Chapter
Genetics of Cardiomyopathy

Evan M. Harvey, Murad Almasri and Hugo R. Martinez

Abstract

Cardiomyopathies (CMs) encompass a heterogeneous group of structural and functional (systolic and diastolic) abnormalities of the myocardium and are either confined to the cardiovascular system or are part of a systemic disorder. CMs represent a leading cause of morbidity and mortality and account for a significant percentage of death and cardiac transplantation. The 2006 American Heart Association (AHA) classification grouped CMs into primary (genetic, mixed, or acquired) or secondary (i.e., infiltrative or autoimmune). In 2008, the European Society of Cardiology classification proposed subgrouping CM into familial or genetic and nonfamilial or nongenetic forms. In 2013, the World Heart Federation recommended the MOGES nosology system, which incorporates a morpho-functional phenotype (M), organ(s) involved (O), the genetic inheritance pattern (G), an etiological annotation (E) including genetic defects or underlying disease/substrates, and the functional status (S) of a particular patient based on heart failure symptoms. Rapid advancements in the biology of cardio-genetics have revealed substantial genetic and phenotypic heterogeneity in myocardial disease. Given the variety of disciplines in the scientific and clinical fields, any desired classification may face challenges to obtaining consensus. Nonetheless, the heritable phenotype-based CM classification offers the possibility of a simple, clinically useful diagnostic scheme. In this chapter, we will describe the genetic basis of dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy (ACM), LV noncompaction cardiomyopathy (LVNC), and restrictive cardiomyopathy (RCM). Although the descriptive morphologies of these types of CM differ, an overlapping phenotype is frequently encountered within the CM types and arrhythmogenic pathology in clinical practice. CMs appear to originate secondary to disruption of “final common pathways.” These disruptions may have purely genetic causes. For example, single gene mutations result in dysfunctional protein synthesis causing downstream dysfunctional protein interactions at the level of the sarcomere and a CM phenotype. The sarcomere is a complex with multiple protein interactions, including thick myofilament proteins, thin myofilament proteins, and myosin-binding proteins. In addition, other proteins are involved in the surrounding architecture of the sarcomere such as the Z-disk and muscle LIM proteins. One or multiple genes can exhibit tissue-specific function, development, and physiologically regulated patterns of expression for each protein. Alternatively, multiple mutations in the same gene (compound heterozygosity) or in different genes (digenic heterozygosity) may lead to a phenotype that may be classic, more severe, or even overlapping with other disease forms.

Keywords: Inherited cardiovascular disease, Syndromic cardiovascular disease, Gene variants, Gene disorders, Genetic syndrome, Pathogenic mutation, Heritable cardiomyopathy, Sarcomeric cardiomyopathy, Metabolic disorders, Neuromuscular disease
Cardiomyopathy - Disease of the Heart Muscle

1. Introduction

Cardiomyopathies (CMs) encompass a heterogeneous group of structural and functional (systolic and diastolic) abnormalities of the myocardium and are either confined to the cardiovascular system or are part of a systemic disorder. CMs represent a leading cause of morbidity and mortality and account for a significant percentage of death and cardiac transplantation [1]. The 2006 American Heart Association (AHA) classification grouped CMs into primary (genetic, mixed, or acquired) or secondary (i.e., infiltrative or autoimmune). In 2008, the European Society of Cardiology classification proposed subgrouping CM into familial or genetic and nonfamilial or nongenetic forms. In 2013, the World Heart Federation recommended the MOGES nosology system, which incorporates a morpho-functional phenotype (M), organ(s) involved (O), the genetic inheritance pattern (G), an etiological annotation (E) including genetic defects or underlying disease/substrates, and the functional status (S) of a particular patient based on heart failure symptoms [2–4]. Rapid advancements in the biology of cardio-genetics have revealed substantial genetic and phenotypic heterogeneity in myocardial disease. Given the variety of disciplines in the scientific and clinical fields, any desired classification may face challenges to obtaining consensus. Nonetheless, the heritable phenotype-based CM classification offers the possibility of a simple, clinically useful diagnostic scheme (for an example, see [5]). In this chapter, we will describe the genetic basis of dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy (ACM), LV noncompaction cardiomyopathy (LVNC), and restrictive cardiomyopathy (RCM). Although the descriptive morphologies of these types of CM differ, an overlapping phenotype is frequently encountered within the CM types and arrhythmogenic pathology in clinical practice. CMs appear to originate secondary to disruption of “final common pathways.” These disruptions may have purely genetic causes. For example, single gene mutations result in dysfunctional protein synthesis causing downstream dysfunctional protein interactions at the level of the sarcomere and a CM phenotype. The sarcomere is a complex with multiple protein interactions, including thick myofilament proteins, thin myofilament proteins, and myosin-binding proteins. In addition, other proteins are involved in the surrounding architecture of the sarcomere such as the Z-disk and muscle LIM proteins (Figure 1). One or multiple genes can exhibit tissue-specific function, development, and physiologically regulated patterns of expression for each protein. Alternatively, multiple mutations in the same gene (compound heterozygosity) or in different genes (digenic heterozygosity) may lead to a phenotype that may be classic, more severe, or even overlapping with other disease forms.

![Figure 1](image1.png)

Schematic image of the sarcomere featuring thick/thin filaments and surrounding protein architecture [13].
2. Heritable cardiomyopathies

2.1 Dilated cardiomyopathy

DCM is mainly characterized by left or biventricular dilatation, increased LV mass, and decreased systolic function (Figure 2) [6]. DCM can present with the clinical syndrome of systolic heart failure or with or without associated arrhythmias or thrombo-embolic disease. Additionally, DCM can be detected in asymptomatic individuals. Globally, DCM is the most common form of CM and the leading cause of heart transplantation in children and adults. The estimated incidence in the pediatric population is between 0.34 to 1.13 cases per 100,000 children per year with differences in demographic characteristics [7]. DCM has many known etiologies with many more to be discovered. Unfortunately, in many cases, no etiology can be found, and the CM is deemed idiopathic. Still, 25 to 50% of patients with idiopathic DCM have a positive family history, suggesting an underlying genetic predisposition [8]. The majority of genetically triggered cases of DCM are transmitted in an autosomal dominant pattern exhibiting variable penetrance. Other forms of inheritance include autosomal recessive, X-linked, and mitochondrial (maternally inherited), which are more frequent in the pediatric population [2]. Familial DCM occurs in 20 to 60% of cases, where approximately 40% of those cases may have a primary monogenic basis. However, this percentage is a variable approximation as a more critical evaluation of the genes linked to DCM continues to evolve and certain types of variations are

Figure 2.
Two-dimensional, apical 4-chamber echocardiographic image depicting an enlarged ventricle with spherical geometry and biatrial enlargement secondary to atrioventricular valve insufficiency in a patient with dilated cardiomyopathy.
excluded from being certified as pathogenic [8]. Another conventional classification of DCM is based on the presence or absence of systemic disease. Thus, dividing DCM into syndromic and non-syndromic forms is a practical approach to evaluating this highly heterogeneous disease. The diagnostic rate for gene testing in non-syndromic DCM is 46 to 73% [9], but this estimation may likely be confounded by insufficient control for population variation. Over the past decade, 47 new genes (for a total of 60 different genes) have been linked to DCM in the Human Gene Mutation Database (HGMD), see Table 1. From these genes, a large-scale analysis revealed truncating variants in the titin gene (TNN) were the most common pathogenic mutations in non-syndromic DCM [10, 11]. Other core-causative genes include MYH7 (encoding beta myosin heavy chain), TNNT2 (encoding troponin T2), LMNA (encoding a nuclear envelope protein, lamin A/C), and TPM1 (encoding Tropomyosin 1). Other rare pathogenic variants (minor allele frequency) implicated in non-syndromic DCM include genes coding for the sarcomere and Z-disk (i.e., actin, myosin-binding protein C3, myopalladin, nebulette, ZASP), cytoskeleton (i.e., dystrophin, desmin), nuclear envelope (emerin), mitochondria (i.e., Tafazzin), sarcoplasmic reticulum, desmosomes, ion channels, and transcription factors [9, 12, 13].

Regardless of the mode of inheritance, pathogenic gene variants result in a cardiomyocyte milieu susceptible to stress, leading to downstream dysfunction of the contractile apparatus and heart failure, “the final common pathway” hypothesis [14]. The term “familial DCM” is frequently applied in the presence of DCM in two or more first-degree relatives. The incidence is likely underestimated due to the diversity of inheritance patterns, timing of presentation, variable penetrance, and lack of symptoms in subclinical disease [15, 16].

2.1.1 Autosomal dominant dilated cardiomyopathy

The most common form of familial DCM is inherited in an autosomal dominant pattern [6]. In this sub-type, arrhythmias associated with DCM (DCM-A) are frequently encountered [17]. Genetic heterogeneity exists with at least 30 unique genes identified in familial non-arrhythmogenic DCM and five genes for DCM-A [17, 18].

2.1.2 X-linked Cardiomyopathy (XLCM)

XLCM has been reported as an isolated disease of the heart or associated with skeletal myopathy such as with Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD). All skeletal myopathies are frequently associated with the development of DCM and/or DCM-A. The causative gene codes for the protein dystrophin located at the short arm of the X chromosome at Xp21. Dystrophin is a cytoskeletal protein that provides structural support to the cardiomyocyte and plays a major role in linking the sarcomeric contractile apparatus to the sarcolemma and extracellular matrix (ECM) [19, 20]. DMD and BMD are severe muscular dystrophies of childhood, affecting ~1 in 3,500 males for DMD and 1 in 300,000 males for BMD. Typically, DMD and BMD are characterized by skeletal myopathy, elevated serum creatine kinase, and calf pseudo-hypertrophy. DMD is the more severe form due to the absence of functional dystrophin, leading to muscle weakness by 3 years of age and wheelchair dependence by 12 years of age [21]. Cardiac involvement varies with age but is nearly universal by 20 years in all DMD patients. The onset of clinical features starts later in life in BMD than in DMD. Histologic studies show cardiac muscle replacement with fibrosis. This fibrosis eventually leads to ventricular dysfunction/enlargement and is associated with conduction system abnormalities and ventricular arrhythmias. Molecular analysis of the DMD gene is indicated for diagnosis. If no mutation is detected, skeletal muscle biopsy should
| Gene   | Protein                                                                 | Pattern of Inheritance | Disease Association                  | OMIM#  | Locus     |
|--------|-------------------------------------------------------------------------|------------------------|--------------------------------------|--------|-----------|
| ABCC9  | ATP-Binding Cassette, Subfamily C, Member 9                             | AD                     | DCM                                  | 601439 | 14q12-q22 |
| ACTC1  | Actin, Alpha, Cardiac Muscle                                           | AD                     | DCM, LVNC, ACM, HCM                 | 102540 | 5q31.1    |
| ACTN2  | Actinin, Alpha-2                                                       | AD                     | DCM, HCM                            | 102573 | 6q22.1    |
| AKAP9  | A-Kinase Anchor Protein 9                                              | AD                     | DCM                                  | 604001 | 2q32.1-q32.3 |
| ALMS1  | Centrosome and Basal Body Associated Protein                           | AR                     | DCM                                  | 606844 | 10p14-p12 |
| ALPK3  | Alpha Kinase 3                                                         | AR                     | DCM, HCM                            | 617608 | 1p36.32   |
| ANKRD1 | Ankyrin Repeat Domain-Containing Protein 1                             | AD                     | DCM, HCM                            | 609999 | 7q36.1    |
| BAG3   | Bcl2-Associated Athanogene 3                                           | AD                     | DCM, RCM, HCM                       | 603883 | 14q24.3   |
| CASQ2  | Calsequestrin 2                                                        | AR, AD                 | DCM, LVNC                           | 114251 | 6q22.31   |
| CAV3   | Caveolin 3                                                             | AD                     | DCM, HCM                            | 601253 | 10q24.13  |
| CHRM2  | Cholinergic Receptor, Muscarinic, 2                                    | AD                     | DCM                                  | 118493 | 11q22.1   |
| CRYAB  | Crystallin, Alpha-B                                                    | AD                     | DCM                                  | 123590 | 12p12.1   |
| CSRP3  | Cysteine-And Glycine-Rich Protein 3                                    | AD                     | DCM, HCM                            | 600824 | 12p12.1   |
| CTF1   | Cardiotrophin 1                                                        | AR, AD                 | DCM                                  | 600435 | 1p33.1    |
| DES    | Desmin                                                                 | AR, AR, AR             | DCM, ACM, RCM                       | 125660 | 17q21     |
| DMD    | Dystrophin                                                             | XL                     | DCM                                  | 300377 | 3p25.3    |
| DOLK   | Dolichol Kinase                                                        | AR                     | DCM                                  | 610746 | 7p33      |
| DSC2   | Desmocollin 2                                                          | AD, AR                 | DCM, ACM, RCM                       | 600271 | Xq22      |
| DSG2   | Desmoglein 2                                                           | AD                     | DCM, ACM, RCM                       | 125671 | 15q24.1   |
| DSP    | Desmoplakin                                                            | AD, AR                 | DCM, ACM, RCM                       | 125485 | 11p15.5   |
| DTNA   | Dystrobrevin Alpha                                                     | AD                     | DCM, LVNC                           | 601239 | 2q31      |
| EMD    | Emerin                                                                 | XL                     | DCM                                  | 300384 | 11q23.1   |

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| Gene     | Protein                                      | Pattern of Inheritance | Disease Association         | OMIM#   | Locus      |
|----------|----------------------------------------------|------------------------|-----------------------------|---------|------------|
| EYA4     | Eyes Absent, Drosophila, Homolog Of, 4       | AD                     | DCM                         | 603550  | 11p15.1    |
| FHL1     | Four-And-A-Half LIM Domains 1               | XL                     | DCM, HCM                    | 300163  | 15q22.31   |
| FHL2     | Four-And-A-Half LIM Domains 2               | Unknown                | DCM                         | 602633  | 16p11.2    |
| FKRTP    | Fukutin-Related Protein                     | AR                     | DCM                         | 60696   | 10q21.3    |
| FKTN     | Fukutin                                      | AR                     | DCM                         | 607440  | 2q35       |
| FLNC     | Filamin C                                   | AD                     | DMC, RCM, HCM, ACM          | 102565  | 10q22.2    |
| GATA4    | Gata-Binding Protein 4                      | AD                     | DCM                         | 600576  | Xq21.2-p21.1|
| GATAD1   | Gata Zinc Finger Domain-Containing Protein 1| AR                     | DCM                         | 614518  | 9q34.11    |
| GLA      | Galactosidase, Alpha                         | XL                     | DCM, HCM                    | 300644  | 18q11.2    |
| ILK      | Integrin-Linked Kinase                       | AD                     | DCM                         | 602366  | 18q12.1    |
| JUP      | Junction Plakoglobin                         | AD, AR                 | DCM, ACM                    | 173325  | 2p13.1     |
| LAMA4    | Laminin, Alpha-4                            | AD                     | DCM                         | 600133  | 18q21.1    |
| LAMP2    | Lysosome-Associated Membrane Protein 2       | XL                     | DCM, HCM                    | 309060  | 3p25.2     |
| LDB3     | Lim Domain-Binding 3                         | AD                     | DCM, LVNC, ACM, HCM         | 605906  | 2p22.1     |
| LMNA     | Lamin A/C                                    | AD, AR                 | DCM, LVNC, ACM, HCM         | 150330  | 1q22       |
| LRRRC10  | Leucine-Rich Repeat-Containing Protein 10    | AD, AR                 | DCM                         | 610846  | 4q21.3     |
| MURC/CAVIN4 | Muscle-Related Coiled-Coil Protein/Caveolae-Associated Protein 4 | AD | DCM | 617714 | 18q12.1 |
| MYBPC3   | Myosin-Binding Protein C, Cardiac            | AD                     | DCM, LVNC, RCM, HCM         | 600958  | Xq28       |
| MYH6     | Myosin, Heavy Chain 6, Cardiac Muscle, Alpha| AD                     | DCM, HCM                    | 160710  | 10q25.2    |
| Gene   | Protein                                                                 | Pattern of Inheritance | Disease Association          | OMIM#    | Locus      |
|--------|-------------------------------------------------------------------------|------------------------|------------------------------|----------|------------|
| MYH7   | Myosin, Heavy Chain 7, Cardiac Muscle, Beta                            | AD                     | DCM, LVNC, RCM, HCM         | 160760   | 7p14.2     |
| MYL2   | Myosin, Light Chain 2, Regulatory, Cardiac, Slow                       | AD                     | DCM, HCM                    | 160781   | 3p21.3-p21.2|
| MYL3   | Myosin, Light Chain 3, Alkali, Ventricular, Skeletal, Slow            | AD, AR                 | DCM, HCM, RCM               | 160790   | 1q32       |
| MYLK2  | Myosin Light Chain Kinase 2                                            | AD                     | DCM, HCM                    | 606566   | 160781     |
| MYOT   | Myotilin                                                               | AD                     | DCM                         | 604103   | Xq28       |
| MYZ2   | Myogenin 2                                                             | AD                     | DCM, RCM, HCM               | 605602   | 3p25.1     |
| MYPN   | Myopalladin                                                            | AD                     | DCM, RCM, HCM               | 608517   | 12q23.1    |
| NEBL   | Nebulette                                                              | AD                     | DCM                         | 605491   | 6q23.2     |
| NEXN   | Nexilin (F Actin Binding Protein)                                      | AD                     | DCM, HCM                    | 613121   | 1q22       |
| NKK2-5 | Nk2 Homeobox 5                                                         | AD                     | DCM                         | 600584   | Xq26.3     |
| PDLIM3 | Pdz And Lim Domain Protein 3                                           | AD                     | DCM, HCM                    | 608999   | 1q43       |
| PKP2   | Plakophilin 2                                                          | AD                     | DCM, ACM                    | 602861   | 11p15.4    |
| PLN    | Phospholamban                                                          | AD                     | DCM, ACM, HCM               | 172405   | 4q12       |
| PRDM16 | Pr Domain-Containing Protein 16                                        | AD                     | DCM, LVNC                   | 605557   | 6q21       |
| PRKAG2 | Protein Kinase, Amp-Activated, Noncatalytic, Gamma-2                   | AD                     | DCM, HCM                    | 602743   | 4q26-q27   |
| RBM20  | RNA-Binding Motif Protein 20                                            | AD                     | DCM                         | 613171   | 2q12.2     |
| RYR2   | Ryanodine Receptor 2 (Cardiac)                                         | AD                     | DCM, HCM, ACM               | 180902   | 12p11      |
| SCNSA  | Sodium Channel, Voltage-Gated, Type V, Alpha Subunit                   | AD                     | DCM, ACM                    | 600163   | 20q13.12   |
| SGCA   | Sarcoglycan Alpha                                                      | AR                     | DCM                         | 600119   | 1q25.2     |
| SGCB   | Sarcoglycan Beta                                                       | AR                     | DCM                         | 600900   | 15q22.1    |
| SGCD   | Sarcoglycan, Delta (35kDa Dystrophin-Associated Glycoprotein)          | AD, AR                 | DCM                         | 601411   | 19q3.32    |
| Gene       | Protein                                        | Pattern of Inheritance | Disease Association | OMIM#  | Locus         |
|------------|-----------------------------------------------|------------------------|---------------------|--------|---------------|
| SLC25A4    | Solute Carrier Family 25, Member 4 (Mitochondrial Carrier Adenine Nucleotide Translocator) | AD, AR                 | DCM                 | 103220 | 7q21-q22      |
| TAZ        | Tafazzin                                      | AR, XL                 | DCM, LVNC           | 300394 | Xq24          |
| TBX20      | T-Box 20                                      | AD                     | DCM, LVNC           | 606061 | 10q22.3-q23.2 |
| TCAP       | Titin-Cap (Telethonin)                        | AR                     | DCM, HCM            | 604488 | 3q21          |
| TMEM43     | Transmembrane Protein 43                      | AD                     | DCM, ACM            | 612048 | 10q23.3       |
| TMPO       | Thymopoietin                                  | AD                     | DCM                 | 188380 | 9q31.2        |
| TNNC1      | Troponin C Type 1 (Slow)                      | AD                     | DCM, HCM            | 191040 | 17q21.33      |
| TNNI3      | Troponin I Type 3 (Cardiac)                   | AD                     | DCM, RCM, HCM       | 191044 | 3p21.1        |
| TNNT2      | Troponin T Type 2 (Cardiac)                   | AD                     | DCM, LVNC, RCM, HCM | 191045 | 17q12         |
| TOR1AIP1   | Torsin-1a-Interacting Protein 1               | AR                     | DCM                 | 614512 | 7q32.1        |
| TPM1       | Tropomyosin 1 (Alpha)                         | AD                     | DCM, RCM, HCM       | 191010 | 19q13.4       |
| TRDN       | Triadin                                       | AR                     | DCM                 | 603283 | 17q25.3       |
| TTN        | Titin                                         | AD, AR                 | DCM, ACM, HCM       | 188840 | 5q33-q34      |
| TTR        | DCMP                                          | AD                     | DCM                 | 176300 | 18q12.1       |
| TXNRD2     | Thioredoxin Reductase 2                       | AD, AR                 | DCM                 | 606448 | 8p23.1        |
| VCL        | Vinculin                                      | AD                     | DCM, LVNC, HCM      | 193065 | 10q25.2       |

AD – Autosomal dominant; AR – Autosomal Recessive; XL – X-linked; DCM – Dilated cardiomyopathy; HCM – Hypertrophic cardiomyopathy; LVNC – Left ventricular non-compaction cardiomyopathy; ACM – Arrhythmogenic cardiomyopathy; RCM – Restrictive cardiomyopathy.

Table 1.
List of common genes and patterns of inheritance in DCM, modified from Tiyal et al. [9].
be considered for Western blot and immunohistochemistry studies, although this is rarely performed in current clinical practice [19, 20, 22–24]. Although less severe, female carriers with clinical DMD and BMD are also at risk to develop DCM but at a later age. Hence, a complete cardiac evaluation for carrier females every 3-5 years starting in adolescence or early adulthood is warranted with concomitant appropriate medical treatment if indicated [25].

2.1.3 Isolated X-Linked Dilated Cardiomyopathy

Isolated XLCM is characterized by consistent early expression and rapid progression of CM in males during childhood, later onset with slower progression in females, and no male-to-male transmission [26]. Linkage analysis of X-chromosome-specific DNA markers performed in suspected individuals demonstrated preferential involvement of cardiac muscle and normal dystrophin by Western blotting in skeletal muscle of the same affected individuals [27]. The phenotype and pathologic features described in this population do not differ from those in patients with DCM. Hence, the medical management should be provided according to the current heart failure guidelines.

2.1.4 Emery-Dreifuss Muscular Dystrophy

Emery-Dreifuss muscular dystrophy (EDMD), also known as humeroperoneal muscular dystrophy, is a heterogeneous disorder with X-linked recessive, autosomal dominant, and autosomal recessive forms of inheritance [28]. Several forms of this disease are considered nuclear envelopopathies because they are associated with mutations in genes encoding nuclear membrane proteins, including the EMD gene encoding for emerin, the LMNA gene encoding for lamin A and lamin C, and the SYNE1 and SYNE2 genes encoding for nesprin 1 and nesprin 2, respectively [29]. The different forms of EDMD have identical symptoms that usually begin in the first or second decade of life. Extremity contractures are often the first manifestation. Muscle weakness and wasting has a humeroperoneal distribution and tends to be slowly progressive. DCM is seen in many patients with EDMD. This condition is typically associated with atrioventricular conduction abnormalities such as first-degree atrioventricular block, sinus bradycardia, or supraventricular tachycardia, which may be early signs of cardiac involvement and may be progressive. Symptoms of hypoperfusion (syncope or near syncope) often result from infranodal or atrioventricular conduction block with the development of slow junctional rhythms, which may require pacemaker placement [30]. The onset of cardiac abnormalities is usually in the third decade of life, but earlier onset during adolescence has been observed. Additionally, there is no correlation between the degree of neuromuscular involvement and the severity of cardiac abnormalities [31].

2.1.5 Barth Syndrome

Barth syndrome (BTS) is another X-linked cardioskeletal myopathy that encompasses abnormal mitochondrial function, short stature, cyclic neutropenia, cardiolipin deficiency, and variable degrees of 3-methylglutaconic aciduria. BTS is caused by mutations in the TAZ gene (previously called G4.5), which is located in the chromosome Xq28 region and encodes for the Tafazzin protein [32]. Pathologic gene variants may result in a wide variety of cardiac phenotypes including DCM, HCM, LVNC, and endocardial fibroelastosis. In many cases, affected infants succumb to heart failure, arrhythmias, or sepsis secondary to leukocyte dysfunction [33, 34].
2.2 Hypertrophic cardiomyopathy

HCM is the second most prevalent CM in children, representing 40% of cases, with an estimated incidence of 0.47 in 100,000 children [35]. HCM is more prevalent in boys than in girls and in African American children than in Caucasian or Hispanic children. In the pediatric population, the incidence of HCM is 10 times higher in patients under 1 year of age than in older children [36]. HCM is a primary myocardial disorder with mainly an autosomal dominant pattern of inheritance characterized by hypertrophy of the left ventricle (with or without hypertrophy of the right ventricle) and histologic features of myocyte hypertrophy, myofibrillar disarray, and interstitial fibrosis. While asymmetric septal hypertrophy is the most common pattern of hypertrophy, the degree and location of hypertrophy vary. Some patients exhibit concentric hypertrophy, harbored in other walls or confined to the left ventricular apex (Figure 3) [37].

The clinical presentation of HCM is highly variable, ranging from asymptomatic hypertrophy, to symptomatic arrhythmias, to refractory heart failure due to diastolic dysfunction, or “burned-out HCM” with the development of systolic dysfunction. Notably, diastolic dysfunction can even be detected in individuals with HCM who have normal LV wall thickness, suggesting that diastolic dysfunction is an early feature of HCM rather than a secondary consequence of hypertrophy [38]. Categorization of HCM includes non-syndromic HCM (without other systemic involvement) and the syndromic form of HCM (in association with inborn errors of metabolism, malformation syndromes, and neuromuscular disorders) [39].

![Figure 3.](image)

Two dimensional images of HCM in the parasternal short axis (A) exhibiting concentric hypertrophy with significant involvement of the interventricular septum (IVS) and corroborated by the parasternal long axis view (B). Cardiac MRI also shows significant thickening of the IVS (C).
Approximately 20–30% of individuals with non-syndromic HCM and no family history of HCM harbor a pathogenic variant in a known gene encoding a component of the sarcomere. However, 50–60% of adults and children with a positive family history of HCM harbor a pathogenic gene variant. Furthermore, 3–5% of affected individuals have more than one sarcomere gene variant (either biallelic variants in 1 gene or heterozygous variants in >1 gene) [40, 41].

### 2.2.1 Non-syndromic Hypertrophic Cardiomyopathy

More than two decades ago, the first chromosome locus (14q11.2-q12) encoding components of the sarcomere (beta-myosin heavy chain) was elucidated as the pathogenic basis for familial HCM [42]. Since then, more than 1,400 mutations in 27 identified genes have been associated with HCM, see Table 2 [43]. The vast majority have autosomal dominant transmission, but mitochondrial and autosomal recessive patterns have been also described [44–46]. Most of the disease-causing mutations implicated in HCM include mutations in the MYH7 gene (encoding beta-myosin heavy chain) and in the MYBPC3 gene (encoding cardiac myosin-binding protein C). These mutations account individually for 40%, and the remaining genes (TNNT2, TPM1, ACTC1, TNNI3, TTN, MYL2, and others) account collectively for 10% of cases [47]. Most of these mutations involve missense mutations (resulting in a direct amino acid change) and frameshift-type mutations (insertions or deletions of the number of nucleotides), which alter the properties of the protein involved. The prevalence of causal genes varies among different populations. Collective results of genetic epidemiologic studies suggest that up to 70% of the causal genes in familial cases and up to 40% in sporadic HCM cases have a genetic mutation identified [44–46]. In our experience in the past 10 years, approximately 70% of non-infantile individuals have an identifiable mutation in a sarcomere-encoding gene, whereas fewer mutations (approximately 20%) are identified in infants.

Mouse models of sarcomeric mutations have shown changes in cardiac chemistry and diastolic function well before myocardial hypertrophy is observed [48]. Moreover, the genetic defect in a gene encoding for a sarcomeric protein may disrupt normal contraction and relaxation with dysregulation of calcium in the sarcomere. Thus, reduced calcium reuptake and decreased stores in the sarcoplasmic reticulum will trigger a remodeling process by several transcription factors, resulting in the hypertrophy of the cardiomyocytes and increased energy demand, which eventually results in ischemia, fibrosis, and death [44]. There is no reliable correlation between the genotype and phenotype among the identified sarcomeric mutations, except for those patients harboring multiple mutations [49].

### 2.2.2 Syndromic hypertrophic cardiomyopathy

HCM has been associated with multiple phenotypically distinct disorders. Improvements in sequencing technologies and phenotypic characterization and the incorporation of epigenetics have expanded our understanding of syndromic CMs.

#### 2.2.2.1 RAS/MAPK pathway syndromes

Since the discovery of the first gene (PTPN11) associated with Noonan syndrome in 2001, multiple genes (RAF1, SOS1, KRAS, NRAS, BRAF, MAP2K1 [MEK1], MAP2K2 [MEK2], HRAS, and SHOC2) have been identified in the RAS/mitogen-activated protein kinase (MAPK) pathway. This pathway is important for control of cell proliferation and differentiation. Thus, dysregulation results in
| Gene   | Protein                                      | Pattern of Inheritance | Disease Association           | OMIM#   | Locus     |
|--------|----------------------------------------------|------------------------|--------------------------------|---------|-----------|
| ACTC1  | Actin, alpha, Cardiac Muscle                 | AD                     | HCM, DCM, ACM                 | 100540  | 5q31.1    |
| ACTN2  | Alpha-Kinase 3                               | AD                     | HCM, DCM                      | 104373  | 6p21.1    |
| ALPK3  | Alpixin Repeat Domain-Containing Protein 1   | AD                     | HCM, DCM, ACM                 | 617608  | 7q36.1    |
| ANKR31 | Ankyrin, Repeat Domain-Containing Protein 1  | AD                     | HCM, DCM, ACM                 | 609593  | 7q36.1    |
| BAG3   | beta-A2-Sarcoglycan A2B                        | AD                     | HCM, DCM, ACM                 | 5q33.3  | 13q12     |
| BRAF   | V-Raf Murine Sarcoma Viral Oncogene Homolog  | AD                     | HCM, DCM                      | 609834  | 12p13.11  |
| CAV3   | Caveolin 3                                    | AD                     | HCM, DCM                      | 601253  | 12q24.13  |
| CRP3   | Caveolin Repeat Domain-Containing Protein 3   | AD                     | HCM, DCM                      | 102540  | 5q31.1    |
| FLNC   | Filamin C                                    | AD                     | HCM, DCM, ACM                 | 60034  | 12p13.11  |
| FH1    | Four-and-A-Half LIM Domains 1                | AD                     | HCM, DCM, ACM                 | 102540  | 5q31.1    |
| GAA    | Glutamidase-Alpha                            | AD                     | HCM, DCM                      | 602587  | 1q21.2    |
| GLA    | Glucosidase-Alpha                            | AD                     | HCM, DCM, ACM                 | 609593  | 7q36.1    |
| HTRAS  | VARs Sarcoma Viral Oncogene Homolog          | AD                     | HCM, DCM                      | 102540  | 5q31.1    |
| JPH2   | Junctophilin 2                                | AD                     | XL                             | 306569  | 16p13.3   |
| JUN   | Junctophilin 2                                | AD                     | HCM, DCM                      | 306569  | 16p13.3   |
| LAM2   | Lysosome-Associated Membrane Protein 2        | AD                     | XL                             | 306569  | 16p13.3   |
| LAM3   | Lysosome-Associated Membrane Protein 2        | AD                     | XL                             | 306569  | 16p13.3   |
| LDMK   | Lim Domain-Binding 3                          | AD                     | XL                             | 306569  | 16p13.3   |
| MAPK1  | Mitogen-Activated Protein Kinase 1            | AD                     | XL                             | 164757  | 12q15     |
| MAPK2  | Mitogen-Activated Protein Kinase 2            | AD                     | XL                             | 164757  | 12q15     |
| MAPK3  | Mitogen-Activated Protein Kinase 1            | AD                     | XL                             | 164757  | 12q15     |
| MYH6   | Myosin, Heavy Chain, Cardiac Muscle, Alpha    | AD                     | XL                             | 164757  | 12q15     |
| Gene  | Protein                                             | Pattern of Inheritance | Disease Association          | OMIM#  | Locus     |
|-------|-----------------------------------------------------|------------------------|------------------------------|--------|-----------|
| MYH7  | Myosin, Heavy Chain 7, Cardiac Muscle, Beta         | AD                     | HCM, DCM, LVNC, RCM          | 160760 | 7p14.2    |
| MYL2  | Myosin, Light Chain 2, Regulatory, Cardiac, Slow   | AD                     | HCM                          | 160781 | 3p21.3-21.2 |
| MYL3  | Myosin, Light Chain 3, Alkali, Ventricular, Skeletal, Slow | AD, AR | HCM, RCM                      | 160790 | 1q32     |
| MYLK2 | Myosin Light Chain Kinase 2                         | AD                     | HCM                          | 606566 | 20q13.31  |
| MYOM1 | Myomesin 1                                          | AD                     | HCM                          | 603508 | 18p11.31  |
| MYOZ2 | Myozenin 2                                          | AD                     | HCM, DCM, RCM                | 605602 | 3p25.1    |
| MYLK2 | Myosin Light Chain Kinase 2                         | AD                     | HCM                          | 606566 | 20q13.31  |
| MYOM1 | Myomesin 1                                          | AD                     | HCM                          | 603508 | 18p11.31  |
| MYOZ2 | Myozenin 2                                          | AD                     | HCM, DCM, RCM                | 605602 | 3p25.1    |
| MYL2  | Myosin, Light Chain 2, Regulatory, Cardiac, Slow   | AD                     | HCM                          | 160781 | 3p21.3-21.2 |
| MYL3  | Myosin, Light Chain 3, Alkali, Ventricular, Skeletal, Slow | AD, AR | HCM, RCM                      | 160790 | 1q32     |
| MYLK2 | Myosin Light Chain Kinase 2                         | AD                     | HCM                          | 606566 | 20q13.31  |
| MYOM1 | Myomesin 1                                          | AD                     | HCM                          | 603508 | 18p11.31  |
| MYOZ2 | Myozenin 2                                          | AD                     | HCM, DCM, RCM                | 605602 | 3p25.1    |
| NEXN  | Nexilin (F Actin Binding Protein)                   | AD                     | HCM, DCM                     | 613121 | 1q22     |
| NRAS  | Neuroblastoma Ras Viral Oncogene Homolog            | AD                     | HCM                          | 164790 | 5q31.2    |
| PDLIM3| Pdz And Lim Domain Protein 3                        | AD                     | HCM, DCM                     | 605899 | 1q43     |
| PLN   | Phospholamban                                       | AD                     | HCM, DCM, ACM                | 172405 | 4q12     |
| PRKAG2| Protein Kinase, Amp-Activated, Noncatalytic, Gamma-2| AD                     | HCM                          | 602743 | 4q26-q27  |
| PTPN1 | Protein-Tyrosine Phosphatase, Nonreceptor-Type, 11  | AD                     | HCM                          | 176876 | 10q21.3   |
| RAF1  | V-Raf-1 Murine Leukemia Viral Oncogene Homolog 1    | AD                     | HCM                          | 164760 | 10p12    |
| RT1   | Ras-Like Without Caax 1                             | AD                     | HCM                          | 609591 | 1p31.1    |
| RYR2  | Ryanodine Receptor 2 (Cardiac)                      | AD                     | HCM, ACM                     | 180902 | 12p11    |
| SHOC2 | Soc-2 Homolog                                       | AD                     | HCM                          | 602775 | 5q35.1    |
| SOS1  | Son Of Sevenless, Drosophila, Homolog 1             | AD                     | HCM                          | 182530 | 1p13.2    |
| TCAP  | Titin-Cap (Telethonin)                              | AR                     | HCM, DCM                     | 604488 | 3p21     |
| TNN1C | Troponin C Type 1 (Slow)                            | AD                     | HCM, DCM                     | 191040 | 17q21.33  |
| TNN1B | Troponin I Type 3 (Cardiac)                         | AD                     | HCM, DCM, RCM                | 191044 | 3p21.1    |
| TNN2  | Troponin T Type 2 (Cardiac)                         | AD                     | HCM, DCM, LVNC, RCM          | 191045 | 17q12     |
| TPM1  | Tropomyosin 1 (Alpha)                               | AD                     | HCM, DCM, RCM                | 191010 | 19q13.4   |
| Gene | Protein | Pattern of Inheritance | Disease Association | OMIM# | Locus |
|------|---------|-----------------------|---------------------|-------|-------|
| TTN  | Titin   | AD, AR                | HCM, DCM, ACM       | 188840| 5q33-q34 |
| TTR  | Transthyretin | AD                | HCM                | 176300| 4q35.1 |
| VCL  | Vinculin | AD                    | HCM, DCM, LVNC     | 193065| 10q25.2 |

AD – Autosomal dominant; AR – Autosomal Recessive; XL – X-linked; DCM – Dilated cardiomyopathy; HCM – Hypertrophic cardiomyopathy; LVNC – Left ventricular non-compaction cardiomyopathy; ACM – Arrhythmogenic cardiomyopathy; RCM – Restrictive cardiomyopathy.

Table 2. List of common genes and patterns of inheritance in HCM.
a spectrum of disorders known as “RASopathies” including Noonan and Noonan-like syndromes such as LEOPARD, Costello, and cardiofaciocutaneous syndrome (CFC) [50].

The management of RASopathies should involve a multidisciplinary team with expertise in the assessment of cardiac structural defects, HCM, and arrhythmias. Surveillance with periodic echocardiography (HCM), electrocardiography (rhythm disturbances), neurologic and eye examination, evaluation for scoliosis, and assessment of growth and cognitive development is also recommended.

2.2.2.1.1 Noonan syndrome

Noonan syndrome is relatively common with a prevalence of ~1 in 3500 people. This disease is inherited in an autosomal dominant pattern, although new cases are common because the de novo mutation rate is high. Clinical manifestations of Noonan syndrome include short stature, as well as dysmorphic features including hypertelorism, down-slanting palpebral fissures, low-set posteriorly rotated ears, lymphatic anomalies, and webbing of the neck. The estimated frequency of cardiac disease is 50 to 80%, and the disease is mainly characterized by pulmonary valve stenosis, branch pulmonary artery stenosis and Tetralogy of Fallot, in addition to HCM. PTPN11 gene mutations are more common in individuals with pulmonary stenosis, characteristic facial features, and short stature, while mutations in the RAF1 gene are associated with HCM in up to 95% of individuals [51]. The myocardial involvement in these patients is typically diagnosed during infancy with findings of asymmetric septal hypertrophy associated with myocyte disarray [52, 53]. With progression of the disease, the combination of biventricular outflow tract obstruction is poorly tolerated and associated with increased mortality. Presentation during infancy without congestive heart failure is associated with a 70% three-year survival rate; when associated with congestive heart failure, the 6-month survival rate decreases to 30% [54].

Surgical relief of right ventricular outflow tract obstruction (RVOTO) is recommended in patients with more than a mild degree of obstruction. Septal myectomy is also advised when left ventricular outflow tract obstruction (LVOTO) is associated with heart failure symptoms, although re-growth of the LVOTO is common when myectomy is performed in patients younger than one year of age. In some children, heart transplantation is necessary.

2.2.2.1.2 LEOPARD syndrome

LEOPARD syndrome, also called Noonan syndrome with multiple lentigines, is a rare autosomal dominant disorder caused by mutations in the protein tyrosine phosphatase gene, PTPN11. LEOPARD is an acronym for the major features of this disorder, including multiple lentigines, electrocardiogram conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness [55]. Multiple lentigines, present in more than 90% of patients, are the most prominent manifestation of LEOPARD syndrome. Lentigines appear during infancy and early childhood and increase in number over time to involve a large portion of the skin, including the face, neck, and upper trunk. The diagnosis of LEOPARD is difficult, given the highly variable expressivity of the syndrome. In the first year of life, before the appearance of lentigines, the diagnosis can be clinically suspected in infants presenting with characteristic facial features, HCM, and café-au-lait macules. The diagnosis can be confirmed by molecular screening for PTPN11 mutations [56].
2.2.2.1.3 Costello syndrome

Costello syndrome is a rare disorder with substantial clinical overlap with other RASopathy syndromes. This disorder is caused by mainly de novo heterozygous mutations in the HRAS gene, with more than 90% of the mutations clustered in codons 12 and 13 [57]. Costello syndrome is characterized by failure-to-thrive in infancy, short stature, characteristic facial features, curly/sparse hair, papillomata, osteoporosis, malignancies (such as embryonal rhabdomyosarcoma), cardiovascular malformations (such as pulmonary stenosis and HCM), rhythm disturbances (such as multifocal atrial tachycardia), and neurological abnormalities including intellectual disability [58].

2.2.2.1.4 Cardiofaciocutaneous (CFC) syndrome

Cardiofaciocutaneous (CFC) syndrome also has substantial clinical overlap with other RASopathy syndromes because of its common ectodermal involvement as well as findings of intellectual impairment and cardiac anomalies. Skin abnormalities can be extensive and include hyperkeratosis, eczema, palmoplantar hyperkeratosis, and keratosis pilaris. The hair is typically sparse and curly. CFC syndrome is characterized by cardiac abnormalities (pulmonary valve stenosis, other valve dysplasias, septal defects, HCM, and rhythm disturbances). HCM is identified in approximately 40% of cases and presents more commonly during infancy, but it can develop at any age [59]. Neoplasia, mostly acute lymphoblastic leukemia (ALL), has been reported in some individuals [50, 60]. Diagnosis is based on clinical findings and molecular genetic testing. Common genes associated with CFC syndrome include BRAF (~75%), MAP2K1 and MAP2K2 (~25%), and MEK2 and KRAS (<2%) [61–63].

2.2.2.2 Metabolic disorders associated with cardiomyopathy

Congenital metabolic disorders result from absent or abnormal enzymes—or their cofactors—which can lead to accumulation or deficiency of a specific metabolite. Although these disorders exhibit different modes of inheritance, most are transmitted in an autosomal recessive or mitochondrial pattern. The possibility of an inborn error of metabolism should be considered in infants, children, and young adults who present with any of the cardiovascular phenotypes or laboratory features described below. Optimal outcomes for children with these disorders depend upon early recognition of the signs and symptoms of metabolic disease, prompt evaluation, and referral to a center with expertise in cardiovascular genetics. Delay in diagnosis may result in acute metabolic/hemodynamic decompensation, progressive neurologic injury, or death.

2.2.2.2.1 Pompe disease

Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive metabolic disorder that affects muscle and nerve cells throughout the body. This condition occurs secondary to accumulation of glycogen in lysosomes due to a deficiency of the lysosomal acid alpha-glucosidase enzyme. The build-up of glycogen leads to progressive myopathy and weakness throughout the body affecting various tissues including the liver, nervous system, and—most notably—skeletal muscle and myocardium. The Pompe phenotype varies widely [64]. In the infantile form, muscles appear normal but are limp and weak, preventing normal development. Elevated creatine kinase, lactate dehydrogenase, and aspartate
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aminotransferase (AST) are common. ECG reveals a short PR interval with giant QRS complexes in all leads, suggesting biventricular hypertrophy. As the disease progresses, HCM may result in cardiorespiratory failure. Without treatment, death usually occurs due to heart failure and respiratory weakness within the first year of life [65]. The juvenile and adult forms present with a variable age of onset. The primary clinical finding is skeletal myopathy with a more protracted course, leading to respiratory failure. Affected children usually present with delayed gross-motor development and progressive weakness in a limb-girdle distribution. Early involvement of the diaphragm is a common feature leading to death in the second or third decade of life. In contrast to the infantile form, mild and non-specific cardiac abnormalities can be detected in patients with late-onset disease [66]. Enzyme replacement therapy usually results in decreased ventricular hypertrophy, reduced LV outflow tract obstruction, and normalization of the conduction system [67].

2.2.2.2 Danon disease

Danon disease, also known as glycogen storage disease type IIb, is an X-linked lysosomal and glycogen storage disorder associated with skeletal muscle weakness and intellectual disability. Danon disease involves a genetic defect in the LAMP2 gene located at chromosome Xq24, which encodes the lysosome-associated membrane protein and alters the normal protein structure. While the function of the LAMP2 gene is not well understood, LAMP2 protein is primarily located in lysosomes. HCM and electrophysiologic abnormalities are the major cardiovascular consequences of glycogen accumulation with resultant myocardial degeneration. Ventricular preexcitation is encountered at a much higher frequency in Danon disease than in sarcomere-related HCM [68, 69]. The cardiac degeneration is usually appreciated clinically by the presence of HCM during childhood or adolescence with subsequent transition to a DCM phenotype with progressive heart failure [70]. Female carriers have also been described in this disorder and are attributed to unfavorable lyonization [71]. They commonly develop symptoms in their 30s to 40s and can be afflicted with DCM.

2.2.2.3 Fabry disease

Fabry disease is considered the most prevalent lysosomal storage disorder. This disease is an X-linked inborn error of the glycosphingolipid metabolic pathway and involves deficiency of the lysosomal hydrolase alpha-galactosidase A (alpha-Gal A) mapped to the long arm of the X chromosome (Xq22.1) [72]. Several hundred mutations in the GLA gene have been identified. Most cases are familial and few originate from de novo mutations [73]. Patients with Fabry disease may present with a spectrum of clinical manifestations, ranging from the severe classic phenotype in males to asymptomatic disease in females. The enzyme deficiency results in accumulation of glycosphingolipids in the lysosomes in nearly all cell types and tissues, leading to multisystem disease including neurologic (paresthesia and pain crises), dermatologic (angiokeratomas and telangiectasias), ophthalmologic (corneal dystrophy), renal (proteinuria and renal insufficiency), and cardiac manifestations by the second to fifth decades of life [74]. Cardiac disease is relatively common in Fabry disease. Patients may develop HCM (similar to that seen in sarcomeric HCM), arrhythmias, and valvar abnormalities. Management of cardiovascular symptoms and the prevention of complications rely on conventional pharmacologic and device-based therapies, but data on the effect of enzyme replacement therapy suggest it has the potential to attenuate and possibly reverse some aspects of cardiac involvement [75, 76].
2.2.2.2.4 Friedreich’s ataxia

Friedreich’s ataxia is an autosomal recessive inherited disease with an estimated incidence of 1 in 50,000 in the general population. The genotype is characterized by trinucleotide repeat expansion of a normal codon affecting the protein frataxin, a mitochondrial inner membrane protein important for iron homeostasis. As the defect lies within an intron (which is removed from the mRNA transcript between transcription and translation), this mutation does not result in the production of abnormal frataxin. Instead, the mutation decreases the transcription of the gene through gene silencing. Low frataxin levels lead to insufficient biosynthesis of iron–sulfur clusters that are required for the mitochondrial electron transport chain to ultimately generate adenosine triphosphate (ATP). The major clinical manifestations of Friedreich’s ataxia include progressive neurologic dysfunction (gait ataxia, optic atrophy, loss of position and vibration sense), diabetes mellitus, and myocardial involvement. The cardiac phenotype is manifested by arrhythmias and HCM. Heart failure remains the leading cause of death in this population [77, 78]. HCM is seen in approximately two-thirds of patients with Friedreich’s ataxia, and one-third of those cases develop during childhood [79].

2.2.2.2.5 Mitochondrial cardiomyopathy

Mitochondria are the main energy source in cells due to the ability to perform oxidative phosphorylation via proteins in the mitochondrial respiratory chain. Several genes are involved in the role of cellular energy production. Mutations in these genes may result in severe involvement in organs that are heavily dependent on energy production, such as the brain, heart, and skeletal muscle. Mitochondrial DNA (mtDNA) is exclusively maternally inherited, whereas nuclear DNA follows Mendelian inheritance. The frequency of cardiac involvement in mitochondrial disease is 17–40%, and the estimated prevalence of inherited mitochondrial disease is at least 1 in 5,000 births [80]. More than 40 different types of mitochondrial disease have been associated with the development of HCM. Many forms of mitochondrial disease associated with HCM present during infancy. Because diagnosing mitochondrial disease can be challenging for clinicians, it is recommended that a multidisciplinary team (including a geneticist or mitochondrial specialist) be involved in the diagnosis and management [81]. Mitochondrial CM is characterized by abnormal heart-muscle structure, function, or both. These abnormalities result from genetic defects involving mitochondrial activity in the absence of concomitant coronary artery disease, hypertension, valvular disease, or CHD. The typical cardiac manifestations of mitochondrial disease include the presence of arrhythmias, hypertrophic HCM, LVNC and DCM. Worsening cardiovascular disease may occur during a metabolic crisis [80–82].

Barth syndrome, described earlier in this chapter, is an X-linked disorder caused by pathogenic variants in the TAZ gene on chromosome Xq28, resulting in an inborn error of lipid metabolism, cardioliopin deficiency, 3-methylglutaconic aciduria, and cyclic neutropenia. BTS patients may occasionally develop any form of CM, including HCM [32].

2.2.2.2.6 MELAS

MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) is a multisystem clinical syndrome. Cardiac involvement is manifested by
nonobstructive concentric hypertrophy (HCM), although DCM, Wolff-Parkinson-White (WPW) syndrome, and atrial tachycardia have also been reported [83–85]. Several genes have been postulated to cause MELAS, including the ones listed in Table 3.

### 2.3 Left ventricular noncompaction cardiomyopathy

LVNC is characterized by the presence of trabeculations, deep intertrabecular recesses, and a thin compacted myocardial layer in the left, right, or both ventricles. The incidence of LVNC is unknown, but some studies estimate 0.014% to 1.3% in the general population [4]. However, with improved echocardiographic and cardiac MRI quality and increasing awareness of LVNC in recent years, the incidence is likely underestimated [34]. Clinically, nine forms of LVNC have been described as follows: [1] the “benign” form of LVNC with normal systolic function, normal chamber sizes and thickness, and no history of arrhythmias; [2] the arrhythmogenic form of LVNC; [3] the DCM form of LVNC; [4] the HCM form of LVNC; [5] the mixed/undulating CM form of LVNC; [6] the RCM form of LVNC; [7] the biventricular noncompaction CM form; [8] the right ventricular noncompaction form (RVNC); and [9] LVNC associated with congenital heart disease [34, 81, 86, 87]. The various phenotypes are depicted in Figure 4. The clinical presentation may range from asymptomatic to a severe course accompanied by heart failure requiring heart transplant, arrhythmias, sudden cardiac death, and thromboembolic phenomena [88]. Familial cases are well-documented, and autosomal dominant transmission is the most common inheritance pattern (with variable penetrance and phenotypic heterogeneity). Other modes of inheritance include X-linked, autosomal recessive, and mitochondrial [43]. In pediatric and adult cohorts, the diagnostic rate of gene testing in patients with LVNC ranges from 17–41% depending on patient selection and the number of genes screened. An estimated 18 to 50% of probands have a family member with LVNC [89, 90].

One of the first genetic causes of isolated LVNC was described in 1997 in the gene G4.5/TAZ located at chromosome Xq28 [88]. Since then, multiple pathologic gene variants have been described as potential causes of LVNC. Genes encoding sarcomeric and cytoskeletal proteins (TTN, ACTN2, RBM20, LMNA, DES, DYS, DTNA, LDB3, MYH7, MYBPC3, ACTC1) as well as genes associated with

| Gene/locus | Gene location |
|------------|---------------|
| MTTL1      | Mitochondrial |
| MTTQ       | Mitochondrial |
| MTT  | Mitochondrial |
| MTNK       | Mitochondrial |
| MTT  | Mitochondrial |
| MTTS1      | Mitochondrial |
| MTND1      | Mitochondrial |
| MTND5      | Mitochondrial |
| MTND6      | Mitochondrial |
| MTTS2      | Mitochondrial |

Table 3. Genes associated with MELAS [83–85].
Cardiomyopathy - Disease of the Heart Muscle

Cardiomyopathy - Disease of the Heart Muscle

Cardiac morphogenesis (FKBP12, MIB1, Tbx20, Nkx2-5, Smad7, NF-ATc, Jarid2), ion channels (SCN5A, HCN4, RYR2), and mitochondria (NNT, TAZ) have been implicated in the development of LVNC [90–93]. Along with sarcomere-encoding and cytoskeleton-encoding genes, pathogenic variants in a variety of genes, including SCN5A, LMNA, RBM20, TTN, and DES, have been associated with LVNC and rhythm disturbance [94–95]. In addition, homozygous deletions in desmoplakin (DSP) and plakophilin 2 (PKP2)—desmosomal protein-encoding genes that cause arrhythmogenic CM and DCM—have been identified in LVNC patients [96]. Moreover, mutations in the mitochondrial genome and chromosomal abnormalities have been associated with LVNC, including 1p36 deletion, 7p14.3p14.1 deletion, 18p subtelomeric deletion, 22q11.2 deletion, distal 22q11.2, trisomies 18 and 13, 8p23.1 deletion, and tetrasomy 5q35.2-5q35 (Table 4) [34, 47, 91, 97–99].

Additionally, LVNC has been associated with several genetic syndromes and inborn errors of metabolism such as Coffin-Lowry syndrome, Sotos syndrome, Charcot–Marie–Tooth disease, Noonan syndrome, and BTS [100–103]. A recent study also demonstrated a higher prevalence of LVNC among patients with heterotaxy than among the general population, suggesting possible common genetic mechanisms [104].

2.4 Arrhythmogenic Cardiomyopathy (ACM)

This CM is an arrhythmogenic myocardial disorder not explained by ischemia, hypertension, or valvular heart disease. ACM was previously referred to as...
| Gene   | Protein                                                                 | Pattern of Inheritance | Disease Association         | OMIM#  | Locus     |
|--------|-------------------------------------------------------------------------|------------------------|-----------------------------|--------|-----------|
| ACTC1  | Actin, Alpha, Cardiac Muscle                                            | AD                     | LVNC, ACM, HCM, DCM         | 102540 | 5q31.1    |
| CASQ2  | Calsequestrin 2                                                         | AR, AD                 | LVNC                        | 114251 | 6q22.31   |
| DTNA   | Dystrobrevin, Alpha                                                     | AD                     | LVNC                        | 601239 | 2q11      |
| HCN4   | Hyperpolarization-Activated Cyclic Nucleotide-Gated Potassium Channel 4 | AD                     | LVNC                        | 605206 | 18q12.1   |
| LDB3   | Lim Domain-Binding 3                                                   | AD                     | LVNC, ACM, HCM, DCM         | 605906 | 2p22.1    |
| LMNA   | Lamin A/C                                                              | AD, AR                 | LVNC, ACM, HCM, DCM         | 150330 | 1q22      |
| MIB1   | E3 Ubiquitin Protein Ligase 1                                           | AD                     | LVNC                        | 608677 | 22q11.21  |
| MYBPC3 | Myosin-Binding Protein C, Cardiac                                       | AD                     | LVNC, RCM, HCM, DCM         | 600958 | Xq28      |
| MYH7   | Myosin, Heavy Chain 7, Cardiac Muscle, Beta                            | AD                     | LVNC, RCM, HCM, DCM         | 160760 | 7p14.2    |
| PRDM16 | Pr Domain-Containing Protein 16                                        | AD                     | LVNC, DCM                   | 605577 | 6q21      |
| TAZ    | Tafazzin                                                               | AR, XL                 | LVNC, DCM                   | 300394 | Xq24      |
| TBX20  | T-Box 20                                                               | AD                     | LVNC, DCM                   | 606061 | 10q22.3-q23.2 |
| TNNT2  | Troponin T-Type 2 (Cardiac)                                            | AD                     | LVNC, RCM, HCM, DCM         | 191045 | 17q12     |
| VCL    | Vinculin                                                               | AD                     | LVNC, HCM, DCM              | 193065 | 10q25.2   |

AD – Autosomal dominant; AR – Autosomal Recessive; XL – X-linked; DCM – Dilated cardiomyopathy; HCM – Hypertrophic cardiomyopathy; LVNC – Left ventricular non-compaction cardiomyopathy; ACM – Arrhythmogenic cardiomyopathy; RCM – Restrictive cardiomyopathy.

Table 4.
List of common genes and patterns of inheritance in LVNC.
arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD, ARVC). The reported prevalence of ACM is as common as 1 in 1,000-5,000 people [105]. The clinical diagnosis may be supported by evidence of conduction disease, supraventricular arrhythmias, and/or ventricular arrhythmias originating from any cardiac structure. ECG abnormalities include right bundle branch block pattern, an epsilon wave (defined as a low-amplitude deflection located between the end of the QRS and the onset of the T wave in leads V1–V3), and T wave inversion(s) recorded in leads V1–V4. Classically, the RV is dilated and contains fibro-fatty infiltration of the myocardium. The left ventricle is overtly affected with less frequent involvement. Notably, ACM clinically overlaps with other CM types, particularly DCM. However, ACM is distinct in that it is marked by arrhythmia at presentation with or without biventricular dilation and/or impaired systolic function [106]. This heritable disorder is usually transmitted in an autosomal dominant pattern (with variable penetrance), although autosomal recessive patterns reportedly affect junctional plakoglobin (JUP) and desmoplakin (DSP) in families with cardiocutaneous disease from Greece, Italy, India, Ecuador, Israel, and Turkey [107]. The most notable autosomal recessive diseases include Naxos disease (a homozygous pathogenic variant in the gene encoding the protein plakoglobin characterized by ACM, a non-epidermolytic palmoplantar keratoderma, and wooly hair) and Carvajal syndrome (caused by a homozygous pathogenic gene variant that truncates the DSP protein) [107, 108]. Analysis of first- and second-degree relatives of patients with ACM suggest that up to 50% of ACM cases are familial [109]. Pathogenic gene variants within the desmosomal proteins are the main cause of “classic” ACM [110]. Pathogenic gene variants in the three main classes of desmosomal proteins account for 60% of affected patients [111]. Overall, the three groups of desmosomal proteins include transmembrane desmosomal cadherins (including DSC2 and DSG2), DSP (a plakin family protein that attaches directly to the intermediate filament desmin in the myocardium), and linker proteins such as armadillo family proteins (including JUP and PKP2 that mediate interactions between the desmosomal cadherin tails and DSP) [112]. Pathogenic variants in the PKP2, DSP and DSG2 genes are found in approximately 80% of classic ACM cases [112]. Overall, the most commonly mutated gene is plakophilin, which accounted for 46–61% of patients from two different registries [113]. In addition to desmosomal proteins, genes encoding proteins that interact with these desmosomal proteins have been found in ACM. These proteins include: transforming growth factor β3 (TGF-β3), which conveys cytokine-stimulating fibrosis and modulates cell adhesion and growth; transmembrane protein 43 (TMEM43), an adipogenic transcription factor; DES, which binds DSP; and TTN, which bridges the sarcomere along its longitudinal axis and forms a continuous filament along the myofibril [18]. To date, approximately 18 causative genes involved in ACM have been identified [106, 109], please see Table 5. Notably, compound and digenic heterozygosity is involved in ACM pathogenesis in up to 20% of cases and leads to more severe disease [114, 115]. Sarcoidosis and Brugada syndrome are commonly mistaken for ACM.

2.5 Restrictive cardiomyopathy (RCM)

RCM is rare, accounting for approximately 5% of all CMs. RCM is characterized by normal or decreased volume of both ventricles associated with atrial enlargement (left or bi-atrial), normal LV wall thickness, normal atrioventricular valve function/structure, impaired ventricular filling with restrictive physiology, and normal (or near normal) systolic function, please see Figure 5 [4, 116]. The clinical course is defined by the inability to fill the ventricles due to poor ventricular relaxation, which limits the cardiac output. The disease may manifest
| Gene     | Protein                                         | Pattern of Inheritance | Disease Association                        | OMIM#   | Locus  |
|----------|------------------------------------------------|------------------------|--------------------------------------------|---------|--------|
| ACTC1    | Actin, Alpha, Cardiac Muscle                    | AD                     | ACM, HCM, DCM, LVNC                       | 102540  | 5q31.1 |
| ARVD3    | Arrhythmogenic Right Ventricular Dysplasia, Familial, 3 | AD                     | ACM                                        | 602086  | 12p12.1|
| ARVD4    | Arrhythmogenic Right Ventricular Dysplasia, Familial, 4 | AD                     | ACM                                        | 602087  | 15q14  |
| ARVD6    | Arrhythmogenic Right Ventricular Dysplasia, Familial, 6 | AD                     | ACM                                        | 604401  | 1q42-q43|
| CTNNA3   | Catenin Alpha 3                                 | AD                     | ACM                                        | 607667  | 7q21.2 |
| DES      | Desmin                                         | AD, AR                 | ACM, RCM, DCM                             | 125660  | 17q21  |
| DSC2     | Desmocollin 2                                  | AD, AR                 | ACM, DCM                                  | 600271  | Xq22   |
| DSG2     | Desmoglein 2                                   | AD                     | ACM, DCM                                  | 125671  | 15q24.1|
| DSP      | Desmoplakin                                    | AD, AR                 | ACM, DCM                                  | 125485  | 11p15.5|
| FLNC     | Filamin C                                      | AD                     | ACM, DMC, RCM, HCM                        | 102565  | 10q22.2|
| JUP      | Junction Plakoglobin                           | AD, AR                 | ACM                                        | 173325  | 2p13.1 |
| LDB3     | Lim Domain-Binding 3                           | AD                     | ACM, HCM, DCM, LVNC                       | 60906   | 2p22.1 |
| LMNA     | Lamin A/C                                      | AD, AR                 | ACM, HCM, DCM, LVNC                       | 150330  | 1p22   |
| PKP2     | Plakophilin 2                                  | AD                     | ACM, DCM                                  | 602861  | 11p15.4|
| PLN      | Phospholamban                                  | AD                     | ACM, HCM, DCM                             | 172405  | 4q12   |
| RYR2     | Ryanodine Receptor 2 (Cardiac)                 | AD                     | ACM, HCM                                  | 180902  | 12p1    |
| SCN5A    | Sodium Channel, Voltage-Gated, Type V, AlphaSubunit | AD                     | ACM, DCM                                  | 600163  | 20q13.12|
| TGFβ3    | Transforming Growth Factor Beta 3              | AD                     | ACM                                        | 190230  |        |
| TMEM43   | Transmembrane Protein 43                       | AD                     | ACM                                        | 612048  | 10q2.33|
| TTN      | Titin                                          | AD, AR                 | ACM, HCM, DCM                             | 188840  | 5q33-34 |

AD – Autosomal dominant; AR – Autosomal Recessive; XL – X-linked; DCM – Dilated cardiomyopathy; HCM – Hypertrophic cardiomyopathy; LVNC – Left ventricular non-compaction cardiomyopathy; ACM – Arrhythmogenic cardiomyopathy; RCM – Restrictive cardiomyopathy.

Table 5.
List of common genes and patterns of inheritance in ACM.
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with exercise intolerance, dyspnea, edema, atrial fibrillation, syncope, or sudden cardiac death. The hallmark of non-invasive imaging is atrial or bi-atrial enlargement. Normal or mild concentric hypertrophy with normal or reduced ventricular cavity can also be seen. Familial disease has been reported in 30% of cases and usually exhibits autosomal dominant inheritance. However, autosomal recessive, X-linked, and mitochondrial-transmitted disease have also been reported [117].

Most patients with RCM harbor gene mutations in sarcomere-encoding genes, such as TNNI3 (most common), TNNT2, MYH7, ACTC1, TPM1, MYL3, and MYL2, see Table 6 [18, 118]. Gene variants in the desmin gene have been reported in association with atrioventricular block and skeletal myopathy [119, 120].

RCM can be classified based on the underlying process: non-infiltrative; infiltrative; associated with storage diseases; idiopathic; or combined with DCM, HCM, and LVNC [116]. As with DCM, many previous cases deemed idiopathic are later found to harbor causative pathogenic variants in sarcomeric genes. Non-infiltrative causes of RCM include scleroderma and systemic sclerosis with well-described polymorphisms in genes coding for ECM proteins [121]. Pseudoxanthoma elasticum is an inherited disorder associated with accumulation of mineralized elastic fibers that may lead to blindness, coronary arterial occlusive disease, and RCM. The ABCC6 gene on chromosome 16p13.1 is responsible for the calcification of elastic fibers [122]. Infiltrative causes of RCM include amyloidosis, a group of diseases characterized by extracellular deposition of insoluble fibrillar proteins with concomitant destruction of normal tissue structure and function. Approximately 20 different proteins cause cardiac amyloidosis. In the hereditary disease type, more than 100 gene mutations are known at present [123, 124]. The Val122Ile variant of transthyretin (TTR) is the most common [125]. Sarcoidosis can also cause systolic dysfunction and arrhythmias. The strongest genetic associations are found within the human leucocyte antigen (HLA) gene and functional polymorphisms within the butyrophilin-like 2 (BTN2L2) gene [126].

Lysosomal storage disorders are characterized by abnormal lysosomal metabolism leading to accumulation of various glycosaminoglycans, glycoproteins, or glycolipids within lysosomes of various tissues, including the myocardium. Gaucher
disease and Fabry disease (two of the most common lysosomal disorders) may manifest as CM (HCM or RCM), valvular disease, coronary artery disease, and/or aortic enlargement [127].

Mucopolysaccharidoses (Hurler and Hunter diseases) are characterized by the deficiency of enzymes required for the breakdown of glycosaminoglycans. Thus, these diseases are considered lysosomal storage disorders. Cardiac manifestations start from childhood and include RCM, endocardial fibroelastosis, and valvular disease including thickening of the leaflets with resultant stenosis and/or insufficiency. Storage diseases such as hemochromatosis (mutation in the *HFE* gene) cause a mixture of systolic and diastolic dysfunction often accompanied by arrhythmias [128].

In summary, CM is a widely variable disease process with a similarly variable pattern of genetic inheritance. Our understanding of the interplay between genetic mutation and disease phenotype is ever-evolving and merits much deeper investigation.

### Table 6.
List of common genes and patterns of inheritance in RCM.

| Gene     | Protein                                   | Pattern of Inheritance | Disease Association                      | OMIM#   | Locus  |
|----------|-------------------------------------------|------------------------|------------------------------------------|---------|--------|
| BAG3     | Bcl2-Associated Athanogene 3              | AD                     | LVNC, HCM, DCM                           | 603883  | 14q24.3|
| DES      | Desmin                                    | AD, AR                 | RCM, DCM, ACM                            | 125660  | 17q21  |
| FLNC     | Filamin C                                 | AD                     | RCM, HCM, ACM                            | 102565  | 10q22.2|
| MYBPC3   | Myosin-Binding Protein C, Cardiac         | AD                     | RCM, HCM, DCM                           | 600958  | Xq28   |
| MYH7     | Myosin, Heavy Chain 7, Cardiac Muscle, Beta | AD                  | RCM, HCM, DCM, LVNC                     | 160760  | 7p14.2 |
| MYL3     | Myosin, Light Chain 3, Alkali, Ventricular, Skeletal, Slow | AD, AR          | RCM, HCM                               | 160790  | 1q32   |
| MYOZ2    | Myozenin 2                                | AD                     | RCM, HCM, DCM                           | 605602  | 3p25.1 |
| MYPN     | Myopalladin                               | AD                     | RCM, HCM, DCM                           | 608517  | 12q23.1|
| TNNI3    | Troponin I Type 3 (Cardiac)               | AD                     | RCM, HCM, DCM                           | 191044  | 3p21.1 |
| TNNT2    | Troponin T Type 2 (Cardiac)               | AD                     | RCM, HCM, DCM, LVNC                    | 191045  | 17q12  |
| TPM1     | Tropomyosin 1 (Alpha)                     | AD                     | RCM, HCM, DCM                           | 191010  | 19q13.4|

*AD – Autosomal dominant; AR – Autosomal Recessive; XL – X-linked; DCM – Dilated cardiomyopathy; HCM – Hypertrophic cardiomyopathy; LVNC – Left ventricular non-compaction cardiomyopathy; ACM – Arrhythmogenic cardiomyopathy; RCM – Restrictive cardiomyopathy.*
Author details

Evan M. Harvey¹, Murad Almasri² and Hugo R. Martinez¹*

¹ Pediatric Cardiology, Le Bonheur Children’s Hospital, University of Tennessee Health Science Center, Memphis, TN, United States
² Department of Pediatrics, University of Texas Medical Branch, Galveston, TX, United States

*Address all correspondence to: hmartinez@uthsc.edu

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References

[1] Wilkinson JD, Landy DC, Colan SD, Towbin JA, Sleeper LA, Orav EJ, et al. The pediatric cardiomyopathy registry and heart failure: key results from the first 15 years. Heart Fail Clin. 2010;6(4):401-13, vii.

[2] Arbustini E, Narula N, Dec GW, Reddy KS, Greenberg B, Kushwaha S, et al. The MOGE(S) Classification for a Phenotype-Genotype Nomenclature of Cardiomyopathy: Endorsed by the World Heart Federation. Glob Heart. 2013;8(4):355-82.

[3] Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2008;29(2):270-6.

[4] Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. 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(14):1807-16.

[5] Lipshultz SE, Law YM, Asante-Korang A, Austin ED, Dipchand AI, Everitt MD, et al. Cardiomyopathy in Children: Classification and Diagnosis: A Scientific Statement From the American Heart Association. Circulation. 2019;140(1):e9-e68.

[6] Jefferies JL, Towbin JA. Dilated cardiomyopathy. Lancet. 2010;375(9716):752-62.

[7] Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA. 2006;296(15):1867-76.

[8] Petretta M, Pirozzi F, Sasso L, Paglia A, Bonaduce D. Review and metaanalysis of the frequency of familial dilated cardiomyopathy. Am J Cardiol. 2011;108(8):1171-6.

[9] Tayal U, Prasad S, Cook SA. Genetics and genomics of dilated cardiomyopathy and systolic heart failure. Genome Med. 2017;9(1):20.

[10] McNally EM, Golbus JR, Puckelwartz MJ. Genetic mutations and mechanisms in dilated cardiomyopathy. J Clin Invest. 2013;123(1):19-26.

[11] Nouhravesh N, Ahlberg G, Ghouse J, Andreasen C, Svendsen JH, Haunso S, et al. Analyses of more than 60,000 exomes questions the role of numerous genes previously associated with dilated cardiomyopathy. Mol Genet Genomic Med. 2016;4(6):617-23.

[12] Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, et al. Genetic Evaluation of Cardiomyopathy-A Heart Failure Society of America Practice Guideline. J Card Fail. 2018;24(5):281-302.

[13] McNally EM, Mestroni L. Dilated Cardiomyopathy: Genetic Determinants and Mechanisms. Circ Res. 2017;121(7):731-48.

[14] Bowles NE, Bowles KR, Towbin JA. The "final common pathway" hypothesis and inherited cardiovascular disease. The role of cytoskeletal proteins in dilated cardiomyopathy. Herz. 2000;25(3):168-75.

[15] Fatkin D, Otway R, Richmond Z. Genetics of dilated cardiomyopathy. Heart Fail Clin. 2010;6(2):129-40.
Cardiomyopathy - Disease of the Heart Muscle

[16] Ware SM. Evaluation of genetic causes of cardiomyopathy in childhood. Cardiol Young. 2015;25 Suppl 2:43-50.

[17] Towbin JA. Genetic arrhythmias complicating patients with dilated cardiomyopathy: How it happens. Heart Rhythm. 2020;17(2):313-4.

[18] Towbin JA. Inherited cardiomyopathies. Circ J. 2014;78(10):2347-56.

[19] Towbin JA, Ortiz-Lopez R. X-linked dilated cardiomyopathy. N Engl J Med. 1994;330(5):369-70.

[20] Davies KE, Nowak KJ. Molecular mechanisms of muscular dystrophies: old and new players. Nat Rev Mol Cell Biol. 2006;7(10):762-73.

[21] Wong BL, Rybalsky I, Shellenbarger KC, Tian C, McMahon MA, Rutter MM, et al. Long-Term Outcome of Interdisciplinary Management of Patients with Duchenne Muscular Dystrophy Receiving Daily Glucocorticoid Treatment. J Pediatr. 2017;182:296-303 e1.

[22] Feng J, Yan J, Buzin CH, Towbin JA, Sommer SS. Mutations in the dystrophin gene are associated with sporadic dilated cardiomyopathy. Mol Genet Metab. 2002;77(1-2):119-26.

[23] Hershberger RE, Givertz M, Ho CY, Judge DP, Kantor P, McBride KL, et al. Genetic Evaluation of Cardiomyopathy - a Heart Failure Society of America Practice Guideline. J Card Fail. 2018.

[24] American Academy of Pediatrics Section on C, Cardiac S. Cardiovascular health supervision for individuals affected by Duchenne or Becker muscular dystrophy. Pediatrics. 2005;116(6):1569-73.

[25] Martinez HR, Pignatelli R, Belmont JW, Craigen WJ, Jefferies JL. Childhood onset of left ventricular dysfunction in a female manifesting carrier of muscular dystrophy. Am J Med Genet A. 2011;155A(12):3025-9.

[26] Berko BA, Swift M. X-linked dilated cardiomyopathy. N Engl J Med. 1987;316(19):1186-91.

[27] Towbin JA, Hejtmancik JF, Brink P, Gelb B, Zhu XM, Chamberlain JS, et al. X-linked dilated cardiomyopathy. Molecular genetic evidence of linkage to the Duchenne muscular dystrophy (dystrophin) gene at the Xp21 locus. Circulation. 1993;87(6):1854-65.

[28] Puckelwartz M, McNally EM. Emery-Dreifuss muscular dystrophy. Handb Clin Neurol. 2011;101:155-66.

[29] Worman HJ, Ostlund C, Wang Y. Diseases of the nuclear envelope. Cold Spring Harb Perspect Biol. 2010;2(2):a000760.

[30] Rakovec P, Zidar J, Sinkovec M, Zupan I, Brecelj A. Cardiac involvement in Emery-Dreifuss muscular dystrophy: role of a diagnostic pacemaker. Pacing Clin Electrophysiol. 1995;18(9 Pt 1):1721-4.

[31] Becane HM, Bonne G, Varnous S, Muchir A, Ortega V, Hammouda EH, et al. High incidence of sudden death with conduction system and myocardial disease due to lamins A and C gene mutation. Pacing Clin Electrophysiol. 2000;23(11 Pt 1):1661-6.

[32] Jefferies JL. Barth syndrome. Am J Med Genet C Semin Med Genet. 2013;163C(3):198-205.

[33] Barth PG, Scholte HR, Berden JA, Van der Klei-Van Moorsel JM, Luyt-Houwen IE, Van ‘t Veer-Korthof ET, et al. An X-linked mitochondrial disease affecting cardiac muscle, skeletal muscle and neutrophil leucocytes. J Neurol Sci. 1983;62(1-3):327-55.

[34] Towbin JA. Left ventricular noncompaction: a new form of heart
failure. Heart Fail Clin. 2010;6(4):453-69, viii.

[35] Lipshultz SE, Orav EJ, Wilkinson JD, Towbin JA, Messere JE, Lowe AM, et al. Risk stratification at diagnosis for children with hypertrophic cardiomyopathy: an analysis of data from the Pediatric Cardiomyopathy Registry. Lancet. 2013;382(9908):1889-97.

[36] Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. Circulation. 2007;115(6):773-81.

[37] Chun EJ, Choi SI, Jin KN, Kwag HJ, Kim YJ, Choi BW, et al. Hypertrophic cardiomyopathy: assessment with MR imaging and multidetector CT. Radiographics. 2010;30(5):1309-28.

[38] Rakowski H, Carasso S. Diastolic dysfunction and histopathology in hypertrophic cardiomyopathy: is relaxation in disarray? J Am Soc Echocardiogr. 2009;22(12):1335-7.

[39] Colan SD. Hypertrophic cardiomyopathy in childhood. Heart Fail Clin. 2010;6(4):433-44, vii-iii.

[40] Alfares AA, Kelly MA, McDermott G, Funke BH, Lebo MS, Baxter SB, et al. Results of clinical genetic testing of 2,912 probands with hypertrophic cardiomyopathy: expanded panels offer limited additional sensitivity. Genet Med. 2015;17(11):880-8.

[41] Burns C, Bagnall RD, Lam L, Semsaian C, Ingles J. Multiple Gene Variants in Hypertrophic Cardiomyopathy in the Era of Next-Generation Sequencing. Circ Cardiovasc Genet. 2017;10(4).

[42] Maass A, Konhilas JP, Stauffer BL, Leinwand LA. From sarcomeric mutations to heart disease: understanding familial hypertrophic cardiomyopathy. Cold Spring Harb Symp Quant Biol. 2002;67:409-15.

[43] Roma-Rodrigues C, Fernandes AR. Genetics of hypertrophic cardiomyopathy: advances and pitfalls in molecular diagnosis and therapy. Appl Clin Genet. 2014;7:195-208.

[44] Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124(24):e783-831.

[45] Konno T, Chang S, Seidman JG, Seidman CE. Genetics of hypertrophic cardiomyopathy. Curr Opin Cardiol. 2010;25(3):205-9.

[46] Jarcho JA, McKenna W, Pare JA, Solomon SD, Holcombe RF, Dickie S, et al. Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. N Engl J Med. 1989;321(20):1372-8.

[47] Tariq M, Ware SM. Importance of genetic evaluation and testing in pediatric cardiomyopathy. World J Cardiol. 2014;6(11):1156-65.

[48] Ho CY. New paradigms in Hypertrophic Cardiomyopathy: Insights from Genetics. Prog Pediatr Cardiol. 2011;31(2):93-8.

[49] Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C, et al. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. Circulation. 2003;107(17):2227-32.

[50] Rauen KA, Schoyer L, McCormick F, Lin AE, Allanson JE,
Cardiomyopathy - Disease of the Heart Muscle

Stevenson DA, et al. Proceedings from the 2009 genetic syndromes of the Ras/MAPK pathway: From bedside to bench and back. Am J Med Genet A. 2010;152A(1):4-24.

[51] Thompson D, Patrick-Esteve J, Surcouf JW, Rivera D, Castellanos B, Desai P, et al. RAF1 variants causing biventricular hypertrophic cardiomyopathy in two preterm infants: further phenotypic delineation and review of literature. Clin Dysmorphol. 2017;26(4):195-9.

[52] Zenker M, Buheitel G, Rauch R, Koenig R, Bosse K, Kress W, et al. Genotype-phenotype correlations in Noonan syndrome. J Pediatr. 2004;144(3):368-74.

[53] Tafazoli A, Eshraghi P, Pantaleoni F, Vakili R, Moghaddassian M, Ghahraman M, et al. Novel mutations and their genotype-phenotype correlations in patients with Noonan syndrome, using next-generation sequencing. Adv Med Sci. 2017;63(1):87-93.

[54] Lee PA, Ross JL, Pedersen BT, Kotnik P, Germak JA, Christesen HT. Noonan syndrome and Turner syndrome patients respond similarly to 4 years' growth-hormone therapy: longitudinal analysis of growth-hormone-naive patients enrolled in the NordiNet(R) International Outcome Study and the ANSWER Program. Int J Pediatr Endocrinol. 2015;2015(1):17.

[55] Sarkozy A, Digilio MC, Dallapiccola B. Leopard syndrome. Orphanet J Rare Dis. 2008;3:13.

[56] Digilio MC, Sarkozy A, de Zorzi A, Pacileo G, Limongelli G, Mingarelli R, et al. LEOPARD syndrome: clinical diagnosis in the first year of life. Am J Med Genet A. 2006;140(7):740-6.

[57] Giannoulatou E, McVean G, Taylor IB, McGowan SJ, Maher GJ, Iqbal Z, et al. Contributions of intrinsic mutation rate and selfish selection to levels of de novo HRAS mutations in the paternal germline. Proc Natl Acad Sci U S A. 2013;110(50):20152-7.

[58] Bertola D, Buscarilli M, Stabley DL, Baker L, Doyle D, Bartholomew DW, et al. Phenotypic spectrum of Costello syndrome individuals harboring the rare HRAS mutation p.Gly13Asp. Am J Med Genet A. 2017;173(5):1309-18.

[59] Gelb BD, Roberts AE, Tartaglia M. Cardiomyopathies in Noonan syndrome and the other RASopathies. Prog Pediatr Cardiol. 2015;39(1):13-9.

[60] Rauen KA, Tidyman WE, Estep AL, Sampath S, Peltier HM, Bale SJ, et al. Molecular and functional analysis of a novel MEK2 mutation in cardio-faciocutaneous syndrome: transmission through four generations. Am J Med Genet A. 2010;152A(4):807-14.

[61] Karaer K, Lissewski C, Zenker M. Familial cardiocutaneous syndrome in a father and a son with a novel MEK2 mutation. Am J Med Genet A. 2015;167A(2):385-8.

[62] Pavithra S, Mallya H, Pai GS. Cardiocutaneous syndrome: a rare entity. Indian J Dermatol. 2012;57(4):299-301.

[63] Terry J, Rauen KA, Nowaczyk MJ. Fetal autopsy findings of cardiofaciocutaneous syndrome with a unique BRAF mutation. Pediatr Dev Pathol. 2014;17(1):59-63.

[64] Hirschhorn R, Huie ML. Frequency of mutations for glycogen storage disease type II in different populations: the delta525T and deltaexon 18 mutations are not generally "common" in white populations. J Med Genet. 1999;36(1):85-6.

[65] Lim JA, Li L, Raben N. Pompe disease: from pathophysiology to
therapy and back again. Front Aging Neurosci. 2014;6:177.

[66] Boentert M, Florian A, Drager B, Young P, Yilmaz A. Pattern and prognostic value of cardiac involvement in patients with late-onset pompe disease: a comprehensive cardiovascular magnetic resonance approach. J Cardiovasc Magn Reson. 2016;18(1):91.

[67] Levine JC, Kishnani PS, Chen YT, Herlong JR, Li JS. Cardiac remodeling after enzyme replacement therapy with acid alpha-glucosidase for infants with Pompe disease. Pediatr Cardiol. 2008;29(6):1033-42.

[68] Arad M, Maron BJ, Gorham JM, Johnson WH, Jr., Saul JP, Perez-Atayde AR, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. N Engl J Med. 2005;352(4):362-72.

[69] Rowland TJ, Sweet ME, Mestroni L, Taylor MR. Danon disease - dysregulation of autophagy in a multisystem disorder with cardiomyopathy. J Cell Sci. 2016;129(11):2135-43.

[70] Maron BJ, Roberts WC, Arad M, Haas TS, Spirito P, Wright GB, et al. Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. JAMA. 2009;301(12):1253-9.

[71] Toib A, Grange DK, Kozel BA, Ewald GA, White FV, Canter CE. Distinct clinical and histopathological presentations of Danon cardiomyopathy in young women. J Am Coll Cardiol. 2010;55(4):408-10.

[72] Brady RO, Gal AE, Bradley RM, Martensson E, Warshaw AL, Laster L. Enzymatic defect in Fabry's disease. Ceramidetrihexosidase deficiency. N Engl J Med. 1967;276(21):1163-7.

[73] Garman SC, Garboczi DN. The molecular defect leading to Fabry disease: structure of human alpha-galactosidase. J Mol Biol. 2004;337(2):319-35.

[74] Mehta A, Ricci R, Widmer U, Dehout F, Garcia de Lorenzo A, Kampmann C, et al. Fabry disease defined: baseline clinical manifestations of 366 patients in the Fabry Outcome Survey. Eur J Clin Invest. 2004;34(3):236-42.

[75] Perrot A, Osterziel KJ, Beck M, Dietz R, Kampmann C. Fabry disease: focus on cardiac manifestations and molecular mechanisms. Herz. 2002;27(7):699-702.

[76] O'Mahony C, Elliott P. Anderson-Fabry disease and the heart. Prog Cardiovasc Dis. 2010;52(4):326-35.

[77] Weidemann F, Rummey C, Bijnen B, Stork S, Jasaityte R, Dhooge J, et al. The heart in Friedreich ataxia: definition of cardiomyopathy, disease severity, and correlation with neurological symptoms. Circulation. 2012;125(13):1626-34.

[78] Peverill RE. Letter by Peverill regarding article, "The heart in Friedreich ataxia: definition of cardiomyopathy, disease severity, and correlation with neurological symptoms". Circulation. 2012;126(17):e272.

[79] Kipps A, Alexander M, Colan SD, Gauvreau K, Smoot L, Crawford L, et al. The longitudinal course of cardiomyopathy in Friedreich's ataxia during childhood. Pediatr Cardiol. 2009;30(3):306-10.

[80] Brunel-Guitton C, Levtova A, Sarasram F. Mitochondrial Diseases and Cardiomyopathies. Can J Cardiol. 2015;31(11):1360-76.

[81] Towbin JA, Jefferies JL. Cardiomyopathies Due to Left Ventricular Noncompaction, Mitochondrial and
Cardiomyopathy - Disease of the Heart Muscle

Storage Diseases, and Inborn Errors of Metabolism. Circ Res. 2017;121(7):838-54.

[82] Meyers DE, Basha HI, Koenig MK. Mitochondrial cardiomyopathy: pathophysiology, diagnosis, and management. Tex Heart Inst J. 2013;40(4):385-94.

[83] Sproule DM, Kaufmann P, Engelstad K, Starc TJ, Hordof AJ, De Vivo DC. Wolff-Parkinson-White syndrome in Patients With MELAS. Arch Neurol. 2007;64(11):1625-7.

[84] Okajima Y, Tanabe Y, Takayanagi M, Aotsuka H. A follow up study of myocardial involvement in patients with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Heart. 1998;80(3):292-5.

[85] Thomas T, Craigen WJ, Moore R, Czosek R, Jefferies JL. Arrhythmia as a cardiac manifestation in MELAS syndrome. Mol Genet Metab Rep. 2015;4:9-10.

[86] Towbin JA. Ion channel dysfunction associated with arrhythmia, ventricular noncompaction, and mitral valve prolapse: a new overlapping phenotype. J Am Coll Cardiol. 2014;64(8):768-71.

[87] Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. Lancet. 2015;386(9995):813-25.

[88] Lee TM, Hsu DT, Kantor P, Towbin JA, Ware SM, Colan SD, et al. Pediatric Cardiomyopathies. Circ Res. 2017;121(7):855-73.

[89] Sedaghat-Hamedani F, Haas J, Zhu F, Geier C, Kayvanpour E, Liss M, et al. Clinical genetics and outcome of left ventricular non-compaction cardiomyopathy. Eur Heart J. 2017;38(46):3449-60.

[90] van Waning JI, Caliskan K, Michels M, Schinkel AFL, Hirsch A, et al. Cardiac Phenotypes, Genetics, and Risks in Familial Noncompaction Cardiomyopathy. J Am Coll Cardiol. 2019;73(13):1601-11.

[91] van Waning JI, Caliskan K, Hoedemaekers YM, van Spaendonck-Zwarts KY, Baas AF, Boekholdt SM, et al. Genetics, Clinical Features, and Long-Term Outcome of Noncompaction Cardiomyopathy. J Am Coll Cardiol. 2018;71(7):711-22.

[92] Bagnall RD, Molloy LK, Kalman JM, Semsarian C. Exome sequencing identifies a mutation in the ACTN2 gene in a family with idiopathic ventricular fibrillation, left ventricular noncompaction, and sudden death. BMC Med Genet. 2014;15:99.

[93] Hastings R, de Villiers CP, Hooper C, Ormondroyd L, Pagnamenta A, Lise S, et al. Combination of Whole Genome Sequencing, Linkage, and Functional Studies Implicates a Missense Mutation in Titin as a Cause of Autosomal Dominant Cardiomyopathy With Features of Left Ventricular Noncompaction. Circ Cardiovasc Genet. 2016;9(5):426-35.

[94] Shan L, Makita N, Xing Y, Watanabe S, Futatani T, Ye F, et al. SCN5A variants in Japanese patients with left ventricular noncompaction and arrhythmia. Mol Genet Metab. 2008;93(4):468-74.

[95] Finsterer J, Stollberger C. Primary myopathies and the heart. Scand Cardiovasc J. 2008;42(1):9-24.

[96] Ramond F, Janin A, Di Filippo S, Chanavat V, Chalabreysse L, Roux-Buisson N, et al. Homozygous PKP2 deletion associated with neonatal left ventricle noncompaction. Clin Genet. 2017;91(1):126-30.

[97] Miller EM, Hinton RB, Czosek R, Lorts A, Parrott A, Shikany AR, et al.
Genetic Testing in Pediatric Left Ventricular Noncompaction. Circ Cardiovasc Genet. 2017;10(6).

[98] Dong X, Fan P, Tian T, Yang Y, Xiao Y, Yang K, et al. Recent advancements in the molecular genetics of left ventricular noncompaction cardiomyopathy. Clin Chim Acta. 2017;465:40-4.

[99] Miszalski-Jamka K, Jefferies JL, Mazur W, Glowacki J, Hu J, Lazar M, et al. Novel Genetic Triggers and Genotype-Phenotype Correlations in Patients With Left Ventricular Noncompaction. Circ Cardiovasc Genet. 2017;10(4).

[100] Oechslin E, Jenni R. Left ventricular non-compaction revisited: a distinct phenotype with genetic heterogeneity? Eur Heart J. 2011;32(12):1446-56.

[101] Blinder JJ, Martinez HR, Craigen WJ, Belmont J, Pignatelli RH, Jefferies JL. Noncompaction of the left ventricular myocardium in a boy with a novel chromosome 8p23.1 deletion. Am J Med Genet A. 2011;155A(9):2215-20.

[102] Martinez HR, Belmont JW, Craigen WJ, Taylor MD, Jefferies JL. Left ventricular noncompaction in Sotos syndrome. Am J Med Genet A. 2011;155A(5):1115-8.

[103] Martinez HR, Niu MC, Sutton VR, Pignatelli R, Vatta M, Jefferies JL. Coffin-Lowry syndrome and left ventricular noncompaction cardiomyopathy with a restrictive pattern. Am J Med Genet A. 2011;155A(12):3030-4.

[104] Martinez HR, Ware SM, Schamberger MS, Parent JJ. Noncompaction cardiomyopathy and heterotaxy syndrome. Prog Pediatr Cardiol. 2017;46:23-7.

[105] Peters S, Trummel M, Meyners W. Prevalence of right ventricular dysplasia-cardiomyopathy in a non-referral hospital. Int J Cardiol. 2004;97(3):499-501.

[106] Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, et al. 2019 HRS expert consensus statement on evaluation, risk stratification, and management of arrhythmogenic cardiomyopathy: Executive summary. Heart Rhythm. 2019;16(11):e373-e407.

[107] Protonotarios N, Tsatsopoulou A. Naxos disease and Carvajal syndrome: cardiocutaneous disorders that highlight the pathogenesis and broaden the spectrum of arrhythmogenic right ventricular cardiomyopathy. Cardiovasc Pathol. 2004;13(4):185-94.

[108] Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. Eur Heart J. 2010;31(7):806-14.

[109] Hamid MS, Norman M, Quraishi A, Firoozi S, Thaman R, Gimeno JR, et al. Prospective evaluation of relatives for familial arrhythmogenic right ventricular cardiomyopathy/dysplasia reveals a need to broaden diagnostic criteria. J Am Coll Cardiol. 2002;40(8):1445-50.

[110] Bauce B, Nava A, Beffagna G, Basso C, Lorenzon A, Smaniotto G, et al. Multiple mutations in desmosomal proteins encoding genes in arrhythmogenic right ventricular cardiomyopathy/dysplasia. Heart Rhythm. 2010;7(1):22-9.

[111] den Haan AD, Tan BY, Zikusoka MN, Llado LI, Jain R, Daly A, et al. Comprehensive desmosomal mutation analysis in north americans with arrhythmogenic right ventricular dysplasia/cardioomyopathy. Circ Cardiovasc Genet. 2009;2(5):428-35.
[112] Delmar M, McKenna WJ. The cardiac desmosome and arrhythmogenic cardiomyopathies: from gene to disease. Circ Res. 2010;107(6):700-14.

[113] Groeneweg JA, Bhonsale A, James CA, te Riele AS, Dooijes D, Tichnell C, et al. Clinical Presentation, Long-Term Follow-Up, and Outcomes of 1001 Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Patients and Family Members. Circ Cardiovasc Genet. 2015;8(3):437-46.

[114] Rigato I, Bause B, Rampazzo A, Zorzi A, Pilichou K, Mazzotti E, et al. Compound and digenic heterozygosity predicts lifetime arrhythmic outcome and sudden cardiac death in desmosomal gene-related arrhythmogenic right ventricular cardiomyopathy. Circ Cardiovasc Genet. 2013;6(6):533-42.

[115] Xu T, Yang Z, Vatta M, Rampazzo A, Beffagna G, Pilichou K, et al. Compound and digenic heterozygosity contributes to arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol. 2010;55(6):587-97.

[116] Denfield SW, Webber SA. Restrictive cardiomyopathy in childhood. Heart Fail Clin. 2010;6(4):445-52, viii.

[117] Kaski JP, Syrris P, Burch M, Tome-Esteban MT, Fenton M, Christiansen M, et al. Idiopathic restrictive cardiomyopathy in children is caused by mutations in cardiac sarcomere protein genes. Heart. 2008;94(11):1478-84.

[118] Caleshu C, Sakhuja R, Nussbaum RL, Schiller NB, Ursell PC, Eng C, et al. Furthering the link between the sarcomere and primary cardiomyopathies: restrictive cardiomyopathy associated with multiple mutations in genes previously associated with hypertrophic or dilated cardiomyopathy. Am J Med Genet A. 2011;155A(9):2229-35.

[119] Sen-Chowdhry S, Morgan RD, Chambers JC, McKenna WJ. Arrhythmogenic cardiomyopathy: etiology, diagnosis, and treatment. Annu Rev Med. 2010;61:233-53.

[120] Goldfarb LG, Vicart P, Goebel HH, Dalakas MC. Desmin myopathy. Brain. 2004;127(Pt 4):723-34.

[121] Worthley MI, Farouque HM, McNeil JD, Worthley SG. Scleroderma cardiomyopathy presenting with thromboembolism. Intern Med J. 2001;31(1):64-5.

[122] Nguyen LD, Terbah M, Daudon P, Martin L. Left ventricular systolic and diastolic function by echocardiogram in pseudoxanthoma elasticum. Am J Cardiol. 2006;97(10):1535-7.

[123] Lahuerta C, Menao S, Gracia-Gutierrez A, Bueno-Juana E, Guillen N, Sorribas V, et al. Diagnosis of genetic amyloidosis through the analysis of transthyretin gene mutation using high-resolution melting. Int J Cardiol. 2020;301:220-5.

[124] Rameev VV, Kozlovskaja LV, Sarkisova IA, Simonian A. [Genetic aspects of periodic diseases and associated amyloidosis]. Ter Arkh. 2002;74(6):80-3.

[125] Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. Circulation. 2009;120(13):1203-12.

[126] Spagnolo P, Sato H, Grutters JC, Renzoni EA, Marshall SE, Ruven HJ, et al. Analysis of BTNL2 genetic polymorphisms in British and Dutch patients with sarcoidosis. Tissue Antigens. 2007;70(3):219-27.
[127] Lindor NM, Karnes PS. Initial assessment of infants and children with suspected inborn errors of metabolism. Mayo Clin Proc. 1995;70(10):987-8.

[128] Pietrangelo A. Hereditary hemochromatosis: pathogenesis, diagnosis, and treatment. Gastroenterology. 2010;139(2):393-408, e1-2.