Genetics of cardiomyopathies in children

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Abstract

Cardiomyopathies are diseases of the heart muscle leading to heart failure and/or an increased risk of arrhythmogenic sudden cardiac death. These disorders represent a major cause of morbidity and mortality in children. In childhood forms of cardiomyopathy, genetic etiologies are frequent, but non-genetic or acquired causes, such viral infection, also play a significant role. In the last twenty years, the genetic causes of cardiomyopathies have been increasingly identified and clinical correlations are beginning to be defined. Here we present an overview of the recent advances in our understanding of the genetics of cardiomyopathies in children and what is known about the pathophysiological mechanisms underlying these gene-related forms of disease.

Introduction

Primary cardiomyopathies remain a major cause of morbidity and mortality in children with an estimated incidence of 1.13/100,000 cases in the U.S., and they represent the leading cause of transplantation in children over one year of age.1-2 Several classified forms of cardiomyopathy exist which have diverse clinical, structural, morphological, and functional presentations. These forms include dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), left ventricular non-compaction (LVNC), arrhythmogenic right ventricular cardiomyopathy (ARVC) and restrictive cardiomyopathy (RCM).3-4 Among the various types of cardiomyopathies, DCM represents approximately 40% of all cases in children, followed by HCM, LVNC and more rarely by ARVC and RCM.1-4 After over two decades of genetic and molecular research, many causative genes have been identified and overlap in the genetic causes of the various forms of cardiomyopathies have also been identified, in which defects in the same gene could lead to allelic disorders.1,4 Here, we will briefly describe the most important forms of cardiomyopathy and what is currently known about their genetic basis and the pathophysiological mechanisms responsible for the disorders.

Dilated cardiomyopathy

DCM is characterized by an enlarged left ventricular chamber, left ventricular wall thinning and systolic dysfunction.1,4 Individuals with DCM commonly present with symptomatic heart failure, arrhythmias or conduction disturbance.1,4 DCM in children has an estimated incidence of approximately 0.57/100,000 cases compared to the report of 1/2,500 incidence in adult subjects.2 However, the actual incidence could be far higher due to reduced detection rate caused by incomplete penetrance and variable expressivity observed in DCM, which can lead to a prolonged asymptomatic period preceding the development of overt heart failure.

Although a significant proportion of childhood DCM could be attributed to infections causing myocarditis (16%),2 a large fraction of pediatric DCM can be genetic in origin, either sporadic, if the child has no previous family history and screening of first degree relatives is negative, or familial if it occurs in two or more close relatives.1,7 Currently, familial DCM is estimated to occur in up to 67% of cases after accurate screening of the relatives of idiopathic DCM subjects.8

A significant percentage of DCM cases may be explained by mutations in single genes that affect critical pathways of contractile function, ion distribution, or cellular function. This was initially demonstrated by the breakthrough identification of dystrophin, the gene responsible for Duchenne (DMD) and Becker muscular dystrophy (BMD) and the associated skeletal myopathy and DCM, as the gene responsible for the X-linked form of DCM (XLCM) by Towbin and colleagues in 1993.9 However, defects in the DMD gene could explain only a fraction of all DCM cases; later, other genes responsible for DCM were identified, defining DCM as a genetically heterogeneous entity. Based on these findings, we formulated the final common pathway hypothesis (1998) in which it was suggested that abnormalities in other genes encoding for dystrophin-associated proteins and proteins involved in the structural formation and maintenance of cardiomyocyte structure and contractile function could also potentially lead to the development of DCM.10 It is now known that perturbation of cardiomyocyte proteins involved in contractile force generation and transmission, such as cytoskeletal, sarcromeric, ion channel and transcription factor proteins, are involved in the pathogenesis of DCM.7 In vitro models and animal models recapitulating the human disease suggest that alteration of the protein continuum connecting the cardiomyocyte plasma membrane (sarcolema) to the sarcromere, and through the intermediate filaments, to the perinuclear membrane, can lead to a transient hypertrophic phase, followed by decompensated systolic performance, left ventricular wall thinning and left ventricular chamber dilation.2

Currently, approximately 33 genes have been identified to cause DCM in isolation, demonstrating a high level of genetic heterogeneity (Table 1), and many private mutations have been observed in unrelated subjects suggesting a high level of allelic heterogeneity.7 In addition, several genes have also been identified that are associated with syndromic forms of DCM, such as genes involved in metabolism and mitochondrial function, besides loci allelic to other cardiomyopathic phenotypes.7,11 In particular, primary diseases of the skeletal muscle, such as various forms of muscular dystrophy and other skeletal myopathies frequently present with a DCM phenotype.12,13

Despite the large number of genes associated with DCM, they account for only approximately 40% of all cases, with LMNA (5%), MYH7 (4%), and TNNT2 (3%) being the most frequently involved in familial DCM, while mutations in all associated sarcomeric genes cover only up to 10% of all DCM cases.7

In addition, genes encoding for ion channels such as the cardiac sodium channel (SCN5A), which causes long-QT syndrome (LQTS) and Brugada syndrome, as well as ABCD3, coding for the Kir6.2 regulatory subunit, an inwardly rectifying cardiac KATP channel, are implicated in the pathogenesis of DCM.7 This suggests that ion channels not only influence the electrocardiographic (ECG) findings and potentiates arrhythmias in DCM,1,4 but may also weaken the cardiomyocytes structure leading to DCM and vice versa, as recently reported in a mouse model harboring the a LDB3-encoded ZASP mutation causing DCM in humans.15

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Key words: sudden cardiac death, dilated cardiomyopathy, hypertrophic cardiomyopathy, left ventricular noncompaction, restrictive cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, Nav1.5, LQTS, ion channels.

Received for publication: 16 May 2011.
Accepted for publication: 20 July 2011.

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Another potential mechanism, particularly in the case of the SCN5A-encoded Nav1.5, is its relationship with dystrophin. Na\(_v\)1.5 binds to dystrophin and could potentially disrupt the function of dystrophin and lead to a dystrophin-related cardiomyopathy, as would be predicted by the final common pathway hypothesis. Clinically, the presentation of idiopathic, acquired and genetic forms of DCM is indistinguishable. This suggests that clinical evaluation of relatives of children with DCM should always be considered when a diagnosis of DCM is reached. Unfortunately, a significant proportion of DCM remains idiopathic, where a firm etiologic diagnosis cannot be reached. This suggests that many more genes are yet to be discovered, and that genetic testing in the clinical setting using the standard Sanger sequencing technique appears to have limitations due to the large number of genes involved. It is likely that the molecular diagnosis of DCM will benefit from the clinical application of high throughput technologies such as whole genome or exome sequencing, multiplex ligation-dependent probe amplification (MLPA), array comparative genomic hybridization (aCGH) and high density arrays combining single nucleotide polymorphism (SNP) and copy number variation (CNV) probes using the currently available platforms.16,17

**Hypertrophic cardiomyopathy**

Hypertrophic cardiomyopathy is one of the most common genetic disorders with a prevalence of 1/500, representing also the most frequent cause of sudden cardiac death in young athletes in the United States.3-4 HCM is characterized by excessive thickening generally limited to the left ventricular myocardium and interventricular septum, in the absence of insults that increase after load such as aortic stenosis or hypertension, and morphologically is typically characterized by myocyte disarray.3-4 The interventricular septal thickening most commonly demonstrates asymmetric hypertrophy but focal areas of septal thickening or concentric hypertrophy may occur.3-4 Left ventricular outflow tract obstruction may also occur. Individuals with HCM may be asymptomatic or present signs of sudden death or heart failure. Clinical presentations therefore include syncope or non-resuscitated sudden death, dyspnea, diaphoresis, chest pain, palpitations, or arrhythmias. The age of onset of HCM-related symptoms varies from infancy to adulthood. However, most appear in adolescence. As previously described for DCM, primary HCM has a genetic basis in most cases. Approximately 21 genes, mostly encoding for sarcomeric proteins and mainly involved in force generation, have been identified to cause HCM, and many of them are allelic to DCM (Table 1).18

Similar to DCM, HCM is characterized by

<table>
<thead>
<tr>
<th>Gene</th>
<th>OMIM*</th>
<th>Locus</th>
<th>Gene name°</th>
<th>Associated phenotypes°</th>
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Continued in the next page
significant genetic and allelic heterogeneity and variable expressivity.23 However, contrary to DCM, genetic testing in HCM using the current technology has a high detection rate because mutations in four sarcomeric genes, \( \beta \)-myosin heavy chain (MYH7), myosin binding protein-C (MYBPC3), cardiac troponin T (TNNT2), and cardiac troponin I (TNNT1), cause approximately 80% of all familial HCM cases. Mutations can also be identified in about 40% of sporadic and idiopathic cases of HCM.21 Although genotype-phenotype correlation is imperfect, it has been reported that mutations in MYH7 are associated with early onset disease, and in some cases, a more severe phenotype, while MYBPC3 mutations have been identified in subjects with later onset presentation, and TNNT2 mutations are associated with a high incidence of sudden cardiac death.20-21

HCM is a monogenic disorder in most cases, although double heterozygote mutations have been described and appear to be associated with earlier-onset and a more dramatic phenotype.11

Despite the high detection rate of clinical genetic testing in HCM, the lack of good genotype-phenotype correlation has lessened the clinical utility of genetic screening in affected patients. However, clinical genetic testing is quite useful for the screening of clinically affected and unaffected family members due to the lack of symptoms in most people with HCM and the relatively high risk of sudden death. Genetic counseling by trained professionals is highly recommended for accurate familial risk assessment and to reduce the potential psychological impact of the genetic testing.

**Arrhythmogenic right ventricular cardiomyopathy**

ARVC is a myocardial disease morphologically characterized by fibrosis with or without fatty infiltration and dilation of the right ventricle, along with thinning of the right ventricular wall, arrhythmias and sudden cardiac death.22 However, left ventricular involvement is being more commonly identified as well typically of the posterior lateral wall, in an age-dependent fashion.22

ARVC is often diagnosed secondary to arrhythmias, palpitations, syncope, and aborted sudden death. ARVC can manifest in the early teenage years with the majority of patients being in their late teenage years or young adulthood, especially in athletes.23 ARVC is predominantly genetically determined and often inherited within families, mostly as an autosomal dominant trait with reduced penetrance and variable expression.23 However, autosomal recessive inheritance has been observed in individuals affected by Naxos disease presenting with ARVC, diffuse non-epi-

### Table 1. Continued from previous page.

<table>
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<td>PKRKG2</td>
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dermolytic palmoplantar keratoderma, and woolly hair, as well as in Cardiagal syndrome, characterized by striate palmoplantar keratoderma, woolly hair, and LV cardiomyopathy. 

ARVC has an estimated prevalence of 1/2000-5000, although regional differences may significantly vary this estimate worldwide. 

Diagnostic assessment for ARVC includes cardiac MRI (CMR), echocardiography, and electrophysiology. The CMR classically demonstrates a dilated LV with RV wall thinning and fatty replacement of the myocardium, systolic dysfunction, and the RV outflow tract may be aneurysmal. Gadolinium late enhancement typically identifies areas of fibrosis. The LV may also be affected with a DCM appearance. The echocardiogram may demonstrate a dilated LV or LV with systolic dysfunction and the electrocardiogram demonstrates T wave inversion in leads V1 through V6, QRS duration 110 msec in V1 through V6, an epsilon wave (an electric potential after the end of the QRS complex), an ST-elevation pattern similar to that seen in Brugada syndrome may be noted, and a prolonged S-wave upstroke in V1 through V6 measuring 55 msec. Right ventricular biopsy may be definitive when typical fibrofatty replacement of the myocardium and inflammation is visible; this is more obvious, in advanced disease. Commonly, only fibrosis and inflammatory infiltrates are seen, particularly in earlier disease presentations. Since the primary area of fibrofatty replacement is in the triangle of dysplasia in the apical and infundibular regions of the RV, making biopsy diagnosis more challenging. Autopsy or explant after transplantation will commonly demonstrate classic histopathologic diagnostic criteria.

Currently, 13 loci and mutations in 9 genes have been identified in ARVC individuals (Table 1). Most of the genes causing ARVC encode proteins of the cardiac desmosome such as plakoglobin (PG), desmoplakin (DSP), plakophilin-2 (PKP2), plakophilin-4 (PKP4), desmocollin-2 (DSC2) and desmoglein-2 (DSCG2), resulting in defective cell-to-cell adhesion and altered nuclear signaling, leading to diminished desmosomal protein localization and dramatic reduction in immunoreactive signal for the GJA1-encoded gap junction protein connexin-43 (Cx43) at the intercalated disks.

Connexin-43 is a highly phosphorylated protein, whose phosphorylation pattern plays important roles in the regulation of protein turnover, trafficking, intercalated disk assembly, internalization, degradation, and channel gating properties. In the failing RV, altered phosphorylation of Cx43 leads to a non-phosphorylated protein, causing a weaker immunoreactive signal to be observed in the RV myocardium of patients and animal models with ARVC. 

Recently, Gehmlich and colleagues suggested that the cytoplasmic portion of a highly phosphorylated Cx43 protein binds the DSC2a isomorph, connecting the gap junction to the desmosome. They identified a novel variant in DSC2 as well as a DSG2 variant in an individual with a family history of sudden death, mild ECG abnormalities in herself and her daughter, and immunohistochemistry demonstrated severe depression of the PG signal at the intercalated disk, whereas Western blot showed minimal reduction of DSG2 and DSC2 expression levels and mild reduction of Cx43. Electrofertrographic mobility of Cx43 was abnormal and consistent with differential phosphorylation, suggesting a lower proportion of the highly phosphorylated protein. All other desmosomal proteins were normal. Therefore, the authors suggested that the DSC2a isomorph provides a critical link between the desmosome and gap junction and that disruption leads to the clinical features of disease upon physiologic trigger. They also suggested that the combination of PG loss and Cx43 disturbance is an early indicator of developing clinical disease, with the risk of arrhythmias (and therefore sudden death) lurking for future clinical presentation. An extension of this suggestion leads to the possibility that mutations in desmosomal proteins could possibly alter Cx43 phosphorylation and weaken the linkage between the gap junction and desmosome, causing loss of electrical coupling between cardiac myocytes, and leading to myocyte cell death, fibrofatty replacement and arrhythmias. We suggested that, if correct, these findings could potentially be used for early genotype-phenotype biomarker disease diagnosis, risk stratification and outcome prediction, and possibly preventive therapy, but that significant caution should be used before assuming this to be correct.

In addition to abnormalities in desmosomal genes, mutations in the TGFβ3, RYR2, and TMEM43 genes have been also associated with ARVC and are thought to cause ARVC via secondary disruption of the desmosome. The TGFβ3-encoded transforming growth factor β3 is a cytokine, which stimulates fibrosis and modulates cell adhesion, while the RYR2-encoded human ryanoside receptor 2 induces the release of calcium from the myocardial sarcoplasmic reticulum. TMEM43, which encodes transmembrane protein 43, is a response element for the peroxisome proliferator-activated receptor gamma (PPARγ) gamma, an adipogenic transcription factor, which may explain the fibrofatty replacement of the myocardium.

Although most ARVC cases follow an autosomal dominant pattern, autosomal recessive pattern was recognized with homozygous mutations in the plakoglobin-encoding gene causing Naxos disease, and homozygous mutations in DSP in Carvalaj syndrome. However, because of the reduced penetrance and variable expressivity, which characterizes ARVC, single mutations in individual genes may not be sufficient to cause the development of the disease. Compound heterozygous mutations or double heterozygous, digenic mutations in desmosomal genes may be required for disease development and clinical manifestation. In fact, although frameshift mutations are regarded as deleterious changes according to the current recommendations, many PKP2 mutations demonstrate low penetrance and an additional mutation in another ARVC gene is necessary to develop the disease. Therefore, despite much literature suggesting that PKP2 mutations cause approximately 25% of ARVC cases, this is not the primary cause of the disease in a high percentage of subjects. This complex genetic behavior makes clinical genetic testing challenging to interpret. Therefore, despite the apparent autosomal dominant mode of inheritance, clinical genetic testing should be comprehensive and multimodal for all the known ARVC genes and genetic-based diagnosis should be conservatively and thoughtfully considered.

Left ventricular noncompaction

Left ventricular non compaction (LVNC) is characterized by a trabeculated left ventricular myocardium associated with deep inter-trabecular recesses in the left ventricular wall, typically most evident in the apical region of the LV but also notable in the LV free wall and, occasionally the septum in some patients. The RV, which normally is trabeculated, may be hypertrabeculated as well in some cases, resulting in biventricular noncompaction. The diagnosis is typically made by echocardiography where apical trabeculations are noted with or without trabeculations in the free wall, septum or RV. Some published criteria use a ratio of compact to noncompact layer of the LV myocardium >2 but this measurement is dependent on the area sampled and measured. In addition, cardiac MRI may demonstrate the trabeculations and inter-trabecular recesses well. Due to the trabeculations and inter-trabecular recesses there is a theoretical increase in the susceptibility to form clots in the LV with high risk of thrombembolism and death, but this usually occurs only in subjects with a dilated and poorly functioning LV. LVNC can be observed with or without congenital heart diseases (CHD) such as ventricular (VSD) and atrial septum defects (ASD), pulmonic stenosis (PS), Elstein’s anomaly, and hypoplastic left heart syndrome (HLHS), amongst others. When not associated with CHD, the associated phenotype may include a DCM-like, HCM-like, combined HCM/DCM-like picture, a restrictive cardiomyopathy (RCM)-like picture, or simply LV trabeculations with normal LV size, thickness and function. The latter phenotype appears...
to be benign unless associated with arrhythmias while the other forms tend to follow a similar course to the associated phenotype. The only exception is the undulating phenotype, a change from one appearance to another, which most commonly occurs in those with the combined HCM/DCM-like picture. LVNC can also present associated with syndromes such as Barth, Marfan, Sotos, trisomy 13, 36 and monosomy of chromosome band 1p36. As well as Duchenne and Becker muscular dystrophy. LVNC is believed to occur due to an arrest in the ventricular development during embryogenesis, in which the initially trabeculated myocardium provides enough surface for the blood to infiltrate and bring oxygen and nutrients to myocardial cells. Subsequently, with a higher blood demand, the coronary artery system develops and the myocardium undergoes remodeling associated with compaction of the hypertrabeculated myocardium. The disruption of this process is believed to cause the ventricular noncompaction.

LVNC was considered a rare disease in the past due to limited awareness and knowledge of the disease and limitations of echocardiography. However, the American Heart Association recently classified LVNC as a separate clinical entity. The actual incidence and prevalence of LVNC remains unclear, but the reported incidence of 0.05% in isolated LVNC in adult subjects appears to be underestimated, and is probably far lower than the true incidence and prevalence in children. In fact, LVNC is now assumed to account for approximately 10% of all cardiomyopathies. Currently, mutations in many genes have been identified in LVNC (Table 1), but the genes more commonly associated with LVNC in children are sarcomere-encoding genes, such as TAZ, DTNA and LDB3. The TAZ gene, located on chromosome 1q28, encodes the tafazzin protein, a cytoskeletal protein encoded by the DTNA gene, which is a component of the dystrophin-associated glycoprotein complex, which provides structural stability during muscle contraction and relaxation. The LIM-domain binding protein 3 (LDB3), also known as ZASP (Z-band alternatively spliced PDZ-domain binding protein), is a component of the sarcomeric Z-line and is encoded by the LDB3 gene and characterized by one PDZ domain at its N-terminus and up to three LIM domains at its C-terminus. Mutations in these genes cause LVNC with or without CHD.

Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is uncommon, accounting for up to 5% of cardiomyopathies in children. Restrictive cardiomyopathies are characterized by dilated atria with normal ventricular size, thickness and systolic function in the face of diastolic ventricular dysfunction with elevated left (and at times right) ventricular end-diastolic pressures. In the 2006 classification consensus statement by the AHA, primary restrictive cardiomyopathy was defined as a rare form of heart disease characterized by normal or decreased volume of both ventricles associated with biatrial enlargement, normal left ventricular wall thickness and atrioventricular valves, impaired ventricular filling with restrictive physiology, and normal (or near normal) systolic function.

The most common presenting signs and symptoms in children with RCM include dyspnea that is frequently exacerbated by an intercurrent respiratory illness or asthma, fatigue, exercise intolerance, syncope, and sudden death. The electrocardiogram is abnormal in approximately 98% of patients. The most common abnormalities are right and/or left atrial enlargement, however ST segment depression and ST-T wave abnormalities are frequently present. Right and/or left ventricular hypertrophy can also be seen as well as conduction abnormalities. Holter and event monitors are useful to evaluate for rhythm disturbances, conduction abnormalities and evidence of ischemia based on ST segment analysis. Arrhythmias have been reported in approximately 15% of pediatric patients and include atrial flutter, high grade second and third degree atrioventricular block, atrial fibrillation, atrial tachycardias, Wolff-Parkinson-White syndrome with supraventricular tachycardia and ventricular tachycardia and torsades. Symptomatic sinus bradycardia requiring pacing has also been reported. The most striking finding on echocardiography is massive atrial dilatation in the absence of atrioventricular valve regurgitation. In children, findings consistent with restrictive filling and increased left ventricular end diastolic pressure are noted. Systolic function is typically preserved although some degree of systolic dysfunction has been seen in some patients at presentation and deterioration of systolic dysfunction over time has also been reported in children. Ventricular hypertrophy is not prominent, but some degree of concentric increase in septal and left ventricular posterior wall thickness is seen in a significant proportion of cases otherwise fulfilling all the other criteria for RCM. Cardiac catheterization may demonstrate elevated LV or RV end diastolic pressures, pulmonary hypertension with elevation in pulmonary artery pressure is frequently present at the time of initial catheterization and markedly elevated pulmonary vascular resistance can occur within 1 to 4 years of diagnosis. Endomyocardial biopsy reveals myofiber hypertrophy and mild to moderate interstitial fibrosis.

In children in the U.S. and Australia, RCM accounts for 2.5-5% of the diagnosed cardiomyopathies, with the majority having no specific cause identified. In Australia, RCM accounted for 2.5% of the cardiomyopathies diagnosed in children <10 years of age, while the U.S report from the Pediatric Cardiomyopathy Registry (PCMR) investigators reported that RCM accounted for 3% of the cardiomyopathies in children <18 years of age. The estimated annual incidence in the U.S. and Australia is 0.04/100,000 and 0.03/100,000 children, respectively. Multiple causes of RCM have been described in adults and children.

Some cases are inherited and most commonly have autosomal dominant transmission. Causative mutations have been reported in sarcomere-encoding genes such as troponin I, troponin T, β-myosin heavy chain, and actin. Another complex subgroup of patients have been identified with RCM associated with atrioventricular block and skeletal myopathy, and these are usually caused by mutations in desmin or lamin AC.

The prognosis in children with RCM is poor. Half of the children die or undergo transplant within 3 years of diagnosis. Sudden cardiac death has been reported to be a common mode of death in children with RCM. Patients who appear to be at greater risk for sudden death include those who present with signs and symptoms of ischemia, such as syncope and chest pain. However, heart failure related deaths are the most common.

Metabolic cardiomyopathies

Although the major focus of this review is the description of primary cardiomyopathies, which present usually in isolation affecting only the cardiac muscle, defects in the metabolism usually appear early in life and may lead to complex clinical phenotype in which the function of multiple tissues including the myocardium results severely hampered. Metabolic cardiomyopathies can be recognized as early as the perinatal period or infancy, and among the best known there are approximately 50 different forms of lysosomal accumulation of substrates, which results to be toxic for the cell, namely the lysosomal storage diseases (LSDs). Among the various LSD here we will mention Pompe disease, Fabry disease and...
Gaucher disease. According to their age of onset, variable clinical presentation and severity, they are also divided in various sub-types. Pompe disease is an autosomal recessive disorder caused by mutations in the GAA gene mapping to chromosome 17q25.2-q25.3 and encoding the enzyme acid alpha-glucosidase, which is essential for the degradation of glycogen to glucose in the lysosomes. Defects in this process lead to glycogen storage disease type II with the toxic accumulation in various organs such as striated muscles, impairing their normal function.56 Pompe disease has an estimated prevalence of 1: 40,000 and may present as early as in infancy with progressive left ventricular hypertrophy, but late-onset forms such as in late adolescents and young adults may not present with heart failure. However, subjects with Pompe disease present a significant risk of sudden cardiac death due to the association of hypertrophic cardiomyopathy along with Wolf-Parkinson-White syndrome, a form of atrioventricular reentrant tachycardia or ventricular pre-excitation.56

Fabry disease is an X-linked form of LSD caused by impaired activity of the enzyme α-galactosidase (α-Gal A) due to mutations in the GLA gene, mapping to chromosome Xq22.56 Subjects with Fabry disease accumulate glycosphingolipid ceramide trihexoside (GL-3), which is deposited into lysosomes in most cell types in the body.

The prevalence of Fabry disease is approximately 1: 40,000, although the prevalence may be much higher in subsets of patients.56 Fabry disease classically occurs in hemizygote males in early childhood or adolescence with periodic crises of severe pain in the extremities (acroparesthesias), vascular cutaneous lesions (angiokeratomas), kidney failure, corneal and lenticular opacities, proteinuria and heart failure or death.56 However, Fabry disease may also present with HCM as the prominent symptom although restrictive cardiomyopathy has also been observed.

Gaucher disease (GD) is an autosomal recessive LSD caused by mutations in the GBA gene (1q21) leading to deficient activity of the encoded acid-β-glucosidase. Gaucher disease has a prevalence of approximately 1: 50,000 to 100,000 people in the general population, affecting 1: 500 to 1000 Ashkenazi Jews.56

Another form of LSDs recently classified in the subgroup of autosomal vacuolar myopathies (AVMs) and that can present with HCM as its predominant feature is represented by Danon disease and it is caused by mutations in the LAMP2 gene, which encodes the lysosome-associated protein-2 and maps to Xq24.57-56 Affected hemizygote males usually present with severe cardiac hypertrophy in early childhood and adolescence, while most female carriers develop dilated cardiomyopathy (DCM) rather than HCM during adulthood (as late as their 40s).57-58 However, DCM has also been observed in males with Danon disease.59 Danon disease individuals suffer of various degree of intellectual disability and skeletal muscle impairment. Skeletal muscle biopsy usually reveals glycogen containing (PAS positive) cytoplasmic vacuoles.57-58

Because LSDs are caused by the deficiency in enzyme activity, this prompted the researchers to develop an enzyme replacement therapy (ERT) using recombinant enzyme, which appears to be effective when administered early in the natural history of the disease. Unfortunately, the enzymes do not pass the blood-brain barrier and they are not effective in ameliorating the neurological symptoms.51,56

Mitochondrial genome and nuclear genes with mitochondrial function and cardiomyopathies

Mitochondria provide the major energy source for the myocardium, and abnormalities of the mitochondrial genome (mtDNA) and nuclear genes encoding proteins involved in mitochondrial respiratory chain function are seen in cardiomyopathies. The mitochondrial respiratory chain consists in five enzyme complexes (I-V) in the inner membrane of the mitochondria and the energy that is generated is used to produce ATP via oxidative phosphorylation.59,60 Defects in oxidative phosphorylation could originate from alterations in any of the five complexes of the respiratory chain, although the most frequently affected include complexes I (NADH-CoQ reductase) and IV (cytochrome-c oxidase).58 Mitochondrial diseases usually manifest in early childhood, although different levels of heteroplasm in various tissues may be associated with pleiotropic effects clinically and age-dependent expressivity. Children affected by mitochondrial diseases commonly present with cardiomyopathy (17%) and cardiac involvement is generally associated with worse prognosis and increased mortality.59-61

Mitochondria occupy a significant portion (20-30%) of cardiac cell volume, and their dynamic nature allow them to respond to the level of energy requirement by altering their unit number.59 In cardiomyocytes, mitochondria are not only functionally related to cardiac contraction and energy homeostasis, but they are also physically linked to the sarcoplasmic reticulum (SR) through the intermediate filament (IF) protein desmin, which provides the necessary ratio of mitochondria to IF for the optimal exchange of ions, lipids, and other metabolites.61

Thus, it should not be surprising that altered integrity of the mitochondria could lead to functional and structural impairment of cardiac cells. In fact, the absence of desmin in mouse hearts leads to an abnormal accumulation of subsarcolemmal clusters of mitochondria, degeneration of the mitochondrial matrix, and proliferation associated with the development of dilated cardiomyopathy and heart failure.61

The mtDNA is approximately 16kb in length and encodes 13 of the 69 proteins required for oxidative metabolism performed by Complex I-V, 22 transfer RNA (tRNAs) and two ribosomal RNA (rRNA). Mitochondria are inherited from the mother and they can vary in number within the cells from various tissues (heteroplasm), accounting for the pleiotropic effect. Recently, mutations leading to mitochondrial defects (mtDNA, nDNA), have been identified in subjects with isolated LVNC,62 as well as DCM and HCM,63 thus supporting the importance of mitochondrial genome screening in primary cardiomyopathies. In addition, complex mitochondrial diseases such as Kearns-Sayre syndrome, myoclonic epilepsy with ragged red muscle fibers (MERRF)53 syndrome and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)64 have also been associated with cardiomyopathies, suggesting that a multimodal approach including novel technologies for the screening of the nuclear DNA (nDNA) and the mtDNA should be employed in both research and clinical testing in individuals with cardiomyopathies, particularly babies. The currently available technologies such as whole genome or exome sequencing, MLPA, aCGH for nDNA and mtDNA and high density array combining single nucleotide polymorphism (SNP) and copy number variation (CNV) probes using the currently available platforms could allow for rapid results with increasingly lower cost, improvements in turn-around times, and facilitating comprehensive investigation of the underlying genetic etiologies involved in cardiomyopathies.

Final remarks

In this review article we discussed the current knowledge about the genetics of cardiomyopathies in children. Despite over three decades of research and the discovery of a large number of causative genes, modest advances have been made about the management and therapies of cardiomyopathies in children as well as in adults. However, the advances in the genetics of heart diseases provided a formidable tool for counseling car-
diomyopathy patients and their relatives to identify at-risk individuals and to evaluate the recurrent risk of the disease within the family. In addition, the use of more sophisticated ultrasound technology for in utero diagnosis, and newborn screening for postnatal ascertainment, have provided the clinicians with an unprecedented ability to obtain an early detection of the disease before symptoms appear and possibly, in the case of metabolic defects, employ prompt therapeutic intervention to halt and possibly, in the case of metabolic defects, the progression of the disease before symptoms appear.


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