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Original Article

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. Although children share these causes, ~30% of children have an underlying metabolic, syndromic, or neuromuscular condition causing their cardiomyopathy, making the aetiologies more diverse in children as compared with adults. Although 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 them. In general, the younger the child, the more extensive the differential. Advantages of identifying the underlying genetic cause of cardiomyopathy in the paediatric population include confirming the diagnosis in ambiguous cases, facilitating appropriate surveillance and management of cardiac and extra-cardiac diseases, 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 recognised as standard of care, and guidelines for genetic counselling, testing, and incorporation of family-based risk assessment have been established. Therapies aimed at treating specific genetic aetiologies of cardiomyopathy are emerging and are exciting new developments that require increasingly sophisticated approaches to diagnosis. As genetic testing capabilities continue to expand technically, careful interpretation, knowledgeable clinical utilisation, and appropriate dissemination of genetic information are important and challenging components of clinical care.

Keywords: Mutation; genetic variant; genetic syndrome; sarcomere

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Aetiology of paediatric cardiomyopathy

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

Familial cardiomyopathy

The term "Familial" as an aetiological class for cardiomyopathy typically implies an underlying pathogenic sarcomeric or cytoskeletal gene variant. The term is somewhat of a misnomer as, for example, Noonan syndrome is heritable and, therefore, may lead to an autosomal dominant family history of hypertrophic cardiomyopathy. In addition, "familial" cases may result from de novo mutations arising for the first time in the patient. Although these pathogenic variants are heritable, the proband is the first in the family with the mutation, and thus there would not be a family history upon presentation. In the last

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Table 1. Genetic causes of paediatric cardiomyopathy.

Category	Cause	Gene examples (non-comprehensive)	Phenotype	Inheritance
"Familial"				
	Sarcomeric genes	*MYH7*, *MYBPC3*, *MYL2*, *MYL3*, *TNNT2*, *TNNI3*, *TNNC1*, *MYH6*, *TPM1*, *ACTC1*, etc.	HCM, DCM, RCM, LVNC	Autosomal dominant
	Cytoskeletal genes	*TTN*, *CSRP3*, *TCAP*, *VCL*, *ACTN2*, *DES*, *LDB3*, *SGCD*, *MYPN*, *ANKRD1*, *BAG3*, *NEBL*, *NEXN*, etc.	HCM, DCM, RCM	Autosomal dominant
	Desmosomal genes	*DSP*, *PKP2*, *DSG2*, *DSC2*, *JUP*, etc.	ARVC, DCM	Autosomal dominant
	Nuclear envelope genes	*LMNA*	DCM	Autosomal dominant
Metabolic				
	Fatty acid oxidation disorders (trifunctional protein, VLCAD, LCHAD),	*ACADVL*, *HADHA*, *HADHB*, etc.	HCM, DCM, LVNC	Autosomal recessive
	Carnitine abnormalities (carnitine acylcarnitine translocase deficiency, carnitine palmitoyltransferase deficiency (CPTII)	*SLC25A20*, *CPT2*	DCM	Autosomal recessive
	Mitochondrial disorders (including Kearns–Sayre syndrome, Barth syndrome, Friedreich's ataxia)	Mt genome mutations/deletion, *TAZ*, *FRDA*, *SC02*, *SURF1*, *C0X* genes, *ANT1*, etc.	HCM, DCM, LVNC	Autosomal recessive, mitochondrial, X-linked (Barth syndrome)
	Organic acidaemias (propionic acidaemia, etc.)	*PCCA*, *PCCB*	DCM	Autosomal recessive
	Storage disorders (glycogen storage disorders, especially Pompe syndrome; mucopolysaccharidoses; Fabry disease, sphingolipidoses; haemochromatosis, Danon disease)	*PRKAG2*, *LAMP2*, *GLA*, *GAA*, *AGL*, etc.	HCM	Autosomal recessive, X-linked (Danon disease)
Syndromic				
	RASopathies (Noonan, Costello, Cardiofaciocutaneous, Noonan with multiple lentigenes, etc.)	*PTPN11*, *RAF1*, *S0S1*, *KRAS*, *HRAS*, *BRAF*, *NRAS*, *MAP2K1*, *MAP2K2*, *CBL*, *SH0C2*	HCM	Autosomal dominant; high de novo mutation rate
	Alstrom syndrome	*ALMS1*	DCM	Autosomal recessive
Neuromuscular				
	Muscular dystrophies (Duchenne, Becker, limb girdle, Emery– Dreifuss, congenital muscular dystrophy, etc.), myotonic dystrophy, myofibrillar myopathy	*DMD*, *DMPK*, *EMD*, *LMNA*, *FHL1*, *FKRP*, *FLNC*, *LGMD2A*, *LGMD2B*, *LGMD2C*, *LGMD2D*, *LGMD2E*, etc.	DCM	Autosomal dominant, X-linked (DMD, EMD)

ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; LVNC = left ventricular non-compaction cardiomyopathy; RCM = restrictive cardiomyopathy

decade, it has been increasingly recognised that pathogenic variants or mutations in the cardiac sarcomere, cytoskeleton, desmosome, and nuclear envelope give rise to an important subset of paediatric cardiomyopathy cases, including disease in infants.[7–9] In a single-centre study of consecutive unrelated paediatric cardiomyopathy patients by Kindel et al, 42% of the cases had a familial aetiology based on molecular testing and/or Mendelian inheritance pattern within the pedigree.[9] The genetic testing for familial cardiomyopathy has been recently reviewed.[10]

Neuromuscular disease and cardiomyopathy

Neuromuscular disease is commonly associated with cardiomyopathy. Mutations in genes that are

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important for the functioning of both skeletal and cardiac muscles result in both myopathy and cardiomyopathy. The classic examples of neuromuscular diseases associated with cardiomyopathy are Duchenne and Becker muscular dystrophy. In Duchenne muscular dystrophy, 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 much interest in better understanding the genotype–phenotype correlations that might predict the severity of cardiac involvement.[11] Cardiac surveillance is indicated beginning with the establishment of the diagnosis of Duchenne muscular dystrophy. Likewise, carrier females of Duchenne muscular dystrophy mutations are at risk for dilated cardiomyopathy 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 characterised by a triad of joint contractures, weakness, and wasting – especially in a humero–peroneal distribution – and cardiac involvement including dilated cardiomyopathy and heart failure. The cardiac features classically present in the second decade. Limb girdle muscular dystrophies are a genetically heterogeneous group of disorders that share weakness of limbs, greater in the proximal than in the 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 in creatine phosphokinase levels 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 dilated cardiomyopathy and heart failure.

Friedreich's ataxia is a neuromuscular disorder that is characterised by hypertrophic cardiomyopathy initially, although dilated cardiomyopathy and heart failure may occur in later stages of disease.[12] Caused most commonly by a bi-allelic triplet repeat expansion in intron 1 of the gene encoding Frataxin, the age of onset of Friedreich's ataxia varies depending on the size of the repeat and residual protein expression. The initial signs are typically clumsiness, falling, and ataxia. Although the symptoms of Friedreich's ataxia are neuromuscular, Friedreich's ataxia can also properly be considered a mitochondrial disorder as its pathogenesis is related to defective mitochondrial function resulting from impaired iron handling and abnormal accumulation of intra-mitochondrial 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 dilated cardiomyopathy and 36% of hypertrophic cardiomyopathy,[12] 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 recognise 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 sub-specialist care. Most inborn errors of metabolism are inherited in an autosomal recessive manner; 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 the mitochondrial genome. Although 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 paediatric cardiomyopathy are shown in Table 1 and include disorders of fatty acid oxidation, carnitine transport, storage disorders, organic acidaemias, congential disorders of glycosylation, and mitochondrial disorders. Typical signs and symptoms associated with these inborn errors of metabolism include hypotonia, developmental delay, hypoglycaemia, acidosis or other evidences 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 snapshot 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 acadaemia, and carnitine-uptake deficiency;[16,17]

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however, mitochondrial disorders, lysosomal disorders, congenital disorders of glycosylation, and glycogen storage disorders are not on current panels. Similar to the metabolic screening described above, false negatives can also 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. As 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.

Although some children present significant extra-cardiac 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 hypertrophic cardiomyopathy, dilated cardiomyopathy, and left ventricular non-compaction cardiomyopathy have all been described.[20] As an example of the subtlety of these disorders, an 8-year-old child with hypertrophic cardiomyopathy 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 the diagnosis of hypertrophic cardiomyopathy occurred after the electrocardiogram performed before tonsillectomy demonstrated bradycardia and left ventricular hypertrophy, prompting a diagnostic evaluation. His physical examination was unremarkable except for his cardiac examination, and importantly his neurological and musculoskeletal evaluations were normal. His previous testing included normal genetic panel testing for familial causes of hypertrophic cardiomyopathy, 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. Tests for lactate, pyruvate, and serum amino acids were ordered. Surprisingly, his lactate level was 12.9 mmol/L and alanine concentrations in the serum were also elevated, consistent with the elevated lactate level. Review of his cardiac biopsy scanning electron micrographs showed evidence of marked mitochondrial proliferation (Fig 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 hypertrophic cardiomyopathy. The diagnosis substantially impacted care, as the patient required surveillance for a number of other medical problems potentially associated with mitochondrial disorders. In addition, specific metabolic precautions were instituted during stressful events 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.

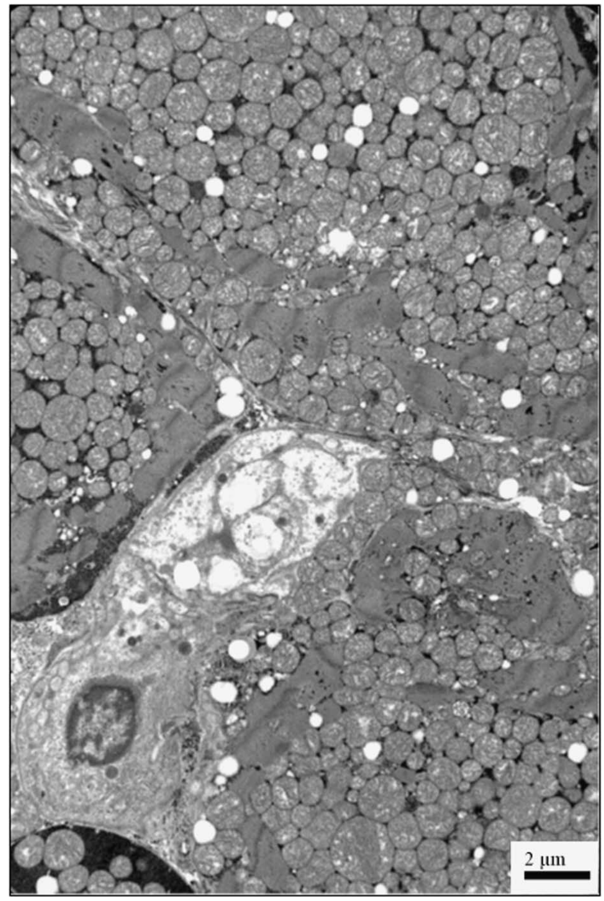

Figure 1.
Cardiac biopsy scanning electron micrograph in a patient with a mitochondrial disorder. The patient had a mutation in the mitochondrial genome, $tRNA^{Leu}$. On the scanning electron micrograph, many inter-myofibrillar and sub-sarcolemmal mitochondrial aggregates were observed. Pathological mitochondria included those with paracrystalline inclusions, thumbprint-like cristae, smudged matrix, and cristae dense inclusions.

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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 recognised; one of the most common genetic syndromes associated with hypertrophic cardiomyopathy is the Noonan syndrome. Part of a larger group of RASopathies that include Cardiofaciocutaneous syndrome, Costello syndrome, and Noonan syndrome with multiple lentigenes – previously known as the LEOPARD syndrome – among others, the Noonan syndrome is classically characterised by short stature, dysmorphic features, and cardiac involvement consisting of cardiovascular malformations, hypertrophic cardiomyopathy, 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. As 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 hypertrophic cardiomyopathy.

Alstrom syndrome is an underrecognised syndrome associated with dilated cardiomyopathy. Infants with Alstrom syndrome may present with dilated cardiomyopathy in infancy but without any other evidence of a syndromic condition.[24,25] Often, dilated cardiomyopathy 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 syndromes including obesity, hyperinsulinaemia, early onset type 2 diabetes, and hypertriglyceridaemia. Alstrom syndrome is inherited in an autosomal recessive pattern.

Genetic and metabolic evaluation

Owing to the significant heterogeneity of causes of paediatric 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 dilated cardiomyopathy, additional testing should include complete blood count, renal and liver function tests, assessment of levels of creatine phosphokinase, 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 dilated cardiomyopathy is ~25%. Additional genetic and enzymatic testing may be useful. Cardiac catheterisation 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 using echocardiography and echocardiography in idiopathic and familial cases.[28]

In hypertrophic cardiomyopathy, the electrocardiogram typically demonstrates left ventricular hypertrophy with ST segment and T-wave abnormalities. Intra-ventricular conduction delays and signs of ventricular pre-excitation (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

Table 2. Suggested evaluation of cardiomyopathy in childhood: non-cardiac parameters.

Detailed family history: minimum three 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 counselling

CPK = creatine phosphokinase

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diagnostic in identifying, localising, and quantifying the degree of myocardial hypertrophy. Additional diagnostic studies in hypertrophic cardiomyopathy patients include metabolic testing, genetic testing for specific syndromic conditions, or genetic testing for mutations in genes known to cause isolated hypertrophic cardiomyopathy. The clinical availability of these tests is expanding rapidly and the yield of testing is quite high for hypertrophic cardiomyopathy (50–75%). As with dilated cardiomyopathy, it is considered standard of care to perform cardiac screening and ongoing surveillance in all first-degree family members for idiopathic or familial cases.

Restrictive cardiomyopathy, left ventricular noncompaction cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy are relatively rare in the paediatric population. Nevertheless, they exhibit the same degree of heterogeneity with regard to cause as hypertrophic cardiomyopathy and dilated cardiomyopathy.[1,4,5] Molecular diagnostic rates using currently available genetic testing are not known with certainty.

Cascade screening: family-based care

The present 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 unknown.[28–33] A recent study of the uptake of cardiac screening and genetic testing amongst first- and second-degree relatives at-risk for hypertrophic cardiomyopathy or dilated cardiomyopathy 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 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 the 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 mutations could be re-assured about the 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 emphasised 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 before initiating known mutation testing in at-risk relatives is recommended.[28,29,31] In the case of a symptomatic relative, or a relative participating in potentially high-risk activities such as competitive athletics, cardiac screening before completion of genetic testing in the proband may be indicated to ensure optimal safety.[30] If no aetiology is identified, all first-degree relatives should undergo routine cardiac screening. If relatives are diagnosed with disease, subsequent relatives should undergo screening based on the cascade approach. If a disease-causing mutation is identified, all the affected relatives and first-degree unaffected relatives should be offered genetic counselling 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 extra-cardiac 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

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screening, and genetic testing and should be carried out 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 may not be offered in a standardised 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 paediatric cardiologists receive training in clinical genetics to facilitate appropriate referral and testing. Further, there is an urgent need for more genetics professionals, including genetic counsellors and geneticists, with cardiac disease-specific 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.

References

1. Colan SD, Lipshultz SE, Lowe AM, et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the pediatric cardiomyopathy registry. Circulation 2007; 115: 773–781.
2. Grenier MA, Osganian SK, Cox GF, et al. Design and implementation of the North American Pediatric Cardiomyopathy registry. Am Heart J 2000; 139: S86–S95.
3. Towbin JA, Lowe AM, Colan SD, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA 2006; 296: 1867–1876.
4. Wilkinson JD, Landy DC, Colan SD, et al. The Pediatric Cardiomyopathy Registry and heart failure: key results from the first 15 years. Heart Fail Clin 2010; 6: 401–413, vii.
5. Cox GF, Sleeper LA, Lowe AM, et al. Factors associated with establishing a causal diagnosis for children with cardiomyopathy. Pediatrics 2006; 118: 1519–1531.
6. Lipshultz SE, Orav EJ, Wilkinson JD, et al. Risk stratification at diagnosis for children with hypertrophic cardiomyopathy: an analysis of data from the Pediatric Cardiomyopathy Registry. Lancet 2013; 382: 1889–1897.
7. Kaski JP, Syrris P, Burch M, et al. Idiopathic restrictive cardiomyopathy in children is caused by mutations in cardiac sarcomere protein genes. Heart 2008; 94: 1478–1484.
8. Kaski JP, Syrris P, Esteban MT, et al. Prevalence of sarcomere protein gene mutations in preadolescent children with hypertrophic cardiomyopathy. Circ Cardiovasc Genet 2009; 2: 436–441.
9. Kindel SJ, Miller EM, Gupta R, et al. Pediatric cardiomyopathy: importance of genetic and metabolic evaluation. J Card Fail 2012; 18: 396–403.
10. Tariq M, Ware SM. Importance of genetic evaluation and testing in pediatric cardiomyopathy. World J Cardiol 2014; 6: 1156–1165.
11. Tandon A, Jefferies JL, Villa CR, et al. Dystrophin genotype-cardiac phenotype correlations in Duchenne and Becker muscular dystrophies using cardiac magnetic resonance imaging. Am J Cardiol 2015; 115: 967–971.
12. Payne RM, Wagner GR. Cardiomyopathy in Friedreich ataxia: clinical findings and research. J Child Neurol 2012; 27: 1179–1186.
13. Cox GF. Diagnostic approaches to pediatric cardiomyopathy of metabolic genetic etiologies and their relation to therapy. Prog Pediatr Cardiol 2007; 24: 15–25.
14. Badertscher A, Bauersfeld U, Arbenz U, Baumgartner MR, Schinzel A, Balmer C. Cardiomyopathy in newborns and infants: a broad spectrum of aetiologies and poor prognosis. Acta Paediatrica 2008; 97: 1523–1528.
15. Byers SL, Ficicioglu C. Infant with cardiomyopathy: when to suspect inborn errors of metabolism? World J Cardiol 2014; 6: 1149–1155.
16. American College of Medical Genetics Newborn Screening Expert G. Newborn screening: toward a uniform screening panel and system – executive summary. Pediatrics 2006; 117: S296–S307.
17. Therrell BL Jr., Lloyd-Puryear MA, Camp KM, Mann MY. Inborn errors of metabolism identified via newborn screening: ten-year incidence data and costs of nutritional interventions for research agenda planning. Mol Genet Metab 2014; 113: 14–26.
18. Laemmle A, Balmer C, Doell C, Sass JO, Haberle J, Baumgartner MR. Propionic acidemia in a previously healthy adolescent with acute onset of dilated cardiomyopathy. Eur J Pediatr 2014; 173: 971–974.
19. Lee TM, Addonizio LJ, Barshop BA, Chung WK. Unusual presentation of propionic acidaemia as isolated cardiomyopathy. J Inherit Metab Dis 2009; 32 (Suppl 1): S97–S101.
20. Scaglia F, Towbin JA, Craigen WJ, et al. Clinical spectrum, morbidity, and mortality in 113 pediatric patients with mitochondrial disease. Pediatrics 2004; 114: 925–931.
21. Tartaglia M, Gelb BD, Zenker M. Noonan syndrome and clinically related disorders. Best Prac Res Clin Endocrinol Metab 2011; 25: 161–179.
22. Wilkinson JD, Lowe AM, Salbert BA, et al. Outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy: a study from the Pediatric Cardiomyopathy Registry. Am Heart J 2012; 164: 442–448.
23. Romano AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. Pediatrics 2010; 126: 746–759.
24. Long PA, Evans JM, Olson TM. Exome sequencing establishes diagnosis of Alstrom syndrome in an infant presenting with non-syndromic dilated cardiomyopathy. Am J Med Genet A 2015; 167A: 886–890.
25. Michaud JL, Heon E, Guilbert F, et al. Natural history of Alstrom syndrome in early childhood: onset with dilated cardiomyopathy. J Pediatr 1996; 128: 225–229.
26. Czosek RJ, Goldenberg P, Miller EM, Spicer R, Towbin JA, Ware SM. Cardiac electrical system involvement in Alström syndrome: uncommon causes of dilated cardiomyopathies. Cardiogenetics 2012; 2: 6–10.
27. Worthley MI, Zeitz CJ. Case of Alstrom syndrome with late presentation dilated cardiomyopathy. Intern Med J 2001; 31: 569–570.
28. Hershberger RE, Lindenfeld J, Mestroni L, et al. Genetic evaluation of cardiomyopathy – a heart failure society of America practice guideline. J Card Fail 2009; 15: 83–97.

29. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm 2011; 8: 1308–1339.
30. Bos JM, Towbin JA, Ackerman MJ. Diagnostic, prognostic, and therapeutic implications of genetic testing for hypertrophic cardiomyopathy. J Am Coll Cardiol 2009; 54: 201–211.
31. Charron P, Arad M, Arbustini E, et al. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2010; 31: 2715–2726.
32. Watkins H, Ashrafian H, Redwood C. Inherited cardiomyopathies. N Engl J Med 2011; 364: 1643–1656.
33. Van Langen I, Arens Y, Baars H, et al. Genetic diagnostics and genetic counselling in Hypertrophic Cardiomyopathy (HCM). Neth Heart J 2010; 18: 144–159.
34. Miller EM, Wang Y, Ware SM. Uptake of cardiac screening and genetic testing among hypertrophic and dilated cardiomyopathy families. J Genet Couns 2013; 22: 258–267.