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TOPIC HIGHLIGHT

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Importance of genetic evaluation and testing in pediatric cardiomyopathy

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Abstract

Pediatric cardiomyopathies are clinically heterogeneous heart muscle disorders that are responsible for significant morbidity and mortality. Phenotypes include hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, left ventricular noncompaction and arrhythmogenic right ventricular cardiomyopathy. There is substantial evidence for a genetic contribution to pediatric cardiomyopathy. To date, more than 100 genes have been implicated in cardiomyopathy, but comprehensive genetic diagnosis has been problematic because of the large number of genes, the private nature of mutations, and difficulties in interpreting novel rare variants. This review will focus on current knowledge on the genetic etiologies of pediatric cardiomyopathy and their diagnostic relevance in clinical settings. Recent developments in sequencing technologies are greatly impacting the pace of gene discovery and clinical diagnosis. Understanding the genetic basis for pediatric cardiomyopathy and establishing genotype-phenotype correlations may help delineate the molecular and cellular events necessary to identify potential novel therapeutic targets for heart muscle dysfunction in children.

Key words: Pediatric; Mutation; Exome sequencing; Sarcomere

Core tip: Pediatric cardiomyopathy is a clinically and genetically heterogeneous heart muscle disease with five major phenotypes: hypertrophic cardiomyopathy, dilated cardiomyopathy, restrictive cardiomyopathy, left ventricular noncompaction cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy. The genetic basis of these cardiomyopathies has been identified using traditional linkage analysis and sequencing. Novel gene discovery has been increased using modern next generation sequencing technologies, however the exact mechanisms of disease development are not fully known. In this review we focus on the current genetic knowledge of cardiomyopathies and their importance in diagnostic settings.

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INTRODUCTION

Cardiomyopathy is a clinically heterogeneous disease with a strong genetic component which affects heart muscle[1]. In the pediatric population, 40% of children progress to death or transplantation within 5 years of diagnosis[2-5]. The overall incidence of cardiomyopathy

Table 1 List of important genes involved in cardiomyopathy

Gene	Total coding exons	Encoded protein (AA)	NCBI GenBank accession #	Chromosomal location	Major phenotype
Sarcomere					
MYH7	38	1935	NG_007884	14q11.2	HCM, RCM, DCM, LVNC
MYBPC3	33	1274	NG_007667	11p11.2	HCM, DCM
TNNT2	15	295	NG_007556	1q32.1	HCM, RCM, DCM, LVNC
TPM1	9	284	NG_007557	15q22.2	HCM, DCM
MYL3	6	195	NG_007555	3q21.31	HCM, LVNC
MYL2	7	166	NG_007554	12q24.11	HCM, LVNC
ACTC1	6	377	NG_007553	15q14	HCM, RCM, DCM, LVNC
TNNI3	6	210	NG_007866	19q13.4	RCM
MYH6	37	1939	NC_000014	14q11.2	HCM, DCM
TNNC1	6	161	NG_008963	3p21.1	HCM, DCM, RCM
Desmosome					
JUP	9	563	NG_009090	17q21.2	ARVC
DSP	24	2871	NG_008803	6p24.3	ARVC
PKP2	14	881	NG_009000	12p11.21	ARVC
DSG2	15	1118	NG_007072	18q12.1	ARVC
DSC2	16	901	NG_008208	18q12.1	ARVC
Cytoskeleton, Z-disc, *etc.*					
ACTN2	21	894	NG_009081	1q43	HCM, DCM
DES	9	470	NG_008043	2q35	HCM, RCM, DCM, ARVC
LDB3	13	732	NG_008876	10q23.2	HCM, DCM, LVNC
CSRP3	5	194	NG_011932	11p15.1	HCM, DCM
TCAP	2	167	NG_008892	17q12	DCM
SGCD	8	290	NG_008693	5q33.3	DCM
TTN	311	33423	NG_011618	2q31.2	DCM
DMD	79	3385	NG_012232.1		DCM
MYPN	19	1320	NM_032578.2	10q21.3	HCM, DCM, RCM
PLN	1	52	NG_009082	6q22.31	HCM, DCM, ARVC
VCL	22	1134	NG_008868	10q22.2	HCM, DCM, LVNC
CRYAB	3	175	NG_009824	11q23.1	DCM
CAV3	2	151	NG_008797	3p25.3	HCM
BAG3	4	575	NM_004281.3	10q26.11	DCM
ANKRD1	9	319	NM_014391.2	10q23.31	HCM, DCM
Syndromic					
TAZ	11	292	NG_009634	Xq28	DCM, LVNC
ALMS1	23	4169	NG_011690	2p13.1	
PTPN11	15	593	NG_007459	12q24.13	HCM
RAF1	16	648	NG_007467	3p25.2	HCM, DCM
Others					
LAMP2	9	411	NG_007995	Xq24	HCM, DCM
LMNA	12	664	NG_008692	1q22	DCM, LVNC
EMD	6	254	NG_008677	Xq28	DCM
RYR2	105	4967	NG_008799	1q43	ARVC
ABCC9	38	1549	NG_012819	12p12.1	DCM
SCN5A	27	2015	NG_008934	3p22.2	DCM
TMEM43	12	400	NG_008975	3p25.1	ARVC

in children < 18 years of age in the United States is 1.13 cases per 100000 annually[6,7]. Cardiomyopathy in the pediatric population is diverse and may be caused by a number of different factors, including both genetic and non-genetic etiologies, posing an intense diagnostic challenge to clinicians. As a result, the majority of cases are still considered idiopathic. More than 100 genes have been identified causing cardiomyopathy related phenotypes and these genes belong to diverse molecular pathways, implicating the involvement of contractile proteins, intracellular calcium handling, and myocardial energetics as etiologies (Table 1)[8,9]. Identification of the underlying causes of cardiomyopathy may lead to improved outcomes with disease-specific treatments. A research-based pediatric cardiomyopathy registry (PCMR) identified familial, syndromic, neuromuscular or metabolic causes in 30% of children[10]. In the pediatric population, sarcomeric mutations, genetic syndromes, and other unique causes such as inborn errors of metabolism, mitochondrial disorders, myopathies and neuromuscular disorders all contribute (Table 1)[11]. However, the PCMR longitudinal outcome data on more than 3500 children with cardiomyopathy demonstrated that 60%-70% of these children are still classified as "idiopathic"[4,5,12]. Recently, Kindel *et al*[13] reported that classifying causes of cardiomyopathy can be increased to 70% with incorporation of evaluation by a geneticist and genetic testing. Because of the inclusion of syndromic, metabolic, and neuromuscular etiologies, genetic causes of pediatric cardiomyopathy are more heterogeneous than adult-onset

cardiomyopathy but also encompass the majority of genetic causes that result in isolated cardiomyopathy in adults (*e.g.*, sarcomeric or cytoskeletal gene mutations)[14]. In the pediatric population, the same genetic causes that result in isolated (also termed familial) cardiomyopathy in adults are prevalent, including causes of hypertrophic cardiomyopathy (HCM; > 35% yield with sarcomeric gene panel testing) or dilated cardiomyopathy (DCM; > 20% yield with current large DCM gene panels used for testing in adults). The genetic screening of these patients for known cardiomyopathy genes helps diagnostic screening of family members, family-based risk assessment, and disease-management[13,15,16]. Historically, this immense genetic and allelic heterogeneity has made molecular analyses difficult, expensive, and time-consuming due to low throughput of traditional sequencing technologies. However, recent advances in sequencing technologies provide rapid, accurate, and cost-effective DNA sequencing. The majority of the clinical diagnostic laboratories are now adopting next generation technologies for their routine gene testing in cardiomyopathy and focusing on coding regions. It is estimated that about 85% of disease-causing mutations lie within the protein-coding regions of the human genome[17-19].

Cardiomyopathy is classified into 5 clinical phenotypes: HCM, DCM, restrictive cardiomyopathy (RCM), left ventricular noncompaction cardiomyopathy (LVNC), and arrhythmogenic right ventricular cardiomyopathy (ARVC)[20,21]. Although these are clinically distinct entities, there is evidence for genetic overlap among them. For example, mutations in beta myosin heavy chain (*MYH7*) are most commonly associated with HCM and DCM but have also been reported in RCM[14,22] and LVNC[23-25]. The majority of pediatric cardiomyopathy cases exhibit dilated (50%) or hypertrophic (42%) phenotypes[6,26]. The PCMR is a valuable source for this population in terms of outcome and clinical features. In this review we will focus on the genetic causes of cardiomyopathy in the pediatric population.

HCM

HCM is the most prevalent inherited cardiac disorder and is defined as the presence of unexplained left ventricular hypertrophy (LVH), a primary myocardial process, with myocyte disarray and fibrosis. Fibrosis is a common endpoint in the pathological process of HCM. HCM was the first cardiomyopathy with a specific genetic etiology identified[27,28]. HCM is also considered the most common cause of sudden cardiac death in young, healthy and athletic individuals[29]. In adults, the diagnosis of HCM implies a sarcomeric gene mutation as the underlying etiology. However, in children, HCM is a heterogenous group of disorders encompassing conditions with diverse genetic origins and clinical phenotypes, including associations with inborn errors of metabolism, neuromuscular disorders, and malformation syndromes[6,10,13,30,31]. This is an important clinical distinction since patients classified in the metabolic, syndromic, or neuromuscular categories have additional medical management needs. At times, these conditions may require a high level of clinical suspicion in order to diagnose at early ages. For example, at our institution, the incorporation of genetic evaluation into the cardiomyopathy population led to the diagnosis of Noonan syndrome or Noonan syndrome with multiple lentigines in several adolescents and young adults who had been followed since early childhood with presumed isolated sarcomeric HCM and who had only very subtle features of a syndromic cause. These diagnoses also have substantial implications for family based cardiac screening recommendations.

HCM is frequently inherited in an autosomal dominant manner with hundreds of mutations affecting more than 27 genes identified to date (Table 1). Over 1000 distinct mutations in sarcomeric genes (*MYBPC3, MYH7, TNNT2, TPM1, ACTC1, TNNI3, TTN, MYL2*) of the contractile apparatus are known to cause adult-onset HCM[32,33] leading to the paradigm that HCM is a disease of the sarcomere[34,35]. Mutations in *MYH7*, encoding beta-myosin heavy chain, and in *MYBPC3*, encoding cardiac myosin-binding protein C, are the most common, each accounting for approximately 40% of all cases and nearly 80% of all mutation positive cases; the remaining seven genes each account for less than 1% to 5% of cases and collectively 10% of cases[36]. Overall, pathogenic mutations have been identified in 50%-70% of HCM cases[37]. Mutations found in these genes are generally missense, incorporating a mutated protein into the sarcomere. An exception is the *MYBPC3* gene, in which half of the mutations are truncations causing haploinsufficiency of the protein[38,39]. Interestingly, in the pediatric population, *MYBPC3* truncating mutations are less common and missense mutations predominate. Until recently, mutations in the sarcomeric machinery were thought to cause HCM in adults only and not contribute significantly to the development of HCM in young children[40]. However, two independent reports have shown that as many as 50% of pediatric HCM cases harbor mutations in sarcomeric genes and 17% of patients with these sarcomeric mutations were diagnosed in the first year of life[14,41], suggesting that sarcomere gene mutations are important cause of HCM both in adults and pediatric populations. Following this, Kindel *et al*[13] reported sarcomeric gene mutations as the major cause of disease in pediatric HCM patients with a family history of the disease. Non-genetic causes rarely cause HCM in children although LVH can occur in response to some environmental triggers, such as transient LVH in infants of diabetic mothers[42]. Both RCM and HCM are characterized by diastolic dysfunction and some reports suggest a clinical overlap with distinct clinical outcomes for patients who exhibit HCM with restrictive physiology[43,44]. In some families, distinct HCM and RCM phenotypes segregate with the same disease causing sarcomeric mutation[45]. Recently, risk factors for the outcomes of death or transplantation were reported for the largest pediatric HCM cohort studied to date[26]. The

results demonstrated that risk was greatest for those who presented as infants, those with inborn errors of metabolism, or those with mixed HCM phenotypes (HCM and DCM or HCM with restrictive physiology). Interestingly, children with mixed HCM with DCM or RCM phenotype frequently have a family history of the disease including family members with isolated HCM or mixed phenotypes[26], suggesting that even in families with Mendelian inheritance of cardiomyopathy, more complex genetic interactions occur to determine phenotype, with genetic modifier factors involved.

In the pediatric population, if metabolic or syndromic causes are ruled out as etiologies, HCM is considered a familial disease caused by the same genes that are causal for isolated cardiomyopathy in adults. The diagnosis of HCM in a child with suspected isolated cardiomyopathy should prompt evaluation of the first-degree relatives[46,47]. Current guidelines indicate that cascade cardiac screening and genetic testing are indicated in this patient population. These cascade screening and testing approaches have been applied particularly successfully in the Netherlands, where a founder *MYBPC3* mutation results in an identifiable at risk population[48]. Miller *et al*[49], assessed the success of cascade cardiac screening and genetic testing in a pediatric population in the United States, the first study to examine this approach in the United States. Cardiac screening of at-risk relatives in HCM families identified disease in a subset of asymptomatic relatives (25%). Interestingly, the study found that the uptake of cardiac screening was significantly higher than the uptake of genetic testing. The reasons for this are unclear given that known familial mutation genetic testing is substantially less expensive than an echocardiogram in the Unites States and also takes less time for the actual procedure (blood draw as compared to echocardiogram). Additional studies are important to determine the best delivery methods of cost effective familial screening and appropriate genetic testing.

RCM

RCM is a rare and distinct form of cardiomyopathy characterized by diastolic dysfunction but intact systolic function until later stages of the disease. The main features are marked atrial enlargement, and normal ventricular wall thickness (no hypertrophy)[50]. It accounts for less than 5% of all cardiomyopathies in the United States and Europe[51,52]. RCM is also an uncommon cardiomyopathy in children, accounting for approximately 3%-5% of all cardiomyopathy cases. Among the different types of cardiomyopathies, RCM has the worst prognosis, especially in pediatric cases where heart transplantation is often the only effective treatment[44,52,53]. To date, dominant mutations causing pediatric RCM have been reported with *DES*, *ACTC1*, *TNNI3*, *TNNT2*, and *MYH7* genes, but the majority of cases are considered idiopathic[8,22,54]. Recently, a *de novo* mutation in titin (*TTN*) was reported causing familial RCM[55]. Webber *et al*[52] described the largest RCM cohort (n = 152; 4.5% of all pediatric cardiomyopathy cases within the PCMR cohort) with one-fourth with a family history of the disease, indicating a genetic contribution to the disease, and one-third (n = 51) with a mixed/overlapping phenotype of RCM/HCM, suggesting that additional shared genetic causes may exist. One of the interesting questions for future research will be to understand how mutations in the same gene can cause distinct phenotypes. For example, mutations in *MYH7* can cause HCM, RCM, DCM, or LVNC. Possible explanations include mutation location resulting in protein domain specific phenotypic effects or effects of genetic modifiers. Future research will further delineate the consequences of specific mutations by highlighting the effects on protein-protein interactions and more precisely delineating specific patterns of genetic network dysregulation in response to mutational change.

DCM

DCM is characterized by left ventricular dilation and systolic dysfunction. The estimated annual incidence of DCM in children is 0.57 cases per 100000, with overall poor prognosis, and with 40% of children undergoing cardiac transplant or dying before 5 years post-diagnosis[4,6,10,56,57]. Pediatric DCM is the commonest form of cardiomyopathy, accounting for approximately 60% of all cases[58]. While environmental causes (predominantly related to infections resulting in myocarditis) contribute substantially to DCM in the pediatric population, a significant family history of DCM is not uncommon in pediatric patients, and the same genes that cause DCM in adults have been shown to lead to earlier onset DCM as well[59,60]. DCM is the most genetically heterogeneous of all cardiomyopathies with all Mendelian patterns of inheritance represented (autosomal dominant, autosomal recessive, X-linked, and mitochondrial)[61,62]. Neuromuscular causes of DCM, such as Duchenne muscular dystrophy, are relatively common in the pediatric population. In addition, inborn errors of metabolism and mitochondrial disorders underlie up to 10%-15% of cases in the pediatric population[13]. Syndromic causes of DCM are rare but do occur and are likely under-recognized[63]. Genetic causes of familial DCM are identified in approximately 30% of cases. To date, more than 40 genes have been identified for non-syndromic forms of DCM in adults, though only 3 of them (*TNNI3, GATAD1* and *DOLK*) show autosomal recessive inheritance[64-66]. Genetic causes of autosomal recessive forms of DCM have rarely been identified, although they are thought to explain approximately 16% of familial DCM and contribute to sudden cardiac death and heart failure, especially in the pediatric population. DCM is predominantly caused by mutations in genes encoding cytoskeletal and sarcomeric proteins[67-69]. Recently, heterozygous truncating mutations in *TTN* were reported in 25% of DCM cases, suggesting that the diagnostic yield for DCM might increase substantially with the addition of *TTN* sequenc-

ing to current gene testing panels[70,71]. However, truncating *TTN* mutations have been also reported in 3% of a healthy control populations[70], raising the possibility of a complex genetic model for DCM and posing a problem for clinical interpretation of many *TTN* variants. The prevalence of mutations in *TTN* has not been reported in children with DCM, although clearly there are shared genetic causes. Identification of the genetic causation of DCM allows for appropriate surveillance in neonates, infants, and children with DCM.

The Heart Failure Society of America has published recommended guidelines for genetic evaluation of DCM including family history, periodic cardiovascular screening of at-risk family members, and consideration of genetic counseling for DCM patients, and, when applicable, their family members. Upon targeted gene testing, unaffected family members with positive genetic testing results should undergo cardiac screening once a year. If mutation testing in the proband is negative or not performed, first degree relatives should undergo cardiac screening every 3-5 years[62]. Gene panels for DCM are quite large with > 50 genes available. However, these panels do not typically include the most common neuromuscular, syndromic, and metabolic causes of DCM in childhood, making it important to identify a differential with regard to cause and perform the correct testing to address suspected cause. This requires an understanding of the most common causes of DCM, careful attention to phenotyping beyond the cardiac condition, and knowledge of different types of genetic testing in order to facilitate the most appropriate and/or tiered testing as applicable.

ARVC

ARVC is characterized by a high incidence of ventricular arrhythmia and sudden death with an estimated prevalence of 1:2000 to 1:5000 in the general population[72,73]. ARVC is an inherited disorder with a family history in 30% to 50% of the cases (Klauke, 2010). ARVC is predominately reported as autosomal dominant trait, though autosomal recessive cases have been observed, frequently with syndromic features including cutaneous findings. ARVC has been considered a desmosomal disease caused by mutations in five desmosomal genes (*PKP2*, *DSP*, *JUP*, *DSG2*, *DSC2*) in approximately 50% of total cases, however other non-desmosomal genes are known to be responsible for the disease (*TMEM43, PLN, RYR2, LMNA, TTN, CTNNA3, TBF-β3*)[74-80]. ARVC is not frequently found in the pediatric population, however a recent Danish nationwide study reported sudden cardiac death in children (n = 4) due to ARVC[81].

LVNC

LVNC is a distinct rare form of primary cardiomyopathy with a genetic origin which is characterized by excessive trabeculation of the left ventricular myocardium, progressive myocardial dysfunction, and early mortality. Clinical presentation includes arrhythmia and sudden cardiac death. Current studies in children estimate that LVNC accounts for approximately 9% of newly diagnosed cardiomyopathies[58,82]. Recently, Brescia *et al*[83] retrospectively reported a cohort of pediatric LVNC (n = 242) with a high mortality rate and a strong association with arrhythmias. Criteria for "excessive" trabeculation have been proposed, but the diagnosis of LVNC is often more controversial than other cardiomyopathy phenotypes. In addition, LVNC may present as a mixed cardiomyopathy seen in combination with DCM or HCM, or may present in conjunction with congenital heart defects[84].

LVNC is a genetically heterogeneous disease that may be inherited in an X-linked, recessive, or autosomal dominant pattern. To date, genetic causes of LVNC have been implicated in genes encoding sarcomeric, cytoskeletal, sodium channel and unknown function proteins, *i.e.*, tafazzin, *DTNA, LDB3, ACTC1, MYH7, TNNT2*, and *SCN5A*[84]. The identification of LVNC in patients with mitochondrial disorders is not uncommon, as was initially seen for patients with Barth syndrome, caused by mutations in tafazzin. Mitochondrial genome mutations have also been revealed in patients with isolated LVNC as evident by biopsies from patients with mitochondrial abnormalities[85]. These causes of LVNC are rare in the general population and the genetic basis of disease remains unknown in a large proportion of patients. We screened 31 cardiomyopathy genes (sarcomeric and non-sarcomeric) in 23 childhood isolated LVNC patients using a custom next generation sequencing platform. This identified 13 previously known and 10 novel disease-causing mutations in 18 patients, predominantly in the *MYBPC3* gene (unpublished results). Further extensive genetic analyses will unravel novel and previously associated with other types of cardiomyopathy cause for LVNC, supporting the hypothesis of shared genetic etiology of cardiomyopathies.

CLINICAL GENETIC TESTING IN CARDIOMYOPATHY

Progress in understanding the genetic basis of cardiomyopathy enhances the value of clinical genetic testing and provides the clinician an additional route to diagnose individuals at risk for cardiomyopathy and understand pathogenesis. Newer technologies are influencing cardiomyopathy genetic testing, where an increased number of genes are now routinely being tested simultaneously, and enhancing the diagnostic yield and utility. However, simple statistics dictate that the more genes that are tested, the more variants of uncertain significance (VUS) will be discovered. VUS results can present a clinical challenge for care providers not comfortable with genetic testing results and can also present challenges for discussion and interpretation for families. Targeted next-generation based sequencing for cardiomyopathy gene panels are available through various laboratories in the United States and worldwide (http://www.genetests.org

and http://www.ncbi.nlm.nih.gov/gtr). Genetic testing in HCM has the highest diagnostic yield and therefore clinical utility[86]. The yield of current testing is approximately approximately 60% for familial and approximately 40% for sporadic HCM cases[36]. The Heart Rhythm Society and European Heart Rhythm Association guidelines recommended the comprehensive screening of 5 sarcomere genes (*MYBPC3, MYH7, TPM1, TNNI3, TNNT2*) for HCM[87], although these recommendations pre-date the rapid expansion in the number of genes tested on current clinical gene panels. Currently, genotype-phenotype correlations in HCM are controversial although there is a general consensus that incorporation of the genetic testing results should be part of management discussions. The sophistication to provide a specific prognosis based on, for example, a mutation in the N-terminal *vs* C-terminal domain of *MYH7* is not currently present. However, genotype-phenotype correlations exist for certain genes. For example, mutations in *LMNA* may result in a number of extra-cardiac features that require surveillance and management, but patients with these mutations may present with isolated DCM. Genetic testing of HCM is particularly useful for screening potential at risk first-degree relatives and subsequent cascade testing of family members as indicated. In a recent Danish study, child relatives (< 18 years of age) of HCM families were assessed based on clinical and predictive genetic testing and 6% of the asymptomatic relatives at-risk of HCM were found to develop HCM after a 12-year follow-up[16]. Hofman *et al*[15] assessed the yield of genetic testing in 648 HCM families from the Netherlands and found a 46% yield for positive genetic testing in probands with cascade screening of mutation positive families revealing 489 mutation-positive subjects over a 15-year follow-up. In DCM, the mutation spectrum is broader and detection rates are less than HCM owing to higher locus and allelic heterogeneity. However recent novel gene discoveries (for example *BAG3, RBM20*) are resulting in continuous additions to DCM gene panels. Also, the recent discovery of the high contribution of *TTN* mutations (25% familial and 18% sporadic) to DCM may increase the mutation detection rates in genetic testing panels to closer to that of HCM although the rates of *TTN* mutations segregating with disease need to be validated in larger populations[70].

CHALLENGES INTO THE GENETICS OF PEDIATRIC CARDIOMYOPATHY

Despite the advancements in genetic and genomic technologies, multiple challenges remain in order to clearly delineate the complete genetic etiologies responsible for pediatric cardiomyopathy. Pediatric cardiomyopathy is a very heterogeneous entity with variable phenotypes are seen within and between families even with identical genetic causes. Another complicating factor is the complex genetics of the disease. Although the majority of known isolated cardiomyopathy cases are caused by single gene mutations, it is important to remember that variants in more than one gene may be involved in disease causation. Identifying genetic modifiers is the next important step in pediatric cardiomyopathy genetic research and may be important to identify the causes of phenotypic variability within members of the same family. The high cost of traditional sequencing technologies posed a severe limitation to the discovery of new disease genes and screening of known disease genes in the past. New technology circumvents this hurdle, but the current challenge is to provide accurate and clinically useful interpretation of the variants identified in order to maximize the clinical utility of testing. Of course, the reproducibility of the next generation sequencing such as exome sequencing, is very high, however we do not have a complete expertise to identify the causative culprits from thousands of genetic variants. Differentiation of pathogenic variants, disease modifiers, and rare, benign variants in the deluge of data emerging from increasingly accessible novel sequencing technologies (> 80 K variants per exome and approximately 3 million per whole genome) is a challenge. This requires another tier of extensive research to understand the nature of disease causing variants available from advanced high-throughput sequencers. In this context, the involvement of pediatric cardiologists is very important in order to provide careful and comprehensive phenotypic information before genetic testing and/or evaluation. Finally, delineating the complex interplay of genes and environment and their relative contribution to phenotypic presentation and disease course is important for management and prognosis.

CONCLUSION

Modern genomics and human genetics have the capability to decipher the complete genetic anatomy of heritable pediatric cardiomyopathy. Early diagnosis and identification of at risk individuals is important as the clinical implications and outcomes may vary depending on both the gene and mutation type. While next-generation sequencing technologies have increased the capacity of genetic testing by an order of magnitude, we need extensive phenotyping expertise in order to inform novel gene discovery and interpretation of identified variants. In addition, genetic counseling of affected families is critical to facilitate testing and ensure appropriate pre- and post-test understanding of testing implications and results. Identification of the genetic modifiers is an important step toward a personalized medicine approach, but will require analysis of large cohorts using newer sequence capture technologies. Identification of the molecular etiology will allow sub-classification of pediatric cardiomyopathy based on cause. Understanding rare variants and SNPs that modify disease presentation and progression hold the promise of allowing new therapies to be developed.

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