HHS Public Access

Author manuscript

Curr Opin Pediatr. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Curr Opin Pediatr. 2017 October ; 29(5): 534–540. doi:10.1097/MOP.0000000000000533.

Genetics of Pediatric Cardiomyopathies

Stephanie M. Ware[1,*]

[1]Departments of Pediatrics and Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN

Abstract

Purpose of review—Pediatric cardiomyopathy is a rare disease with a genetic basis. The purpose of this review is to discuss the current status of genetic findings in the pediatric cardiomyopathy population and present recent progress in utilizing this information for management and therapy.

Recent findings—With increased clinical genetic testing, an understanding of the genetic causes of cardiomyopathy is improving and novel causes are identified. Recent progress in identifying the scope of genetic variation in large population datasets has led to reassessment and refinement of our understanding of the significance of rare genetic variation. As a result, the stringency of variant interpretation has increased, at times leading to revision of previous mutation results. Transcriptome and epigenome studies are elucidating important pathways for disease progression and highlight similarities and differences from adult cardiomyopathy. Therapy targeted toward the underlying cause of cardiomyopathy is emerging for a number of rare syndromes such as Pompe and Noonan syndromes, and genome editing and induced pluripotent stem cells provide promise for additional precision medicine approaches.

Summary—Genetics is moving at a rapid pace in pediatric cardiomyopathy. Genetic testing is increasingly being incorporated into clinical care. While challenges in interpretation of rare genetic variation remains challenging, the opportunity to provide management and therapy targeted toward the underlying genetic cause is beginning to be realized.

Keywords

Genetic variant; genome editing; Noonan syndrome; induced pluripotent stem cells; transcriptome

Introduction

Cardiomyopathy is a rare disease in the pediatric population, estimated to affect 1 in 100,000 individuals.(1, 2) The causes of cardiomyopathy are diverse and include infectious, environmental, and genetic causes. Since the original identification of mutations in *MYH7*, a gene encoding the thick filament ATPase β myosin heavy chain, as causative of hypertrophic cardiomyopathy (HCM) 25 years ago, there has been ongoing discovery of genes that cause

*Corresponding author: Stephanie M. Ware, MD, PhD, Indiana University School of Medicine, 1044 W. Walnut Street, Indianapolis, IN 46202, Phone: 317-274-8938, Fax: 317-274-8679, stware@iu.edu.

Conflicts of interest: None

this disease. The speed of discovery has been enhanced by improved sequencing technologies that allow rapid, efficient, and cost effective testing. As a result, the array of clinically available genetic tests has expanded rapidly. With many of the technical barriers to molecular testing surmounted, the challenge has shifted to improving our interpretation of the consequences of genetic variation.

In addition to mutations that cause isolated or familial cardiomyopathy, inborn errors of metabolism, neuromuscular diseases and genetic syndromes also cause cardiomyopathy in the pediatric population and the differential and diagnostic approach can be complex.(3, 4) Because there is practice variation in the approach to genetic diagnosis, there is still much to be learned about the genetic basis of pediatric cardiomyopathy. Improved genetic diagnostic capabilities promise novel therapeutic approaches and genome editing technologies create prospects for the future. In this review, we will discuss the recent novel findings and interpretive challenges for genetic testing, highlight some important new genetic discoveries across etiologic categories, and present recent progress in utilizing this information for management and therapy.

Isolated non-syndromic cardiomyopathy

Mutations in genes encoding sarcomeric proteins are the primary genetic cause of HCM in adults and likely the most common cause in children as well.(5) Genetic causes of dilated cardiomyopathy (DCM) are identified less frequently, but include genes encoding sarcomeric, cytoskeletal, or desmosomal proteins, amongst others. Restrictive cardiomyopathy (RCM) and arrhythmogenic ventricular cardiomyopathy (AVC) are rarer forms of cardiomyopathy but also are caused by mutations in sarcomeric (RCM) or desmosomal (AVC) genes.

Novel gene discoveries for cardiomyopathy often first occur in adults because of increased disease prevalence in this age group. The genetic architecture of disease in the pediatric population has not been comprehensively studied across all cardiomyopathy phenotypes. Of the cardiomyopathy phenotypes, the genetic basis of HCM is the best understood. *MYH7* and *MYBPC3* are the most common genes with mutations in isolated HCM and the overall diagnostic yield with clinical testing for HCM is high. These two genes appear to account for the largest proportion of pediatric cardiomyopathy cases as well.(6) Single center studies indicate that the yield of genetic testing may be higher in pediatric HCM patients than in adults.(7) Two recent studies have looked at genotype positive, phenotype negative patients to determine the penetrance of HCM and find rates of 6–7% during childhood but caution that severe hypertrophy and cardiac events can develop.(8, 9) Case reports of multiple mutations in pediatric patients with HCM have led to speculation that early onset cardiomyopathy may result from “multiple hits”. A recent retrospective review of sarcomere mutation carriers showed that 25% of patients < 18 had two or more pathogenic or likely pathogenic variants versus 4.8% for adults, but the overall number of pediatric patients studied was small (n=24).(10) To date, many studies are limited by their single site status and the potential ascertainment bias that occurs at tertiary referral centers. Ascertainment bias also exists because genetic assessment and testing of pediatric cardiomyopathy patients is rarely standardized and comprehensive. Numbers at single sites are relatively small, and

comparison of results between centers is difficult because the populations are not identical. A major problem, discussed further below, is that genetic testing interpretation of variant pathogenicity has changed due to new evidence provided by large population based sequencing datasets.(11, 12) Unless retrospective studies reinterpret “mutation positive” patients using updated findings, the likelihood of misclassification is high. Finally, many studies do not age stratify the pediatric patients and this may be important in order to define whether the genetic etiologies and outcomes are different in infants and preadolescent children as compared to adolescent and adult patients.

HCM is classically defined as a disease of the sarcomere. However, in the pediatric population, causes are more heterogenous. It is not rare to identify individuals with *LAMP2* (Danon disease) or *PRKAG2* (cardiac glycogenosis) mutations that result in early, severe hypertrophy. These genetic causes are important to distinguish from sarcomeric mutations because of differences in clinical course and prognosis.(13–15) Similarly, individuals with Noonan syndrome are sometimes diagnosed with this genetic syndrome years after their development of HCM. Because of the increased prevalence of syndromic associations, inborn errors of metabolism, mitochondrial disorders, and neuromuscular disease, evaluation by a medical geneticist is highly recommended for all types of cardiomyopathy, especially in younger children.(4, 16, 17)

The underlying genetic cause of DCM is less frequently identified than for other types of cardiomyopathy. Recent data indicate that in the pediatric population there is no survival difference between familial DCM and idiopathic DCM after adjustment for other factors. (18) However, the majority of patients in this study did not undergo genetic testing and therefore it is unclear whether there might be a survival difference based on genotype. Overall, older age, heart failure, and greater left ventricular dilation at diagnosis were independently associated with increased risk of the combined endpoint of transplantation and death. Determining whether genotype is predictive of outcome is an important future goal.

Mutations in the large cytoskeletal protein titin have emerged as the most common genetic cause of DCM in adults and have also been shown to be a risk factor for peripartum cardiomyopathy.(19–21) The large size of the *TTN* gene, encoding titin, creates challenges for interpretation of rare variants. Progress has been made in identifying protein domains and mutation types that are more likely to be pathogenic if mutated.(20, 22) These findings have not been extended to studies in the pediatric population. In analogy to the peripartum cardiomyopathy findings, it will be interesting to determine whether rare variants in *TTN* are identified at a higher rate in pediatric patients with concomitant stressors such as myocarditis, indicating a genetic susceptibility to the development of disease. Extending genetic analyses outside the structural apparatus of the sarcomere, several genes have been identified relatively recently that suggest new mechanisms of disease causation. For example, mutations in the chaperone protein *BAG3* and the splicing factor *RBM20* are each thought to represent approximately 2% of causes in adult idiopathic DCM. The frequency of mutations in these genes in the pediatric population is not known.

Genetic testing and variant interpretation

Current guidelines recommend genetic testing in children and adults with HCM, and consideration of testing in individuals with DCM or RCM.(23–26) Cardiac surveillance is recommended for first degree relatives. If genetic testing is positive in the patient, then cascade genetic testing of family members is recommended for risk stratification. We previously identified that at a single institution, uptake of cardiac surveillance was significantly higher than uptake of genetic testing for known familial mutations.(27) Khouzam et al. studied factors associated with underutilization of genetic services and identified specific health beliefs and awareness important to facilitate care.(28) Genetic testing is cost effective as part of the care for families with cardiomyopathy (29) and additional investigation of barriers to incorporation of genetic testing into practice is needed.

Genetic testing is probabilistic and results must be interpreted in the context of the patient and family history. Choosing the proper genetic testing requires an understanding of the genes associated with specific cardiomyopathy phenotypes, variable presentations, diagnostic yields of available tests, and the a priori probability of a positive result.(10, 29, 30) Ideally, a medical geneticist, genetic counselor, or other medical provider well versed in cardiovascular genetics and molecular testing should review the interpretation of results. Increasing the genetic literacy among cardiovascular genetic care providers is necessary to improve the provision of care to this patient population.(31)

In 2015, the American College of Medical Genetics and Genomics and the Association for Molecular Pathology released standards for the interpretation of genetic variants identified by clinical testing.(32) These standards delineate 5 potential interpretations for molecular testing results (Table 1) and are intended to improve the consistency of variant interpretation. Interpretation of variants is a rapidly evolving as widespread sequencing efforts and public databases such as the Exome Aggregation Consortium (http://exac.broadinstitute.org), and the 1000 Genomes Project Exome Sequencing Project (http://evs.gs.washington.edu/EVS) lend insight into the frequency of rare variants in the population and allow comparison to cardiomyopathy cohorts.(11, 12, 33, 34) These studies have highlighted that rare genetic variation is, in aggregate, much more common than anticipated and is present to a substantial degree within healthy individuals. There has been a significant effort to reassess past interpretation of genetic variation in cardiomyopathy patients. In some cases, this has led to revision of previous clinical genetic test reports and serves as a reminder that it is imperative to assess testing results in the context of the dynamic family history and to update interpretations frequently. ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) is an important resource for reporting human genetic variation and phenotypes. It allows the deposition of supporting evidence and assertion criteria that aid in the communication about interpretation of human variation and health status. ClinGen (https://www.ncbi.nlm.nih.gov/clinvar/docs/clingen/) reviews data about genotype-phenotype relationships from ClinVar and additional sources and generates a report, including medical actionability. These resources represent important efforts to share genetic and clinical information to inform variant interpretation.

Integrative genomics: the transcriptome in pediatric cardiomyopathy

In addition to novel discoveries at the gene level, there have been important new discoveries resulting from the assessment of the transcriptome in patients with cardiomyopathy. DCM and heart failure in adults is molecularly characterized by transcriptional alterations in metabolic networks; in addition, there are distinct mRNA splicing patterns, including activation of embryonic splicing patterns and alterations in RBM20-mediated splicing in diseased hearts.(35–39) Far less is known about the transcriptome in pediatric hearts. While animal models indicate that fetal and neonatal gene expression differs from adult hearts, the temporal shifts in transcriptional profiles have not been well characterized in pediatric patients. Several recent studies investigate the molecular findings in explanted hearts from children with heart failure and demonstrate age-related differences. Pediatric patients with DCM showed a differential adaptation of the β-adrenergic signaling pathway when compared to adults with DCM or non-failing controls.(40) Specifically, down-regulation of β1- and β2-adrenergic receptors is identified in children, whereas β2-AR expression is maintained in adults. Differences in the phosphorylation status of phospholamban are also noted in children versus adults.(40) Phosphodiesterase isoform expression and responsiveness to phosphodiesterase inhibition also differed in pediatric versus adult samples.(41, 42) Defining normal transcriptional profiles during infancy and other pediatric age ranges is important to better understand how to optimize treatment approaches.

In addition to these investigations in DCM patients, RNA-Seq was recently performed on a cohort of pediatric RCM patients and compared to other forms of adult cardiomyopathy and controls.(43) This identified molecular pathway dysregulation that was common to the cardiomyopathies, as well as those unique to RCM. Transcripts selectively induced in RCM include many known and novel G-protein coupled receptors linked to calcium handling and contractile regulation. In-depth comparisons of alternative splicing implicate RBM20 as a potential mediator of alternative splicing in RCM. Interestingly, the disruption of alternative splicing patterns in pediatric RCM occurs in the inverse direction as in adult DCM. Taken together, these initial investigations of the pediatric cardiomyopathy transcriptome indicate that while there are molecular signatures that overlap with adult cardiomyopathy, phenotype- and age-specific profiles exist that can provide useful mechanistic data for possible intervention.

Epigenetics and pediatric cardiomyopathy

MicroRNAs (miRNAs), noncoding RNAs that consist of 18 to 22 nucleotides, are important regulators of gene expression at the post-transcriptional level and act as important modulators of cardiac hypertrophy, heart failure, and fibrosis.(44) Study of miRNAs in mouse models has shown that overexpression can result in cardiac hypertrophy and heart failure and that deletion can be protective. Upregulation of specific miRNAs can also be seen in patients with heart failure.(45) For these reasons, combined with the fact that miRNAs are relatively stable in the blood, miRNAs have generated interest as circulating biomarkers for use in clinical care. To date, miRNAs have not been well studied in pediatric cardiomyopathy patients, but an early study indicates that children with heart failure have unique miRNA profiles.(46) Long noncoding RNAs (lncRNAs) are another group of RNA

molecules that play important roles in development and disease through their function in the regulation of transcriptional and post-transcriptional events. For example, the mitochondrial lncRNA LIPCAR identified patients undergoing cardiac remodeling who were independently at risk for future cardiovascular deaths.(47) Identifying miRNAs and lncRNAs that are important in the pediatric population and understanding developmental-specific regulation may provide additional insight into epigenetic mechanisms in pediatric cardiomyopathy.

Toward novel disease-specific therapeutics

Precision medicine is increasingly viewed as a means to establish individualized management and therapeutic plans that will lead to improved outcomes. In pediatric cardiomyopathy a first step toward precision medicine is understanding the underlying cause of the patient's disease. Recent progress in disease specific therapeutics has produces some exciting results. For example, infants with Pompe disease are now treated with enzyme replacement therapy (ERT) in order to ameliorate HCM. Early diagnosis is critical in order to optimize outcomes.(48) There is recent evidence that the development of HCM is not limited to the classic infantile-onset disease and that Pompe disease represents a continuum.(49) An interesting recent report also showed the use of ERT for storage caused by a *PRKAG2* mutation.(50)

Whereas treatment of HCM in Pompe disease uses replacement of the deficient enzyme, new therapy in Noonan syndrome and Noonan syndrome with multiple lentigenes (NSML, formerly LEOPARD syndrome) is directed at correcting the dysregulation of RAS-MAPK signaling. Mutations in *PTPN11* are the most common cause of Noonan syndrome, where they result in constitutive activation of the protein. New genes causing Noonan syndrome and related RASopathies continue to be identified (Table 2). In contrast, in NSML mutations in *PTPN11* render the protein catalytically impaired. Greater than 80% of patients with NSML have HCM that is caused by hyperactivation of the AKT/mTOR pathway. Thus mutations in the same gene can both cause HCM but via different mechanisms. This has important therapeutic implications. The ability to prevent HCM was investigated in a mouse model of NSML by early treatment with the mTOR inhibitor rapamycin. Mice treated early did not develop HCM, and those treated at later stages demonstrated reversal of disease.(53) Recently, the first trial of a mTOR inhibitor was reported in an infant with NSML and rapidly progressive HCM. Therapy was initiated with a goal of halting progression of hypertrophy and outflow tract obstruction until transplant.(54) Pathway specific inhibitors allow therapeutics to be tailored to the underlying genetic cause of disease.

Antagomirs, molecules used to inhibit miRNAs, have shown promise in animal models for inhibiting the development and progression of cardiomyopathy. For example, blocking profibrotic miRNAs with antagomirs in a mouse model of HCM resulted in decreased interstitial fibrosis and increased cardiac function. The development of antagomirs for therapeutic use in heart failure is reportedly in preclinical development.(55)

Finally, the ability to perform genome editing has generated substantial enthusiasm about the ability to "correct" mutations and restore normal function. When paired with research using

human induced pluripotent stem cells (iPSC), these new technologies provide opportunities to understand the consequence of a pathogenic variant in the context of the patient's individual genetic variation. For example, recent studies of *TAZ* variants causing Barth syndrome using gene replacement and genome editing in iPSC demonstrated the necessity and sufficiency of the variants for phenotypes including sarcomere assembly and myocardial contraction abnormalities.(56) Human engineered cardiac tissues from a patient with a *BRAF* mutation recapitulated the HCM phenotype, providing a cell culture approach to study disease mechanisms and therapies *in vitro*.(57) Genome editing capabilities have also generated specific interest as a mechanism to correct a mutant allele encoding a structural component of the sarcomere in isolated non-syndromic cardiomyopathy. In a mouse model of HCM, adenoviral constructs were used to silence the mutant allele but not the wild-type allele, ameliorating the disease phenotype.(58) In another study using iPSCs, a mutation in phospholamban was shown to impair cardiomyocyte contractility and targeted genetic correction of the mutation rescued this defect.(59) These studies illustrate the power of combining iPSC and genome editing to understand the functional significance of genetic variation.

Conclusion

Cardiomyopathy is not a single disease but multiple diseases with different underlying causes. Understanding the genetic basis of disease is a critical first step to design patient-specific management and therapy. Improving our ability to interpret genetic variation is necessary to properly assign causality. Ongoing investigation of the transcriptome and epigenome in pediatric patients will provide novel information about disease progression and outcome and may provide novel targets for therapeutic intervention. Genome editing and induced pluripotent stem cells provide novel tools to investigate genetic variation. Several disease-specific or gene-specific approaches have emerged and have promising results.

Acknowledgments

Financial support and sponsorship: SMW is supported by funding from March of Dimes Research Foundation (grant nos. 6-FY13-167 and 6-FY16-176), the National Institutes of Health (P01 HL 134599-01), an American Heart Association Established Investigator Award (AHA 13EIA13460001) and the Indiana University Health—Indiana University School of Medicine Strategic Research Initiative and Physician Scientist Initiative.

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Key points

- Pediatric cardiomyopathy is genetically heterogeneous and may be isolated or occur as part of a syndrome, neuromuscular disorder or metabolic disease.
- Enhanced sequencing capabilities allow rapid identification of novel candidate genes or alleles causing cardiomyopathy; proof of causality is more challenging.
- In aggregate, rare genetic variation is relatively common in the population. Understanding the scope of genetic variation in healthy individuals has allowed refinement and increased stringency of interpretation of variant pathogenicity.
- Transcriptome and epigenome analyses are contributing new information to our understanding of pediatric cardiomyopathy and its similarities to and differences from adult cardiomyopathy.
- Management and therapy directed to the underlying genetic cause of cardiomyopathy is becoming available and highlights the promise of precision medicine.

Table 1

Variant classification	Criteria
Pathogenic	Predicted null variant in gene where loss of function is known disease mechanism; de novo variant; absent in population databases or MAF very low; co-segregation in multiple families; computational predictions support deleterious effect; functional data support deleterious effect
Likely Pathogenic	Criteria similar to pathogenic but with less supporting evidence such as fewer available families for co-segregation data, contradictory computational predictions or weaker functional data
Variant Uncertain Significance	Very low population frequency or absent from databases but lacking co-segregation, computational, and/or functional evidence for pathogenicity
Likely Benign	Allele frequency greater than expected for disease incidence; allele identified in young, healthy individuals; no effect in functional assays; lack of segregation in family members; and/or mutation type not consistent with known disease mechanism
Benign	MAF >5% in ExAC or ESP OR 2 or more of the likely benign criteria

ESP, Exome Sequencing Project; ExAC, Exome Aggregation Consortium; MAF, minor allele frequency. For detailed criteria, see Richards et al. (32)

Table 2

Noonan syndrome and other RASopathies

Gene	% of Patients	Comments
PTPN11	50%	Also causes NSML
SOS1	10–15%	High prevalence of ectodermal abnormalities
RAF1	5%	HCM in > 80%; also causes NSML
RIT1	5%	High incidence of congenital heart disease; HCM in 70%
KRAS	2%	Also associated with CFC syndrome
BRAF	1–2%	Usually seen in CFC syndrome
NRAS	<1%	
A2ML1	unknown	candidate
LZTR1	unknown	candidate
RASA2	unknown	candidate
SOS2	unknown	candidate; ectodermal defects
RRAS		candidate; Noonan like syndrome
HRAS		Costello syndrome; activating mutations
MAP2K1	2%	CFC syndrome
MAP2K2		CFC syndrome
SHOC2	2%	Noonan-like syndrome
CBL		Noonan-like syndrome

CFC, Cardiofaciocutaneous syndrome; NSML, Noonan syndrome with multiple lentigenes; Table compiled from (51, 52) and GeneReviews.