

Evaluation of Genetic Causes of Cardiomyopathy in Childhood

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Abstract

Cardiomyopathy frequently has a genetic basis. In adults, mutations in genes encoding components of the sarcomere, cytoskeleton, or desmosome are frequent genetic causes of cardiomyopathy. While children share these causes, approximately 30% of children have an underlying metabolic, syndromic, or neuromuscular condition causing their cardiomyopathy, making the etiologies more diverse in children as compared to adults. While some children present with obvious signs or symptoms of metabolic, syndromic, or neuromuscular disease, other cases may be quite subtle, requiring a high level of suspicion in order to diagnose. In general, the younger the child, the more extensive the differential. Advantages of identifying the underlying genetic cause of cardiomyopathy in the pediatric population include confirming the diagnosis in ambiguous cases, facilitating appropriate surveillance and management of cardiac and extra-cardiac disease, providing prognostic information, and establishing the genetic basis in the family, thereby allowing the identification of at risk relatives and institution of appropriate family screening as indicated. For these reasons, genetic testing is increasingly recognized as standard of care, and guidelines for genetic counseling, testing, and incorporation of family based risk assessment have been established. Therapies aimed at treating specific genetic etiologies of cardiomyopathy are emerging and are exciting new developments that require increasingly sophisticated approaches to diagnosis. As genetic testing capabilities continue to expand technically, the interpretation, knowledgeable clinical utilization, and appropriate dissemination of genetic information are important and challenging components of clinical care.

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Etiology of pediatric cardiomyopathy

An etiologic classification of cardiomyopathy was presented by the Pediatric Cardiomyopathy Registry (PCMR) in 2000 in which five major categories were identified: familial, metabolic, syndromic, neuromuscular, and idiopathic.¹⁻⁴ In addition, infectious causes are an important cause of DCM and heart failure. Data demonstrate that prognosis varies depending on the etiologic category.^{1, 4-6} The most common causes within each category are shown in Table 1.

Familial cardiomyopathy

The term “Familial” as an etiologic class for cardiomyopathy typically implies an underlying pathogenic sarcomeric or cytoskeletal gene variant. The term is somewhat of a misnomer since, for example, Noonan syndrome is heritable and therefore may lead to an autosomal dominant family history of HCM. In addition, “familial” cases may result from *de novo* mutations arising for the first time in the patient. While these pathogenic variants are heritable, the proband is the first in their family with the mutation and thus there would not be a family history upon presentation. In the last decade, it has been increasingly recognized that pathogenic variants (mutations) in the cardiac sarcomere, cytoskeleton, desmosome, and nuclear envelope cause an important subset of pediatric cardiomyopathy cases, including disease in infants.⁷⁻⁹ In a single center study of consecutive unrelated pediatric cardiomyopathy patient by Kindel et al., 42% of pediatric cardiomyopathy had a familial etiology based on molecular testing and/or Mendelian inheritance pattern within the pedigree.⁹ The genetic testing for familial cardiomyopathy has been recently reviewed.¹⁰

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Neuromuscular disease and cardiomyopathy

Neuromuscular disease is commonly associated with cardiomyopathy. Mutations in genes that are important for function of both skeletal and cardiac muscle result in both myopathy and cardiomyopathy. The classic examples of neuromuscular diseases associated with cardiomyopathy are Duchenne (DMD) and Becker muscular dystrophy. In DMD, an X-linked condition, boys typically present in childhood with clumsiness, weakness, and progressive difficulty with ambulation. They typically develop evidence of cardiomyopathy in adolescence, but great variability in age of onset exists and there is interest in better understanding the genotype-phenotype correlations that might predict severity of cardiac involvement.¹¹ Cardiac surveillance is indicated beginning with the establishment of the diagnosis of DMD. Likewise, carrier females of DMD mutations are at risk for DCM in adulthood and require ongoing cardiac screening. Other myopathies that have cardiac involvement include Emery-Dreifuss muscular dystrophy, inherited as an autosomal dominant or X-linked condition and classically characterized by a triad of joint contractures, weakness and wasting especially in a humero-peroneal distribution, and cardiac involvement including DCM and heart failure. The cardiac features classically present in the second decade. Limb girdle muscular dystrophies (LGMD), a genetically heterogeneous group of disorders that share weakness of limbs, greater in the proximal than distal limbs, and muscle wasting. Many LGMD are associated with cardiomyopathy, and cardiac surveillance is indicated at the time of diagnosis. It is unusual for cardiomyopathy to be the initial presenting feature in these disorders. However, elevations of creatine phosphokinase (CPK) should prompt further evaluation for an underlying myopathy if a diagnosis has not been made. Myotonic dystrophy, myofibrillar myopathies, and congenital myopathies can all have cardiac involvement as well, typically with DCM and heart failure.

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Friedreich's ataxia (FRDA) is a neuromuscular disorder that is characterized by HCM initially, although DCM and heart failure may occur in later stages of disease.¹² Caused most commonly by a biallelic triplet repeat expansion in intron 1 of the gene encoding Frataxin, the age on onset of FRDA varies depending on the size of the repeat and residual protein expression. The initial signs are typically clumsiness, falling, and ataxia. While the symptoms of FRDA are neuromuscular, FRDA can also properly be considered a mitochondrial disorder since its pathogenesis is related to defective mitochondrial function resulting from impaired iron handling and abnormal accumulation of intramitochondrial iron.

Metabolic disease and cardiomyopathy

The exact incidence of inborn errors of metabolism associated with cardiomyopathy is uncertain. Initial reports quoted 5%¹³ but more recent small studies have demonstrated incidences of 16% of DCM and 36% of HCM¹² with a second study showing an overall incidence of 13.5%.¹⁴ The term inborn error of metabolism refers to diseases caused by defects in proteins encoded by genes important for intermediary metabolism or energy production (Table 1). Inborn errors of metabolism are important to recognize causes of cardiomyopathy in children because there are specific treatments for many of them. In addition, they are associated with medical problems in other organ systems that need subspecialist care. Most inborn errors of metabolism are inherited in an autosomal recessive fashion, therefore recurrence risk estimates within a family differ from "familial" cases of cardiomyopathy. If caused by an autosomal recessive inborn error of metabolism, the recurrence risk would be 25%, whereas autosomal dominant familial cardiomyopathy has a recurrence risk of 50%. Mitochondrial disorders may have an autosomal recessive inheritance pattern if caused by a mutation in the nuclear genome, or exhibit mitochondrial inheritance if caused by a mutation in

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the mitochondrial genome. While individual inborn errors of metabolism are quite rare, as an aggregate they occur in approximately 1 in 4000 individuals and are likely an underappreciated cause of cardiomyopathy in childhood.¹⁵

The major categories of inborn errors of metabolism associated with pediatric cardiomyopathy are shown in Table 1 and include disorders of fatty acid oxidation, carnitine transport, storage disorders, organic acidemias, congenital disorders of glycosylation, and mitochondrial disorders. Typical signs and symptoms associated with these inborn errors of metabolism include hypotonia, developmental delay, hypoglycemia, acidosis or other evidence of metabolic derangement, liver involvement, or evidence of storage such as hepatomegaly or coarse features. Pathognomonic biochemical abnormalities are identifiable in specific disorders, but it must be remembered that metabolic screening represents a snap shot in time, and false negatives can be seen. The metabolic findings in specific disorders have been the subject of a recent review.¹⁵

Newborn screening has increased the ascertainment of some inborn errors of metabolism for which there are risks of cardiomyopathy. The American College of Medical Genetics has recommended a core panel of disorders for inclusion in newborn screening, and this includes fatty acid oxidation disorders, propionic academia, and carnitine uptake deficiency.^{16, 17} However, mitochondrial disorders, lysosomal disorders, congenital disorders of glycosylation, and glycogen storage disorders are not on current panels. Similar to metabolic screening described above, false negatives also can occur on newborn screening. In addition, depending on the timing of each states' implementation of screening, some children and adolescents with cardiomyopathy have not been screened. Because therapy exists for a number of these inborn errors of metabolism, for example enzyme replacement therapy for Pompe disease, an early and accurate diagnosis is essential.

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While some children have significant extracardiac signs and symptoms associated with their inborn error of metabolism, in others the diagnosis requires a high degree of suspicion.

There is evidence that some inborn errors of metabolism can present later in childhood acutely, with cardiomyopathy as the only symptom of disease, suggesting that ongoing consideration of these disorders in the differential of cardiomyopathy in childhood is warranted.^{18, 19}

Cardiomyopathy is a relatively common presenting symptom of mitochondrial disorders, and HCM, DCM, and LVNC have all been described.²⁰ As an example of the subtlety of these disorders, an 8 year old child with HCM without outflow tract obstruction recently presented after an extensive evaluation at an outside hospital. His medical history was unremarkable except for attention deficit disorder diagnosed at the relatively young age of 3. His evaluation leading to diagnosis of HCM occurred after ECG performed prior to tonsillectomy demonstrated bradycardia and left ventricular hypertrophy, prompting a diagnostic evaluation. His physical exam was unremarkable except for his cardiac exam, and importantly his neurologic and musculoskeletal evaluations were normal. His prior testing included normal genetic panel testing for familial causes of HCM, normal urine organic acids, normal acylcarnitine profile, normal urine glycosaminoglycans and genetic testing for Pompe disease. By report, cardiac biopsy was concerning for storage material, but review of pathology was not immediately available. Lactate, pyruvate, and serum amino acids were ordered. Surprisingly, his lactate was 12.9 mmol/L and alanine on serum amino acids was also elevated, consistent with the elevated lactate. Review of his cardiac biopsy scanning electron micrographs showed evidence of marked mitochondrial proliferation (Figure 1), with some mitochondrial irregularity. The sarcomeres were grossly abnormal. Based on these findings, a mitochondrial disorder was suspected, and sequencing of the mitochondrial genome showed a mutation, m.3303C>T in tRNA^{leu}. The mutation had been previously described in a number of individuals with HCM. The diagnosis substantially impacted

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care since the patient requires surveillance for a number of other medical problems potentially associated with mitochondrial disorders. In addition, specific metabolic precautions were instituted in the event of stresses such as illness, dehydration, or surgery. Finally, risk assessment for family members and the requirement for familial cardiac surveillance could be precisely determined by testing for the mitochondrial mutation in at risk individuals.

Genetic syndromes and cardiomyopathy

There are over 100 genetic syndromes in which cardiomyopathy has been described, and the underlying genetic causes of these syndromes are increasingly recognized. One of the most common genetic syndromes associated with HCM is Noonan syndrome. Part of a larger group of rasopathies that include Cardiofaciocutaneous syndrome, Costello syndrome, and Noonan syndrome with multiple lentigenes (previously known as LEOPARD syndrome) amongst others, Noonan syndrome is classically characterized by short stature, dysmorphic features, and cardiac involvement consisting of cardiovascular malformations, HCM, or both.²¹
²² Patients with Noonan syndrome are at risk for learning disability. In addition, they are at increased risk for a number of medical problems and health supervision guidelines exist to guide appropriate management and surveillance.²³ For this reason, it is important to diagnose patients with Noonan syndrome as early as possible. Noonan syndrome is inherited as an autosomal dominant condition, but there is a high *de novo* rate. Because first degree relatives of patients with *de novo* mutations are not at risk for cardiomyopathy, cardiac screening would not be required. Genotype-phenotype correlations exist for Noonan syndrome. For example, PTPN11 mutations are more strongly associated with cardiovascular malformations, whereas RAF1 mutations are associated with HCM.

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Alstrom syndrome is an underrecognized syndrome associated with DCM. Infants with Alstrom syndrome may present with DCM in infancy but without other evidence of a syndromic condition^{24, 25}. Often, DCM will resolve only to recur during adolescence.^{26, 27} Other medical complications in Alstrom syndrome are age related in onset and include sensorineural hearing loss and retinal dystrophy leading to blindness. Patients with Alstrom syndrome also have findings similar to metabolic syndrome, including obesity, hyperinsulinemia, early onset type 2 diabetes, and hypertriglyceridemia. Alstrom syndrome is inherited in an autosomal recessive pattern.

Genetic and metabolic evaluation

Because of the significant heterogeneity of causes of pediatric cardiomyopathy, evaluation by a geneticist knowledgeable in cardiac genetics is important. In general, the younger the child, the larger the differential due to limited history and medical information. The parameters for establishing a diagnosis of cardiomyopathy have been well described. For DCM additional testing should include complete blood count (CBC), renal and liver function tests, creatine phosphokinase (CPK), lactate, pyruvate, plasma amino acids, urine organic acids, and an acylcarnitine profile (Table 2). The yield of testing by next generation sequencing panels for familial DCM is approximately 25%. Additional genetic and enzymatic testing may be useful. Cardiac catheterization and endomyocardial biopsy are not routine but may be useful in patients with acute dilated cardiomyopathy. Biopsy samples can also be assessed for the presence of mononuclear cell infiltrates, myocardial damage, storage abnormalities, and viral infection or genomes. It is considered standard of care to screen first-degree family members utilizing echocardiography and ECG in idiopathic and familial cases.²⁸

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In HCM, the electrocardiogram typically demonstrates left ventricular hypertrophy with ST segment and T-wave abnormalities. Intraventricular conduction delays and signs of ventricular preexcitation (Wolff-Parkinson-White syndrome) may be present and should raise the possibility of Danon disease (X-linked, caused by LAMP2 mutations) or Pompe disease (autosomal recessive, caused by GAA mutations). Echocardiography is diagnostic in identifying, localizing, and quantifying the degree of myocardial hypertrophy. Additional diagnostic studies in HCM patients include metabolic testing, genetic testing for specific syndromic conditions, or genetic testing for mutations in genes known to cause isolated HCM. The clinical availability of these tests is expanding rapidly and the yield of testing is quite high for HCM (50-75%). As with DCM, it is considered standard of care to perform cardiac screening and ongoing surveillance in all first degree family members for idiopathic or familial cases.

RCM, LVNC, and ARVC are relatively rare in the pediatric population. Nevertheless, they exhibit the same degree of heterogeneity with regard to cause as HCM and DCM.^{1, 4, 5} Molecular diagnostic rates using currently available genetic testing is not known with certainty.

Cascade screening: family based care

Current consensus guidelines recommend cardiac screening and known mutation testing for individuals at-risk of developing cardiomyopathy, however, the clinical impact of these recommendations is largely unknown²⁸⁻³³. A recent study of the uptake of cardiac screening and genetic testing amongst first and second degree relatives at-risk for HCM or DCM indicated an uptake rate of 57% and 39% respectively.³⁴ Not surprisingly, first degree relatives were more likely to complete cardiac screening and genetic testing than second degree relatives. When the proband was mutation positive and both cardiac screening and known mutation testing were recommended, relatives were more likely to complete cardiac screening. The number of living

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affected individuals in a family also impacted the uptake of cardiac screening. In this study, cascade cardiac screening found that 25% of identified at-risk first and second degree relatives had cardiomyopathy that was asymptomatic and previously undiagnosed. Genetic testing led to identification of 22 asymptomatic at-risk relatives for whom ongoing cardiac surveillance was indicated. Known familial mutation testing also identified 33 not-at-risk individuals. Relatives who tested negative for the known familial mutation could be reassured about potential risk of disease and ongoing cardiac surveillance could be discontinued. In addition, children of these individuals could be spared genetic testing and cardiac screening.

It should be emphasized that family histories are dynamic, and the indications of testing for affected family members change as new individuals in the family are diagnosed. Therefore, it is important to address family history at each clinic visit and update screening recommendations accordingly. Increasingly, clinicians are being called to incorporate family based care into medical practice, thus treating the entire family rather than a single individual. This is paradigm-altering in medical practice and has significant implications to the responsibilities and clinical encounters.

Timing of cardiac screening and genetic testing

The timing of genetic testing and cardiac screening needs to be carefully considered for each patient and family. As in other genetic diseases, testing the most severely affected family member prior to initiating known mutation testing in at-risk relatives is recommended.^{28, 29, 31} In the case of a symptomatic relative, or relative participating in potentially high-risk activities such as competitive athletics, cardiac screening prior to completion of genetic testing in the proband may be indicated to ensure optimal safety.³⁰ If no etiology is identified, all first degree relatives should undergo routine cardiac screening. If relatives are diagnosed with disease, subsequent

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relatives should undergo screening based on the cascade approach. If a disease-causing mutation is identified, all affected relatives and first degree unaffected relatives should be offered genetic counseling and genetic testing. Recommendations for genetic testing and cardiac screening are unique to each family and depend upon accurate interpretation of results by professionals with expertise in molecular genetics. An important benefit of establishing a cause of cardiomyopathy in a family is risk stratification for potentially affected family members. A cascade approach to genetic testing in family members is likely to lead to significant cost savings but future studies are warranted to further define the benefit.

Implications for Clinical Practice

The genetic basis of cardiomyopathy in childhood is complex. An accurate and precise diagnosis is important to better direct patient management, including extracardiac management, and to assess risk to family members. Genetic testing for cardiomyopathy is increasingly available. The yield of testing continues to increase, but the interpretation of results is also becoming more complex. Accurate interpretation of genetic test results is necessary to make appropriate recommendations for cardiac screening and genetic testing and should be done in the context of the family history. It is not uncommon to identify more than one genetic variant in a proband and/or a variant of uncertain significance making interpretation more complicated. Frequently, family-based cardiac screening recommendations may not routinely be discussed and/or genetic testing not offered in a standardized manner. In addition, this increasingly brings new scenarios for which most physicians have little training, such as the disclosure of family based information. It is important that pediatric cardiologists receive training in clinical genetics to facilitate appropriate referral and testing. Further, there is an urgent need for more genetics professionals, including genetic counselors and geneticists, with cardiac disease specific

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knowledge. Developing the appropriate infrastructure to increasingly incorporate genetics in the care of patients and families is an important goal.

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Conflicts of Interest

None

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Figure Legend

Figure 1. Cardiac biopsy scanning electron micrograph in a patient with a mitochondrial disorder. The patient had a mutation in the mitochondrial genome, tRNA^{Leu}. On scanning electron micrograph many intermyofibrillar and subsarcolemmal mitochondrial aggregates were seen. Pathological mitochondrial included those with paracrystalline inclusions, thumbprint like cristae, smudged matrix and cristae dense inclusions.

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Table 1. Genetic Causes of Pediatric Cardiomyopathy

Category	Cause	Gene Examples (non-comprehensive)	Phenotype	Inheritance
"Familial"				
	Sarcomeric genes	<i>MYH7, MYBPC3, MYL2, MYL3, TNNT2, TNNI3, TNNC1, MYH6, TPM1, ACTC1,</i> etc.	HCM, DCM, RCM, LVNC	Autosomal dominant
	Cytoskeletal genes	<i>TTN, CSRP3, TCAP, VCL, ACTN2, DES, LDB3, SGCD, MYPN, ANKRD1, BAG3, NEBL, NEXN,</i> etc.	HCM, DCM, RCM	Autosomal dominant
	Desmosomal genes	<i>DSP, PKP2, DSG2, DSC2, JUP,</i> etc.	ARVC, DCM	Autosomal dominant

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	Nuclear envelope genes	<i>LMNA</i>	DCM	Autosomal dominant
Metabolic				
	Fatty acid oxidation disorders (trifunctional protein, VLCAD, LCHAD),	<i>ACADVL, HADHA, HADHB, etc.</i>	HCM, DCM, LVNC	Autosomal recessive
	Carnitine abnormalities (carnitine acylcarnitine translocase deficiency, carnitine palmitoyltransferase deficiency (CPTII)	<i>SLC25A20, CPT2</i>	DCM	Autosomal recessive
	mitochondrial disorders (including Kearns-Sayre syndrome, Barth syndrome, Friedreich's ataxia)	Mt genome mutations/deletion, <i>TAZ, FRDA, SCO2, SURF1, COX genes, ANT1, etc.</i>	HCM, DCM, LVNC	Autosomal recessive, mitochondrial, X-linked (Barth syndrome)
	organic acidemias (propionic acidemia, etc.)	<i>PCCA, PCCB</i>	DCM	Autosomal recessive

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	storage disorders (glycogen storage disorders, especially Pompe syndrome; mucopolysaccharidoses; Fabry disease, sphingolipidoses; hemochromatosis, Danon disease)	<i>PRKAG2, LAMP2, GLA, GAA, AGL,</i> etc.	HCM	Autosomal recessive, X-linked (Danon disease)
Syndromic				
	RASopathies (Noonan, Costello, Cardiofaciocutaneous, Noonan with multiple lentigenes, etc.)	<i>PTPN11, RAF1, SOS1, KRAS, HRAS, BRAF, NRAS, MAP2K1, MAP2K2, CBL, SHOC2</i>	HCM	Autosomal dominant; high <i>de novo</i> mutation rate
	Alstrom syndrome	<i>ALMS1</i>	DCM	Autosomal recessive
Neuromuscular				
	Muscular dystrophies (Duchenne, Becker, limb girdle, Emery- Dreifuss,	<i>DMD, DMPK, EMD, LMNA, FHL1, FKRP,</i>	DCM	Autosomal dominant, X-

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	congenital muscular dystrophy, etc.), myotonic dystrophy, myofibrillar myopathy	<i>FLNC, LGMD2A, LGMD2B, LGMD2C, LGMD2D, LGMD2E, etc.</i>		linked (DMD, EMD)
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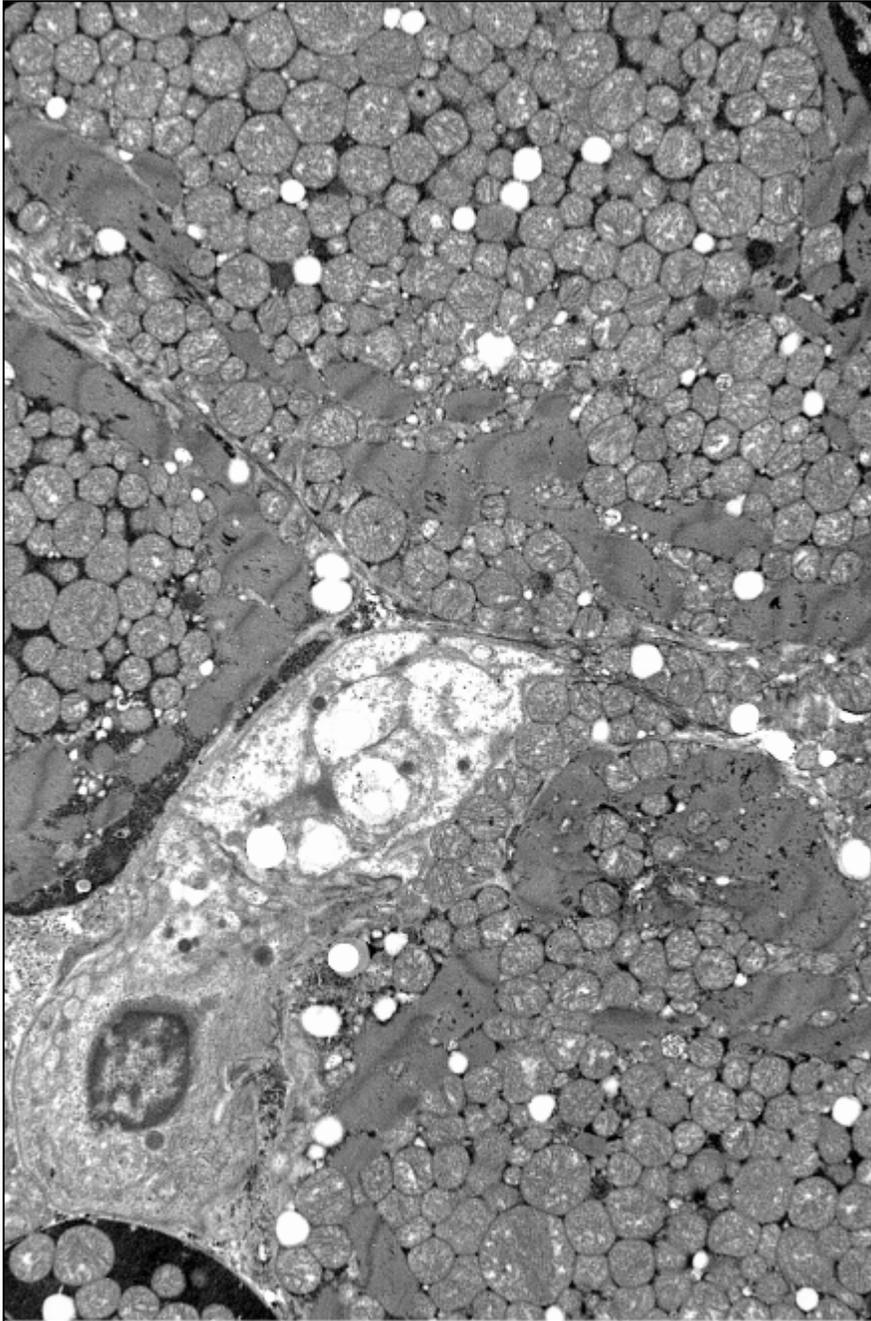
Table 2. Suggested evaluation of cardiomyopathy in childhood: non cardiac parameters

Detailed family history: minimum 3 generation pedigree; update at each visit
History and physical: with attention to developmental history, school performance, other chronic medical problems, growth, dysmorphic features, muscle strength and tone, neurologic exam, vision, hearing
Initial laboratory testing considerations: Metabolic: serum amino acids, urine organic acids, acylcarnitine profile, lactate, pyruvate, electrolytes and glucose, CPK Genetic: consideration of next generation sequencing panel for cardiomyopathy or appropriate genetic testing for genetic syndromes based on evaluation
Recommendation/facilitation of cardiac imaging in first degree family members
Genetic counseling

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Figure 1.



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