Chapter

Genetics of Cardiomyopathy

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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

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.

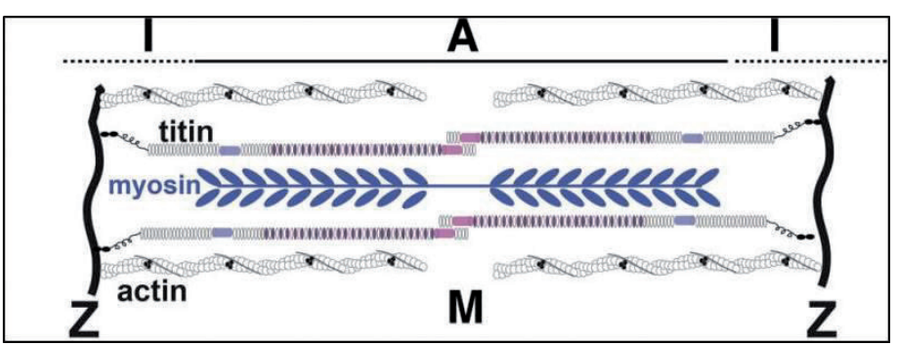

Figure 1.
Schematic image of the sarcomere featuring thick/thin filaments and surrounding protein architecture [13].

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

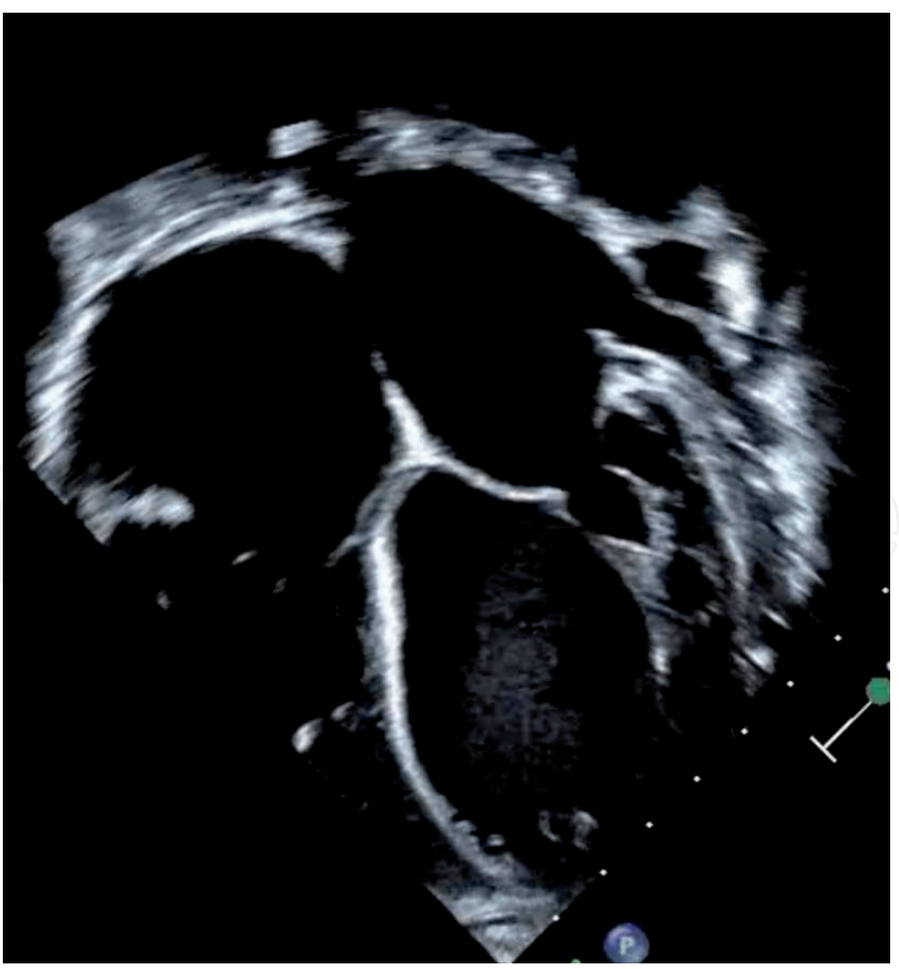

Figure 2.
Two-dimensional, apical 4-chamber echocardiographic image depicting an enlarged ventricle with spherical geometry and biatrial enlargement secondary to atrioventricular valve insufficiency in a patient with dilated cardiomyopathy.

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	609599	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	12q24.13
CHRM2	Cholinergic Receptor, Muscarinic, 2	AD	DCM	118493	10q25.2-q26.2
CRYAB	Crystallin, Alpha-B	AD	DCM	123590	11q23.1
CSRP3	Cysteine- And Glycine-Rich Protein 3	AD	DCM, HCM	600824	12p12.1
CTF1	Cardiotrophin 1	AR, AD	DCM	600435	1p13.1
DES	Desmin	AD,AR	DCM, ACM, RCM	125660	17q21
DMD	Dystrophin	XL	DCM	300377	3p25.3
DOLK	Dolichol Kinase	AR	DCM	610746	7q33
DSC2	Desmocollin 2	AD, AR	DCM, ACM	600271	Xq22
DSG2	Desmoglein 2	AD	DCM, ACM	125671	15q24.1
DSP	Desmoplakin	AD, AR	DCM, ACM	125485	11p15.5
DTNA	Dystrobrevin Alpha	AD	DCM, LVNC	601239	2q31
EMD	Emerin	XL	DCM	300384	11q23.1

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
FKRP	Fukutin-Related Protein	AR	DCM	606596	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	18q12.1
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
LRRC10	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	20q13.31
MYOT	Myotilin	AD	DCM	604103	Xq28
MYOZ2	Myozenin 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
NKX2-5	Nk2 Homeobox 5	AD	DCM	600584	Xq26.3
PDLIM3	Pdz And Lim Domain Protein 3	AD	DCM, HCM	605899	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
SCN5A	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	19q13.32

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	3p21
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	DCM	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 Tayal 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 envelopathies 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].

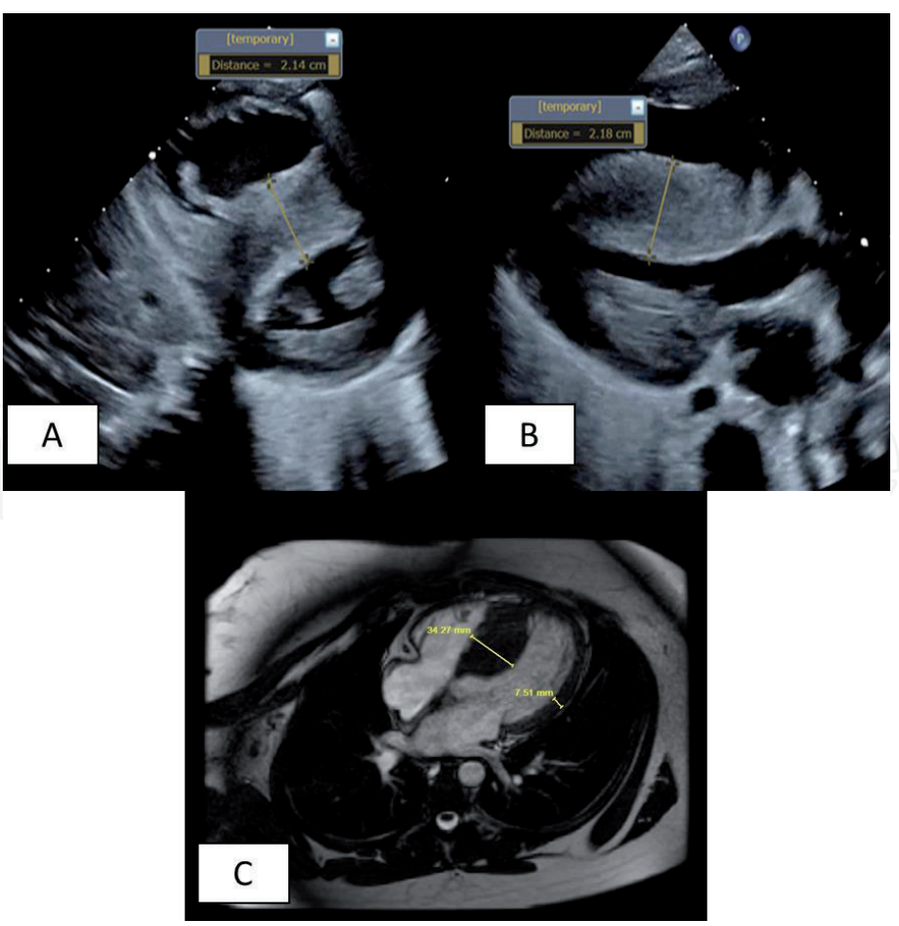

Figure 3.
Two dimensional images of HCM in the parasternal short axis (A) exhibiting concentric hypertrophy with significant involvement of the interventricular septum (IVS) and corroborated by the parasternal long axis view (B). Cardiac MRI also shows significant thickening of the IVS (C).

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, LVNC, ACM	102540	5q31.1
ACTN2	Actinin, Alpha-2	AD	HCM, DCM	102573	6q22.1
ALPK3	Alpha Kinase 3	AR	HCM, DCM	617608	1p36.32
ANKRD1	Ankyrin Repeat Domain-Containing Protein 1	AD	HCM, DCM	609599	7q36.1
BAG3	Bcl2-Associated Athanogene 3	AD	HCM, DCM, RCM	603883	14q24.3
BRAF	V-Raf Murine Sarcoma Viral Oncogene Homolog B1	AD	HCM	164757	12q15
CAV3	Caveolin 3	AD	HCM, DCM	601253	12q24.13
CSRP3	Cysteine- And Glycine-Rich Protein 3	AD	HCM, DCM	600824	12p12.1
FHL1	Four-And-A-Half LIM Domains 1	XL	HCM	300163	15q22.31
FLNC	Filamin C	AD	HCM, ACM, DMC, RCM	102565	10q22.2
GAA	Glucosidase, Alpha, Acid	AR	HCM	606800	19p13.3
GLA	Galactosidase, Alpha	XL	HCM	300644	18q11.2
HRAS	V-Ha-Ras Harvey Rat Sarcoma Viral Oncogene Homolog	AD	HCM	190020	9q31.1
JPH2	Junctophilin 2	AD	HCM	605267	11p11.2
KRAS	V-Ki-Ras2	AD	HCM	190070	14q12
LAMP2	Lysosome-Associated Membrane Protein 2	XL	HCM, DCM	309060	3p25.2
LDB3	Lim Domain-Binding 3	AD	HCM, DCM, LVNC, ACM	605906	2p22.1
LMNA	Lamin A/C	AD, AR	HCM, DCM, LVNC, ACM	150330	1q22
MAP2K1	Mitogen-Activated Protein Kinase Kinase 1	AD	HCM	176872	14q12
MAP2K2	Mitogen-Activated Protein Kinase Kinase 2	AD	HCM	601263	12q24.11
MYBPC3	Myosin-Binding Protein C, Cardiac	AD	HCM, DCM, LVNC, RCM	600958	Xq28
MYH6	Myosin, Heavy Chain 6, Cardiac Muscle, Alpha	AD	HCM, DCM	160710	10q25.2

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-p21.2
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
MYPN	Myopalladin	AD	HCM, DCM, RCM	608517	12q23.1
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
PTPN11	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
RIT1	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
TNNC1	Troponin C Type 1 (Slow)	AD	HCM, DCM	191040	17q21.33
TNNI3	Troponin I Type 3 (Cardiac)	AD	HCM, DCM, RCM	191044	3p21.1
TNNT2	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 track 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

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].

2.2.2.2.2 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.

2.2.2.2.3 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, cardiolipin 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
MTTH	Mitochondrial
MTTK	Mitochondrial
MTTC	Mitochondrial
MTTS1	Mitochondrial
MTND1	Mitochondrial
MTND5	Mitochondrial
MTND6	Mitochondrial
MTTS2	Mitochondrial

Table 3.
Genes associated with MELAS [83–85].

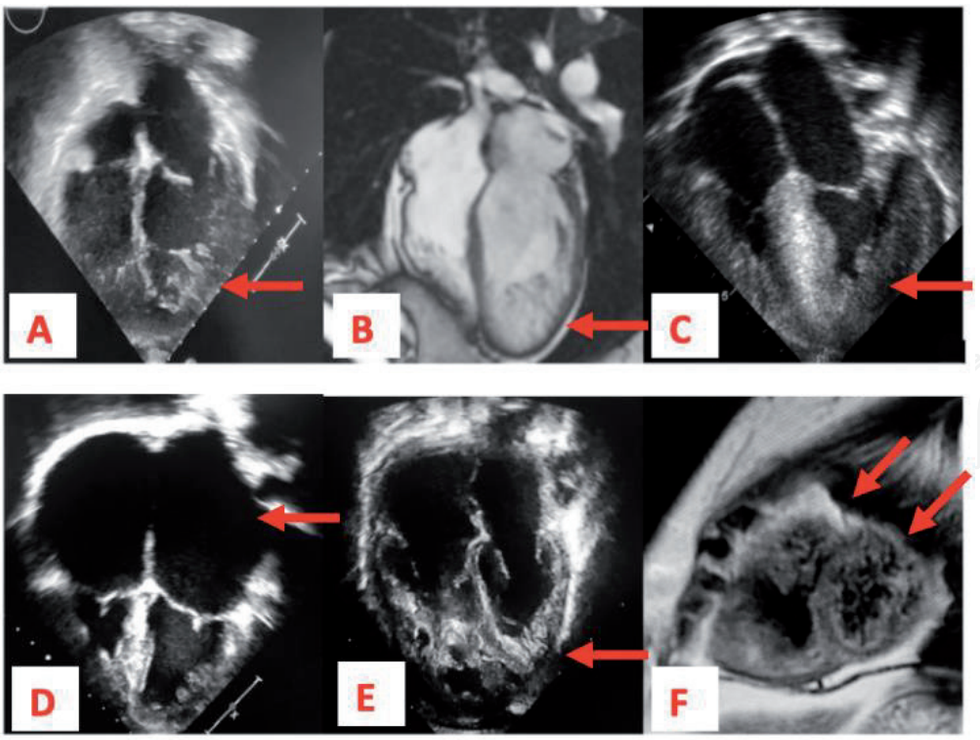

Figure 4.
LVNC phenotypes. (A) Echocardiographic 4-chamber view displays the benign type of LVNC characterized by the cardinal feature of left ventricular trabeculations (arrow) with normal anatomy and function; (B) cardiac magnetic resonance (cMRI) 4-chamber view displays the dilated type of LVNC, notice the enlargement of the LV and the presence of apical and lateral trabeculations (arrow); (C) echocardiographic 4-chamber view shows the hypertrophic type of LVNC represented by asymmetric hypertrophy of the interventricular septum and the presence of lateral LV trabeculations (arrow); (D) echocardiography displaying the restrictive type of LVNC, notice the significant bilateral atrial enlargement (arrows) and the left ventricular dysfunction showing spontaneous cavitary contrast; (E) echocardiography shows features suggestive of bilateral ventricular hypertrabeculations (arrows); (F) cMRI in a short axis view displays a mixed LVNC phenotype represented by dilated and dysfunctional ventricles in a patient with ventricular arrhythmias and biventricular trabeculations (arrows).

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	2q31
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	605557	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	605906	2p22.1
LMNA	Lamin A/C	AD, AR	ACM, HCM, DCM, LVNC	150330	1q22
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	12p11
SCN5A	Sodium Channel, Voltage-Gated, Type V, Alpha Subunit	AD	ACM, DCM	600163	20q13.12
TGFB3	Transforming Growth Factor Beta 3	AD	ACM	190230	
TMEM43	Transmembrane Protein 43	AD	ACM	612048	10q23.3
TTN	Titin	AD, AR	ACM, HCM, DCM	188840	5q33-q34

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.

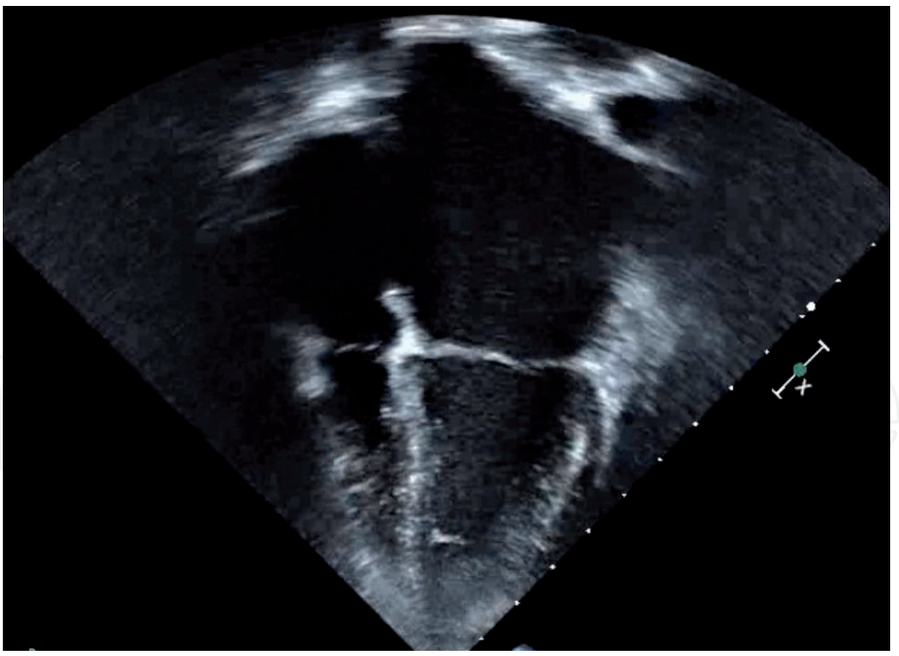

Figure 5.
Two-dimensional, apical 4-chamber echocardiographic image depicting small, restrictive ventricles and significant biatrial enlargement in a patient with restrictive cardiomyopathy.

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 (*BTNL2*) 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

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, LVNC	102565	10q22.2
MYBPC3	Myosin-Binding Protein C, Cardiac	AD	RCM, HCM, DCM, LVNC	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.

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

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.

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