations identified | Mutations and variations within | Mutations |
| Genes | 180,000 oligonucleotide probes | LMNA | LDB1/ZASP | TTN12 | DE3 | SGCD | ACTC1 | PLN | MYH7 | TPM1 | TNNA3 | TAZ |
| | | ATGC1 | CCDC50 | CDH23 | CLDN14 | CURN1 | COCH | COL11A2 | CRYM | DRNNA5 | DIAPH1 | DSPP |
| | | Cx26/GJB2 | Cx30/GJB6 | | | | | | | |
| | | Per published protocol Reid et al. | | | | MT-TC (m.5814T–C) | | |

(continued on next page)
| Gene test | Gene Dx Microarray 2011 | GeneDX dilated cardiomyopathy panel 2011 | Otoscope | Saint Francis | Whole exome | Mitochondrial DNA |
|-----------|-------------------------|------------------------------------------|----------|--------------|-------------|------------------|
|           | No deletions duplication| No mutations identified                  | No mutations identified | No mutations identified | Mutations and variations within | Mutations |
| TTR       |                         | ESPN                                     |          |              |             |                  |
| MYBPC3    |                         | ESRB                                     |          |              |             |                  |
| LAMP2     |                         | EYA4                                     |          |              |             |                  |
| MTTK      |                         | GIPC3                                    |          |              |             |                  |
| MTTL1     |                         | CX26/GJB2                                 |          |              |             |                  |
| MTTL2     |                         | GJB3                                     |          |              |             |                  |
| MTTQ      |                         | C30/GJB6                                 |          |              |             |                  |
| MTT1      |                         | GPR96                                    |          |              |             |                  |
| MTTD      |                         | GPM2                                     |          |              |             |                  |
| MTTI      |                         | GHRKL2                                   |          |              |             |                  |
| MTTV      |                         | GRXCR1                                   |          |              |             |                  |
| MTT51     |                         | HGF                                      |          |              |             |                  |
| MTT52     |                         | ILDR1                                    |          |              |             |                  |
| MTND1     |                         | KCNQ4                                    |          |              |             |                  |
| MTND5     |                         | LHFPL5                                   |          |              |             |                  |
| MTND6     |                         | LOXH1D1                                  |          |              |             |                  |
| LRTOMT    |                         | MARVELD2                                 |          |              |             |                  |
| miR-96    |                         | miR-182                                  |          |              |             |                  |
| miR-183   |                         | MTRNR1                                   |          |              |             |                  |
| MTT1      |                         | MYH14                                    |          |              |             |                  |
| MTT1      |                         | MYH9                                     |          |              |             |                  |
| MTT1      |                         | MYO1A                                    |          |              |             |                  |
| MTT1      |                         | MYO15A                                   |          |              |             |                  |
| MTT1      |                         | MYO3A                                    |          |              |             |                  |
| MTT1      |                         | MYO6                                     |          |              |             |                  |
| MTT1      |                         | MYO7A                                    |          |              |             |                  |
| MTT1      |                         | OTOF                                     |          |              |             |                  |
| MTT1      |                         | PCDH15                                   |          |              |             |                  |
| MTT1      |                         | PIVK                                     |          |              |             |                  |
| MTT1      |                         | POU3F4                                   |          |              |             |                  |
| MTT1      |                         | POX4F3                                   |          |              |             |                  |
| MTT1      |                         | PRPS1                                    |          |              |             |                  |
| MTT1      |                         | PTPRQ                                    |          |              |             |                  |
| MTT1      |                         | RDX                                      |          |              |             |                  |
| MTT1      |                         | SLC17A3                                  |          |              |             |                  |
| MTT1      |                         | SLC26A4                                  |          |              |             |                  |
| MTT1      |                         | SLC26A5                                  |          |              |             |                  |
| MTT1      |                         | STRC                                     |          |              |             |                  |
| MTT1      |                         | TECTA                                    |          |              |             |                  |
| MTT1      |                         | TJF2                                     |          |              |             |                  |
| MTT1      |                         | TMC1                                     |          |              |             |                  |
| MTT1      |                         | TMIE                                     |          |              |             |                  |
| MTT1      |                         | TMPRSS3                                  |          |              |             |                  |
| MTT1      |                         | TPRN                                     |          |              |             |                  |
| MTT1      |                         | TROI8P                                   |          |              |             |                  |
| MTT1      |                         | USH1C                                    |          |              |             |                  |
| MTT1      |                         | USH1G                                    |          |              |             |                  |
| MTT1      |                         | USH2A                                    |          |              |             |                  |
| MTT1      |                         | WFS1                                     |          |              |             |                  |
| MTT1      |                         | 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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