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**Importance of genetic evaluation and testing in pediatric cardiomyopathy**

Tariq M *et al.* Genetic 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.

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**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](#_ENREF_1)]. In the pediatric population, 40% of children progress to death or transplantation within 5 years of diagnosis[[2-5](#_ENREF_2)]. The overall incidence of CM in children < 18 years of age in the United States is 1.13 cases per 100000 annually[[6](#_ENREF_6),[7](#_ENREF_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](#_ENREF_8),[9](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_4),[5](#_ENREF_5),[12](#_ENREF_12)]. Recently, Kindel *et al*[[13](#_ENREF_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](#_ENREF_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](#_ENREF_13),[15](#_ENREF_15),[16](#_ENREF_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 (NGS) 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](#_ENREF_17)].

Cardiomyopathy is classified into 5 clinical phenotypes: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), left ventricular noncompaction cardiomyopathy (LVNC), and arrhythmogenic right ventricular cardiomyopathy (ARVC)[[20](#_ENREF_20),[21](#_ENREF_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](#_ENREF_14),[22](#_ENREF_22)] and LVNC[[23-25](#_ENREF_23)]. The majority of pediatric cardiomyopathy cases exhibit dilated (50%) or hypertrophic (42%) phenotypes[[6](#_ENREF_6),[26](#_ENREF_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.

**HYPERTROPHIC CARDIOMYOPATHY**

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 end-point in the pathological process of HCM. HCM was the first cardiomyopathy with a specific genetic etiology identified[[27](#_ENREF_27),[28](#_ENREF_28)]. HCM is also considered the most common cause of sudden cardiac death in young, healthy and athletic individuals[[29](#_ENREF_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](#_ENREF_6),[10](#_ENREF_10),[13](#_ENREF_13),[30](#_ENREF_30),[31](#_ENREF_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 LEOPARD syndrome 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](#_ENREF_32),[33](#_ENREF_33)] leading to the paradigm that HCM is a disease of the sarcomere[[34](#_ENREF_34),[35](#_ENREF_35)]. Mutations in *MYH7*, encoding beta-myosin heavy chain, and in *MYBPC3*, encoding cardiac myosin-binding protein C (cMyBP-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](#_ENREF_36)]. Overall, pathogenic mutations have been identified in 50%-70% of HCM cases[[37](#_ENREF_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](#_ENREF_38),[39](#_ENREF_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](#_ENREF_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](#_ENREF_14),[41](#_ENREF_41)], suggesting that sarcomere gene mutations are important cause of HCM both in adults and pediatric populations. Following this, Kindel *et al*[[13](#_ENREF_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](#_ENREF_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](#_ENREF_43),[44](#_ENREF_44)]. In some families, distinct HCM and RCM phenotypes segregate with the same disease causing sarcomeric mutation[[45](#_ENREF_45)]. Recently, risk factors for the outcomes of death or transplantation were reported for the largest pediatric HCM cohort studied to date[[26](#_ENREF_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](#_ENREF_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](#_ENREF_46),[47](#_ENREF_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](#_ENREF_48)]. Miller *et al*[[49](#_ENREF_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.

**RESTRICTIVE CARDIOMYOPATHY**

Restrictive cardiomyopathy (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](#_ENREF_50)]. It accounts for less than 5% of all cardiomyopathies in the United States and Europe[[51](#_ENREF_51),[52](#_ENREF_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](#_ENREF_44),[52](#_ENREF_52),[53](#_ENREF_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](#_ENREF_8),[22](#_ENREF_22),[54](#_ENREF_54)]. Recently, a *de novo* mutation in titin (*TTN*) was reported causing familial RCM[[55](#_ENREF_55)]. Webber *et al*[[52](#_ENREF_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.

**DILATED CARDIOMYOPATHY**

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](#_ENREF_4),[6](#_ENREF_6),[10](#_ENREF_10),[56](#_ENREF_56),[57](#_ENREF_57)]. Pediatric DCM is the commonest form of cardiomyopathy, accounting for approximately 60% of all cases[[58](#_ENREF_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](#_ENREF_59),[60](#_ENREF_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](#_ENREF_61),[62](#_ENREF_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](#_ENREF_13)]. Syndromic causes of DCM are rare but do occur and are likely under-recognized[[63](#_ENREF_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](#_ENREF_64)]. 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](#_ENREF_67)]. 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* sequencing to current gene testing panels[[70](#_ENREF_70),[71](#_ENREF_71)]. However, truncating *TTN* mutations have been also reported in 3% of a healthy control populations[[70](#_ENREF_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](#_ENREF_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.

**ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY**

Arrhythmogenic Right Ventricular Cardiomyopathy (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](#_ENREF_72),[73](#_ENREF_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](#_ENREF_74)]. 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](#_ENREF_81)].

**LEFT VENTRICULAR NON-COMPACTION CARDIOMYOPATHY**

Left ventricular non-compaction (LVNC) is a distinct rare form of primary cardiomyopathy with a genetic origin and 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](#_ENREF_58),[82](#_ENREF_82)]. Recently, Brescia *et al*[[83](#_ENREF_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](#_ENREF_84)].

LVNC is a genetically heterogeneous disease more 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 (*TAZ*), *DTNA, LDB3, ACTC1, MYH7, TNNT2, and SCN5A*[[84](#_ENREF_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](#_ENREF_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 US 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](#_ENREF_86)]. The yield of current testing is approximately approximately 60% for familial and approximately 40% for sporadic HCM cases[[36](#_ENREF_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](#_ENREF_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](#_ENREF_16)]. Hofman *et al*[[15](#_ENREF_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](#_ENREF_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 in terms of variable phenotypes within the same family as well as between families with identical genetic causes, diverse genetic causes, and bad outcomes in comparison to the adult population. 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 mutations, disease modifiers, and rare, benign variants in the deluge of data emerging from increasingly accessible novel sequencing technologies (> 80K 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.

**REFERENCES**

1 **Towbin JA**, Bowles NE. The failing heart. *Nature* 2002; **415**: 227-233 [PMID: 11805847 DOI: 10.1038/415227a]

2 **Arola A**, Jokinen E, Ruuskanen O, Saraste M, Pesonen E, Kuusela AL, Tikanoja T, Paavilainen T, Simell O. Epidemiology of idiopathic cardiomyopathies in children and adolescents. A nationwide study in Finland. *Am J Epidemiol* 1997; **146**: 385-393 [PMID: 9290498]

3 **Daubeney PE**, Nugent AW, Chondros P, Carlin JB, Colan SD, Cheung M, Davis AM, Chow CW, Weintraub RG. Clinical features and outcomes of childhood dilated cardiomyopathy: results from a national population-based study. *Circulation* 2006; **114**: 2671-2678 [PMID: 17116768 DOI: 10.1161/CIRCULATIONAHA.106.635128]

4 **Towbin JA**, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, Messere J, Cox GF, Lurie PR, Hsu D, Canter C, Wilkinson JD, Lipshultz SE. Incidence, causes, and outcomes of dilated cardiomyopathy in children. *JAMA* 2006; **296**: 1867-1876 [PMID: 17047217 DOI: 10.1001/jama.296.15.1867]

5 **Colan SD**, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, Lurie PR, Orav EJ, Towbin JA. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. *Circulation* 2007; **115**: 773-781 [PMID: 17261650 DOI: 10.1161/CIRCULATIONAHA.106.621185]

6 **Wilkinson JD**, Landy DC, Colan SD, Towbin JA, Sleeper LA, Orav EJ, Cox GF, Canter CE, Hsu DT, Webber SA, Lipshultz SE. The pediatric cardiomyopathy registry and heart failure: key results from the first 15 years. *Heart Fail Clin* 2010; **6**: 401-13, vii [PMID: 20869642 DOI: 10.1016/j.hfc.2010.05.002]

7 **Roger VL**, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J. Heart disease and stroke statistics--2011 update: a report from the American Heart Association. *Circulation* 2011; **123**: e18-e209 [PMID: 21160056 DOI: 10.1161/CIR.0b013e3182009701]

8 **Tariq M**, Le T, Putnam P, Kindel SJ, Jamison C, Keddache M, Ware SM. Targeted capture and massively parallel sequencing in pediatric cardiomyopathy: development of novel diagnostics. *Cardiogenetics* 2012: **2:** 32-41

9 **Teekakirikul P**, Kelly MA, Rehm HL, Lakdawala NK, Funke BH. Inherited cardiomyopathies: molecular genetics and clinical genetic testing in the postgenomic era. *J Mol Diagn* 2013; **15**: 158-170 [PMID: 23274168 DOI: 10.1016/j.jmoldx.2012.09.002]

10 **Lipshultz SE**, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, Lurie PR, McCoy KL, McDonald MA, Messere JE, Colan SD. The incidence of pediatric cardiomyopathy in two regions of the United States. *N Engl J Med* 2003; **348**: 1647-1655 [PMID: 12711739 DOI: 10.1056/NEJMoa021715]

11 **Colan SD.** Clinical Issues in the Pediatric Hypertrophic Cardiomyopathies. *Prog Pediatr Cardiol* 2009; **25**: 27-29 [PMID: 20161173 DOI: 10.1016/j.ppedcard.2007.11.004]

12 **Cox GF**, Sleeper LA, Lowe AM, Towbin JA, Colan SD, Orav EJ, Lurie PR, Messere JE, Wilkinson JD, Lipshultz SE. Factors associated with establishing a causal diagnosis for children with cardiomyopathy. *Pediatrics* 2006; **118**: 1519-1531 [PMID: 17015543 DOI: 10.1542/peds.2006-0163]

13 **Kindel SJ**, Miller EM, Gupta R, Cripe LH, Hinton RB, Spicer RL, Towbin JA, Ware SM. Pediatric cardiomyopathy: importance of genetic and metabolic evaluation. *J Card Fail* 2012; **18**: 396-403 [PMID: 22555271 DOI: 10.1016/j.cardfail.2012.01.017]

14 **Morita H**, Rehm HL, Menesses A, McDonough B, Roberts AE, Kucherlapati R, Towbin JA, Seidman JG, Seidman CE. Shared genetic causes of cardiac hypertrophy in children and adults. *N Engl J Med* 2008; **358**: 1899-1908 [PMID: 18403758 DOI: 10.1056/NEJMoa075463]

15 **Hofman N**, Tan HL, Alders M, Kolder I, de Haij S, Mannens MM, Lombardi MP, Dit Deprez RH, van Langen I, Wilde AA. Yield of molecular and clinical testing for arrhythmia syndromes: report of 15 years' experience. *Circulation* 2013; **128**: 1513-1521 [PMID: 23963746 DOI: 10.1161/CIRCULATIONAHA.112.000091]

16 **Jensen MK**, Havndrup O, Christiansen M, Andersen PS, Diness B, Axelsson A, Skovby F, Køber L, Bundgaard H. Penetrance of hypertrophic cardiomyopathy in children and adolescents: a 12-year follow-up study of clinical screening and predictive genetic testing. *Circulation* 2013; **127**: 48-54 [PMID: 23197161 DOI: 10.1161/CIRCULATIONAHA.111.090514]

17 **Ng SB**, Buckingham KJ, Lee C, Bigham AW, Tabor HK, Dent KM, Huff CD, Shannon PT, Jabs EW, Nickerson DA, Shendure J, Bamshad MJ. Exome sequencing identifies the cause of a mendelian disorder. *Nat Genet* 2010; **42**: 30-35 [PMID: 19915526 DOI: 10.1038/ng.499]

18 **Ng SB**, Turner EH, Robertson PD, Flygare SD, Bigham AW, Lee C, Shaffer T, Wong M, Bhattacharjee A, Eichler EE, Bamshad M, Nickerson DA, Shendure J. Targeted capture and massively parallel sequencing of 12 human exomes. *Nature* 2009; **461**: 272-276 [PMID: 19684571 DOI: 10.1038/nature08250]

19 **Tariq M**, Belmont JW, Lalani S, Smolarek T, Ware SM. SHROOM3 is a novel candidate for heterotaxy identified by whole exome sequencing. *Genome Biol* 2011; **12**: R91 [PMID: 21936905 DOI: 10.1186/gb-2011-12-9-r91]

20 **Callis TE**, Jensen BC, Weck KE, Willis MS. Evolving molecular diagnostics for familial cardiomyopathies: at the heart of it all. *Expert Rev Mol Diagn* 2010; **10**: 329-351 [PMID: 20370590 DOI: 10.1586/erm.10.13]

21 **Maron BJ**, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation* 2006; **113**: 1807-1816 [PMID: 16567565 DOI: 10.1161/CIRCULATIONAHA.106.174287]

22 **Ware SM**, Quinn ME, Ballard ET, Miller E, Uzark K, Spicer RL. Pediatric restrictive cardiomyopathy associated with a mutation in beta-myosin heavy chain. *Clin Genet* 2008; **73**: 165-170 [PMID: 18076673 DOI: 10.1111/j.1399-0004.2007.00939.x]

23 **Hoedemaekers YM**, Caliskan K, Majoor-Krakauer D, van de Laar I, Michels M, Witsenburg M, ten Cate FJ, Simoons ML, Dooijes D. Cardiac beta-myosin heavy chain defects in two families with non-compaction cardiomyopathy: linking non-compaction to hypertrophic, restrictive, and dilated cardiomyopathies. *Eur Heart J* 2007; **28**: 2732-2737 [PMID: 17947214 DOI: 10.1093/eurheartj/ehm429]

24 **Hoedemaekers YM**, Caliskan K, Michels M, Frohn-Mulder I, van der Smagt JJ, Phefferkorn JE, Wessels MW, ten Cate FJ, Sijbrands EJ, Dooijes D, Majoor-Krakauer DF. The importance of genetic counseling, DNA diagnostics, and cardiologic family screening in left ventricular noncompaction cardiomyopathy. *Circ Cardiovasc Genet* 2010; **3**: 232-239 [PMID: 20530761 DOI: 10.1161/CIRCGENETICS.109.903898]

25 **Klaassen S**, Probst S, Oechslin E, Gerull B, Krings G, Schuler P, Greutmann M, Hürlimann D, Yegitbasi M, Pons L, Gramlich M, Drenckhahn JD, Heuser A, Berger F, Jenni R, Thierfelder L. Mutations in sarcomere protein genes in left ventricular noncompaction. *Circulation* 2008; **117**: 2893-2901 [PMID: 18506004 DOI: 10.1161/CIRCULATIONAHA.107.746164]

26 **Lipshultz SE**, Orav EJ, Wilkinson JD, Towbin JA, Messere JE, Lowe AM, Sleeper LA, Cox GF, Hsu DT, Canter CE, Hunter JA, Colan SD. Risk stratification at diagnosis for children with hypertrophic cardiomyopathy: an analysis of data from the Pediatric Cardiomyopathy Registry. *Lancet* 2013; **382**: 1889-1897 [PMID: 24011547 DOI: 10.1016/S0140-6736(13)61685-2]

27 **Epstein ND**, Cohn GM, Cyran F, Fananapazir L. Differences in clinical expression of hypertrophic cardiomyopathy associated with two distinct mutations in the beta-myosin heavy chain gene. A 908Leu----Val mutation and a 403Arg----Gln mutation. *Circulation* 1992; **86**: 345-352 [PMID: 1638703]

28 **Watkins H**, Rosenzweig A, Hwang DS, Levi T, McKenna W, Seidman CE, Seidman JG. Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy. *N Engl J Med* 1992; **326**: 1108-1114 [PMID: 1552912 DOI: 10.1056/NEJM199204233261703]

29 **Towbin JA**. Molecular genetic basis of sudden cardiac death. *Pediatr Clin North Am* 2004; **51**: 1229-1255 [PMID: 15331282 DOI: 10.1016/j.pcl.2004.04.012]

30 **Schwartz ML**, Cox GF, Lin AE, Korson MS, Perez-Atayde A, Lacro RV, Lipshultz SE. Clinical approach to genetic cardiomyopathy in children. *Circulation* 1996; **94**: 2021-2038 [PMID: 8873681]

31 **Wilkinson JD**, Lowe AM, Salbert BA, Sleeper LA, Colan SD, Cox GF, Towbin JA, Connuck DM, Messere JE, Lipshultz SE. Outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy: a study from the Pediatric Cardiomyopathy Registry. *Am Heart J* 2012; **164**: 442-448 [PMID: 22980313 DOI: 10.1016/j.ahj.2012.04.018]

32 **Seidman JG**, Seidman C. The genetic basis for cardiomyopathy: from mutation identification to mechanistic paradigms. *Cell* 2001; **104**: 557-567 [PMID: 11239412]

33 **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 [PMID: 19589432 DOI: 10.1016/j.jacc.2009.02.075]

34 **Lind JM**, Chiu C, Semsarian C. Genetic basis of hypertrophic cardiomyopathy. *Expert Rev Cardiovasc Ther* 2006; **4**: 927-934 [PMID: 17173506 DOI: 10.1586/14779072.4.6.927]

35 **Osio A**, Tan L, Chen SN, Lombardi R, Nagueh SF, Shete S, Roberts R, Willerson JT, Marian AJ. Myozenin 2 is a novel gene for human hypertrophic cardiomyopathy. *Circ Res* 2007; **100**: 766-768 [PMID: 17347475 DOI: 10.1161/01.RES.0000263008.66799.aa]

36 **Ho CY.** New Paradigms in Hypertrophic Cardiomyopathy: Insights from Genetics. *Prog Pediatr Cardiol* 2011; **31**: 93-98 [PMID: 21686060 DOI: 10.1016/j.ppedcard.2011.02.005]

37 **Maron BJ**. Sudden death in hypertrophic cardiomyopathy. *J Cardiovasc Transl Res* 2009; **2**: 368-380 [PMID: 20559995 DOI: 10.1007/s12265-009-9147-0]

38 **Marston S**, Copeland O, Jacques A, Livesey K, Tsang V, McKenna WJ, Jalilzadeh S, Carballo S, Redwood C, Watkins H. Evidence from human myectomy samples that MYBPC3 mutations cause hypertrophic cardiomyopathy through haploinsufficiency. *Circ Res* 2009; **105**: 219-222 [PMID: 19574547 DOI: 10.1161/CIRCRESAHA.109.202440]

39 **van Dijk SJ**, Dooijes D, dos Remedios C, Michels M, Lamers JM, Winegrad S, Schlossarek S, Carrier L, ten Cate FJ, Stienen GJ, van der Velden J. Cardiac myosin-binding protein C mutations and hypertrophic cardiomyopathy: haploinsufficiency, deranged phosphorylation, and cardiomyocyte dysfunction. *Circulation* 2009; **119**: 1473-1483 [PMID: 19273718 DOI: 10.1161/CIRCULATIONAHA.108.838672]

40 **Maron BJ**. Hypertrophic cardiomyopathy in childhood. *Pediatr Clin North Am* 2004; **51**: 1305-1346 [PMID: 15331286 DOI: 10.1016/j.pcl.2004.04.017]

41 **Kaski JP**, Syrris P, Esteban MT, Jenkins S, Pantazis A, Deanfield JE, McKenna WJ, Elliott PM. Prevalence of sarcomere protein gene mutations in preadolescent children with hypertrophic cardiomyopathy. *Circ Cardiovasc Genet* 2009; **2**: 436-441 [PMID: 20031618 DOI: 10.1161/CIRCGENETICS.108.821314]

42 **Hayati AR**, Cheah FC, Tan AE, Tan GC. Insulin-like growth factor-1 receptor expression in the placentae of diabetic and normal pregnancies. *Early Hum Dev* 2007; **83**: 41-46 [PMID: 16750336 DOI: 10.1016/j.earlhumdev.2006.04.002]

43 **Kubo T**, Gimeno JR, Bahl A, Steffensen U, Steffensen M, Osman E, Thaman R, Mogensen J, Elliott PM, Doi Y, McKenna WJ. Prevalence, clinical significance, and genetic basis of hypertrophic cardiomyopathy with restrictive phenotype. *J Am Coll Cardiol* 2007; **49**: 2419-2426 [PMID: 17599605 DOI: 10.1016/j.jacc.2007.02.061]

44 **Maskatia SA**, Decker JA, Spinner JA, Kim JJ, Price JF, Jefferies JL, Dreyer WJ, Smith EO, Rossano JW, Denfield SW. Restrictive physiology is associated with poor outcomes in children with hypertrophic cardiomyopathy. *Pediatr Cardiol* 2012; **33**: 141-149 [PMID: 21892651 DOI: 10.1007/s00246-011-0106-6]

45 **Mogensen J**, Kubo T, Duque M, Uribe W, Shaw A, Murphy R, Gimeno JR, Elliott P, McKenna WJ. Idiopathic restrictive cardiomyopathy is part of the clinical expression of cardiac troponin I mutations. *J Clin Invest* 2003; **111**: 209-216 [PMID: 12531876 DOI: 10.1172/JCI16336]

46 **Charron P**, Héron D, Gargiulo M, Richard P, Dubourg O, Desnos M, Bouhour JB, Feingold J, Carrier L, Hainque B, Schwartz K, Komajda M. Genetic testing and genetic counselling in hypertrophic cardiomyopathy: the French experience. *J Med Genet* 2002; **39**: 741-746 [PMID: 12362031]

47 **Christiaans I**, Birnie E, Bonsel GJ, Wilde AA, van Langen IM. Uptake of genetic counselling and predictive DNA testing in hypertrophic cardiomyopathy. *Eur J Hum Genet* 2008; **16**: 1201-1207 [PMID: 18478037 DOI: 10.1038/ejhg.2008.92]

48 **Christiaans I**, Nannenberg EA, Dooijes D, Jongbloed RJ, Michels M, Postema PG, Majoor-Krakauer D, van den Wijngaard A, Mannens MM, van Tintelen JP, van Langen IM, Wilde AA. Founder mutations in hypertrophic cardiomyopathy patients in the Netherlands. *Neth Heart J* 2010; **18**: 248-254 [PMID: 20505798]

49 **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 [PMID: 23054336 DOI: 10.1007/s10897-012-9544-4]

50 **Denfield SW**, Rosenthal G, Gajarski RJ, Bricker JT, Schowengerdt KO, Price JK, Towbin JA. Restrictive cardiomyopathies in childhood. Etiologies and natural history. *Tex Heart Inst J* 1997; **24**: 38-44 [PMID: 9068138]

51 **Felker GM**, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000; **342**: 1077-1084 [PMID: 10760308 DOI: 10.1056/NEJM200004133421502]

52 **Webber SA**, Lipshultz SE, Sleeper LA, Lu M, Wilkinson JD, Addonizio LJ, Canter CE, Colan SD, Everitt MD, Jefferies JL, Kantor PF, Lamour JM, Margossian R, Pahl E, Rusconi PG, Towbin JA. Outcomes of restrictive cardiomyopathy in childhood and the influence of phenotype: a report from the Pediatric Cardiomyopathy Registry. *Circulation* 2012; **126**: 1237-1244 [PMID: 22843787 DOI: 10.1161/CIRCULATIONAHA.112.104638]

53 **Murtuza B**, Fenton M, Burch M, Gupta A, Muthialu N, Elliott MJ, Hsia TY, Tsang VT, Kostolny M. Pediatric heart transplantation for congenital and restrictive cardiomyopathy. *Ann Thorac Surg* 2013; **95**: 1675-1684 [PMID: 23561807 DOI: 10.1016/j.athoracsur.2013.01.014]

54 **Kaski JP**, Syrris P, Burch M, Tomé-Esteban MT, Fenton M, Christiansen M, Andersen PS, Sebire N, Ashworth M, Deanfield JE, McKenna WJ, Elliott PM. Idiopathic restrictive cardiomyopathy in children is caused by mutations in cardiac sarcomere protein genes. *Heart* 2008; **94**: 1478-1484 [PMID: 18467357 DOI: 10.1136/hrt.2007.134684]

55 **Peled Y**, Gramlich M, Yoskovitz G, Feinberg MS, Afek A, Polak-Charcon S, Pras E, Sela BA, Konen E, Weissbrod O, Geiger D, Gordon PM, Thierfelder L, Freimark D, Gerull B, Arad M. Titin mutation in familial restrictive cardiomyopathy. *Int J Cardiol* 2014; **171**: 24-30 [PMID: 24315344 DOI: 10.1016/j.ijcard.2013.11.037]

56 **Grenier MA**, Osganian SK, Cox GF, Towbin JA, Colan SD, Lurie PR, Sleeper LA, Orav EJ, Lipshultz SE. Design and implementation of the North American Pediatric Cardiomyopathy Registry. *Am Heart J* 2000; **139**: S86-S95 [PMID: 10650321]

57 **Michels VV**, Olson TM, Miller FA, Ballman KV, Rosales AG, Driscoll DJ. Frequency of development of idiopathic dilated cardiomyopathy among relatives of patients with idiopathic dilated cardiomyopathy. *Am J Cardiol* 2003; **91**: 1389-1392 [PMID: 12767445]

58 **Nugent AW**, Daubeney PE, Chondros P, Carlin JB, Cheung M, Wilkinson LC, Davis AM, Kahler SG, Chow CW, Wilkinson JL, Weintraub RG. The epidemiology of childhood cardiomyopathy in Australia. *N Engl J Med* 2003; **348**: 1639-1646 [PMID: 12711738 DOI: 10.1056/NEJMoa021737]

59 **Rampersaud E**, Siegfried JD, Norton N, Li D, Martin E, Hershberger RE. Rare variant mutations identified in pediatric patients with dilated cardiomyopathy. *Prog Pediatr Cardiol* 2011; **31**: 39-47 [PMID: 21483645 DOI: 10.1016/j.ppedcard.2010.11.008]

60 **Pahl E**, Sleeper LA, Canter CE, Hsu DT, Lu M, Webber SA, Colan SD, Kantor PF, Everitt MD, Towbin JA, Jefferies JL, Kaufman BD, Wilkinson JD, Lipshultz SE. Incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report from the Pediatric Cardiomyopathy Registry. *J Am Coll Cardiol* 2012; **59**: 607-615 [PMID: 22300696 DOI: 10.1016/j.jacc.2011.10.878]

61 **Burkett EL**, Hershberger RE. Clinical and genetic issues in familial dilated cardiomyopathy. *J Am Coll Cardiol* 2005; **45**: 969-981 [PMID: 15808750 DOI: 10.1016/j.jacc.2004.11.066]

62 **Hershberger RE**, Lindenfeld J, Mestroni L, Seidman CE, Taylor MR, Towbin JA. Genetic evaluation of cardiomyopathy--a Heart Failure Society of America practice guideline. *J Card Fail* 2009; **15**: 83-97 [PMID: 19254666 DOI: 10.1016/j.cardfail.2009.01.006]

63 **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

64 **Hershberger RE**, Siegfried JD. Update 2011: clinical and genetic issues in familial dilated cardiomyopathy. *J Am Coll Cardiol* 2011; **57**: 1641-1649 [PMID: 21492761 DOI: 10.1016/j.jacc.2011.01.015]

65 **Theis JL**, Sharpe KM, Matsumoto ME, Chai HS, Nair AA, Theis JD, de Andrade M, Wieben ED, Michels VV, Olson TM. Homozygosity mapping and exome sequencing reveal GATAD1 mutation in autosomal recessive dilated cardiomyopathy. *Circ Cardiovasc Genet* 2011; **4**: 585-594 [PMID: 21965549 DOI: 10.1161/CIRCGENETICS.111.961052]

66 **Lefeber DJ**, de Brouwer AP, Morava E, Riemersma M, Schuurs-Hoeijmakers JH, Absmanner B, Verrijp K, van den Akker WM, Huijben K, Steenbergen G, van Reeuwijk J, Jozwiak A, Zucker N, Lorber A, Lammens M, Knopf C, van Bokhoven H, Grünewald S, Lehle L, Kapusta L, Mandel H, Wevers RA. Autosomal recessive dilated cardiomyopathy due to DOLK mutations results from abnormal dystroglycan O-mannosylation. *PLoS Genet* 2011; **7**: e1002427 [PMID: 22242004 DOI: 10.1371/journal.pgen.1002427]

67 **Møller DV**, Andersen PS, Hedley P, Ersbøll MK, Bundgaard H, Moolman-Smook J, Christiansen M, Køber L. The role of sarcomere gene mutations in patients with idiopathic dilated cardiomyopathy. *Eur J Hum Genet* 2009; **17**: 1241-1249 [PMID: 19293840 DOI: 10.1038/ejhg.2009.34]

68 **Towbin JA**, Solaro RJ. Genetics of dilated cardiomyopathy: more genes that kill. *J Am Coll Cardiol* 2004; **44**: 2041-2043 [PMID: 15542289 DOI: 10.1016/j.jacc.2004.08.028]

69 **Lakdawala NK**, Dellefave L, Redwood CS, Sparks E, Cirino AL, Depalma S, Colan SD, Funke B, Zimmerman RS, Robinson P, Watkins H, Seidman CE, Seidman JG, McNally EM, Ho CY. Familial dilated cardiomyopathy caused by an alpha-tropomyosin mutation: the distinctive natural history of sarcomeric dilated cardiomyopathy. *J Am Coll Cardiol* 2010; **55**: 320-329 [PMID: 20117437 DOI: 10.1016/j.jacc.2009.11.017]

70 **Herman DS**, Lam L, Taylor MR, Wang L, Teekakirikul P, Christodoulou D, Conner L, DePalma SR, McDonough B, Sparks E, Teodorescu DL, Cirino AL, Banner NR, Pennell DJ, Graw S, Merlo M, Di Lenarda A, Sinagra G, Bos JM, Ackerman MJ, Mitchell RN, Murry CE, Lakdawala NK, Ho CY, Barton PJ, Cook SA, Mestroni L, Seidman JG, Seidman CE. Truncations of titin causing dilated cardiomyopathy. *N Engl J Med* 2012; **366**: 619-628 [PMID: 22335739 DOI: 10.1056/NEJMoa1110186]

71 **Norton N**, Li D, Rampersaud E, Morales A, Martin ER, Zuchner S, Guo S, Gonzalez M, Hedges DJ, Robertson PD, Krumm N, Nickerson DA, Hershberger RE. Exome sequencing and genome-wide linkage analysis in 17 families illustrate the complex contribution of TTN truncating variants to dilated cardiomyopathy. *Circ Cardiovasc Genet* 2013; **6**: 144-153 [PMID: 23418287 DOI: 10.1161/CIRCGENETICS.111.000062]

72 **Cox M**, Hauer R. Arrhythmogenic right ventricular dysplasia/ cardiomyopathy from desmosome to disease. In Baars H, van der Smagt, J, Doevendans P, editors. Clinical Cardiogenetics: Springer, 2011: 80-96

73 **Peters S**. Advances in the diagnostic management of arrhythmogenic right ventricular dysplasia-cardiomyopathy. *Int J Cardiol* 2006; **113**: 4-11 [PMID: 16737750 DOI: 10.1016/j.ijcard.2005.12.015]

74 **Merner ND**, Hodgkinson KA, Haywood AF, Connors S, French VM, Drenckhahn JD, Kupprion C, Ramadanova K, Thierfelder L, McKenna W, Gallagher B, Morris-Larkin L, Bassett AS, Parfrey PS, Young TL. Arrhythmogenic right ventricular cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the TMEM43 gene. *Am J Hum Genet* 2008; **82**: 809-821 [PMID: 18313022 DOI: 10.1016/j.ajhg.2008.01.010]

75 **van der Zwaag PA**, van Rijsingen IA, Asimaki A, Jongbloed JD, van Veldhuisen DJ, Wiesfeld AC, Cox MG, van Lochem LT, de Boer RA, Hofstra RM, Christiaans I, van Spaendonck-Zwarts KY, Lekanne dit Deprez RH, Judge DP, Calkins H, Suurmeijer AJ, Hauer RN, Saffitz JE, Wilde AA, van den Berg MP, van Tintelen JP. Phospholamban R14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: evidence supporting the concept of arrhythmogenic cardiomyopathy. *Eur J Heart Fail*2012; **14**: 1199-1207 [PMID: 22820313 DOI: 10.1093/eurjhf/hfs119]

76 **Klauke B**, Kossmann S, Gaertner A, Brand K, Stork I, Brodehl A, Dieding M, Walhorn V, Anselmetti D, Gerdes D, Bohms B, Schulz U, Zu Knyphausen E, Vorgerd M, Gummert J, Milting H. De novo desmin-mutation N116S is associated with arrhythmogenic right ventricular cardiomyopathy. *Hum Mol Genet* 2010; **19**: 4595-4607 [PMID: 20829228 DOI: 10.1093/hmg/ddq387]

77 **Quarta G**, Syrris P, Ashworth M, Jenkins S, Zuborne Alapi K, Morgan J, Muir A, Pantazis A, McKenna WJ, Elliott PM. Mutations in the Lamin A/C gene mimic arrhythmogenic right ventricular cardiomyopathy. *Eur Heart J* 2012; **33**: 1128-1136 [PMID: 22199124 DOI: 10.1093/eurheartj/ehr451]

78 **Taylor M**, Graw S, Sinagra G, Barnes C, Slavov D, Brun F, Pinamonti B, Salcedo EE, Sauer W, Pyxaras S, Anderson B, Simon B, Bogomolovas J, Labeit S, Granzier H, Mestroni L. Genetic variation in titin in arrhythmogenic right ventricular cardiomyopathy-overlap syndromes. *Circulation* 2011; **124**: 876-885 [PMID: 21810661 DOI: 10.1161/CIRCULATIONAHA.110.005405]

79 **Tiso N**, Stephan DA, Nava A, Bagattin A, Devaney JM, Stanchi F, Larderet G, Brahmbhatt B, Brown K, Bauce B, Muriago M, Basso C, Thiene G, Danieli GA, Rampazzo A. Identification of mutations in the cardiac ryanodine receptor gene in families affected with arrhythmogenic right ventricular cardiomyopathy type 2 (ARVD2). *Hum Mol Genet* 2001; **10**: 189-194 [PMID: 11159936]

80 **Beffagna G**, Occhi G, Nava A, Vitiello L, Ditadi A, Basso C, Bauce B, Carraro G, Thiene G, Towbin JA, Danieli GA, Rampazzo A. Regulatory mutations in transforming growth factor-beta3 gene cause arrhythmogenic right ventricular cardiomyopathy type 1. *Cardiovasc Res* 2005; **65**: 366-373 [PMID: 15639475 DOI: 10.1016/j.cardiores.2004.10.005]

81 **Winkel BG**, Risgaard B, Sadjadieh G, Bundgaard H, Haunsø S, Tfelt-Hansen J. Sudden cardiac death in children (1-18 years): symptoms and causes of death in a nationwide setting. *Eur Heart J* 2014; **35**: 868-875 [PMID: 24344190 DOI: 10.1093/eurheartj/eht509]

82 **Pignatelli RH**, McMahon CJ, Dreyer WJ, Denfield SW, Price J, Belmont JW, Craigen WJ, Wu J, El Said H, Bezold LI, Clunie S, Fernbach S, Bowles NE, Towbin JA. Clinical characterization of left ventricular noncompaction in children: a relatively common form of cardiomyopathy. *Circulation* 2003; **108**: 2672-2678 [PMID: 14623814 DOI: 10.1161/01.CIR.0000100664.10777.B8]

83 **Brescia ST**, Rossano JW, Pignatelli R, Jefferies JL, Price JF, Decker JA, Denfield SW, Dreyer WJ, Smith O, Towbin JA, Kim JJ. Mortality and sudden death in pediatric left ventricular noncompaction in a tertiary referral center. *Circulation* 2013; **127**: 2202-2208 [PMID: 23633270 DOI: 10.1161/CIRCULATIONAHA.113.002511]

84 **Oechslin E**, Jenni R. Left ventricular non-compaction revisited: a distinct phenotype with genetic heterogeneity? *Eur Heart J* 2011; **32**: 1446-1456 [PMID: 21285074 DOI: 10.1093/eurheartj/ehq508]

85 **Tang S**, Batra A, Zhang Y, Ebenroth ES, Huang T. Left ventricular noncompaction is associated with mutations in the mitochondrial genome. *Mitochondrion* 2010; **10**: 350-357 [PMID: 20211276 DOI: 10.1016/j.mito.2010.02.003]

86 **Seidman CE**, Seidman JG. Identifying sarcomere gene mutations in hypertrophic cardiomyopathy: a personal history. *Circ Res* 2011; **108**: 743-750 [PMID: 21415408 DOI: 10.1161/CIRCRESAHA.110.223834]

87 **Ackerman MJ**, Priori SG, Willems S, Berul C, Brugada R, Calkins H, Camm AJ, Ellinor PT, Gollob M, Hamilton R, Hershberger RE, Judge DP, Le Marec H, McKenna WJ, Schulze-Bahr E, Semsarian C, Towbin JA, Watkins H, Wilde A, Wolpert C, Zipes DP. 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 [PMID: 21787999 DOI: 10.1016/j.hrthm.2011.05.020]

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**Table 1 A 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* |  |  |  |  | DCM |
| *ANKRD1* |  |  |  |  | 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 |