The Genetic Landscape of Cardiomyopathies

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Abstract

Insights into genetic causes of cardiomyopathies have tremendously contributed to the understanding of the molecular basis and pathophysiology of hypertrophic, dilated, arrhythmogenic, restrictive and left ventricular noncompaction cardiomyopathy. More than thousand mutations in approximately 100 genes encoding proteins involved in many different subcellular systems have been identified indicating the diversity of pathways contributing to pathological cardiac remodeling. Moreover, the classical view based on morphology and physiology

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has been shifted toward genetic and molecular patterns defining the etiology of cardiomyopathies. Today, novel high-throughput genetic technologies provide an opportunity to diagnose individuals based on their genetic findings, sometimes before clinical signs of the disease occur. However, the challenge remains that rapid research developments and the complexity of genetic information are getting introduced into the clinical practice, which requires dedicated guidance in genetic counselling and interpretation of genetic test results for the management of families with inherited cardiomyopathies.

2.1 Introduction

Over the last three decades, genetic research has significantly contributed to the etiology of cardiomyopathies. In fact, most primary cardiomyopathies are influenced by genetic factors predisposing to the development of heart failure, one of the most common causes of death in industrialized countries. Cardiomyopathies (CMPs) are commonly grouped by their morphological signs leading to subtypes called hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), left ventricular noncompaction (LVNC), arrhythmogenic cardiomyopathy (ACM), and restrictive cardiomyopathy (RCM) (Fig. 2.1) [1].

Since, in 1990, the sarcomere gene beta-myosin heavy chain (*MYH7*) was identified as the first disease gene for HCM, it turned out that the sarcomere plays a major role in the genetic etiology of HCM but also of other CMPs [2, 3]. HCM can primarily be defined as a disease of the sarcomere, but the genetic basis for CMPs has evolved to be diverse. Genetic causes of ACM have been unraveled with disease genes involved in cell-cell contacts called desmosomes [4, 5]. But, in fact, today there are about hundred known disease genes associated with different subtypes of CMPs, which are expressed in various subcellular systems responsible for transcription, cardiac development, energy utilization, electrolyte imbalances, and others. The diversity is making it difficult to define a final common pathway leading from disturbed gene function to the disease phenotype.

Despite the genetic complexity, with the application of high-throughput genetic technology, we are able to analyze large amounts of data in a cost-effective and timely manner which makes it possible to use this technology not only for research but also for comprehensive cardiomyopathy diagnostics [6–8]. However, there are challenges that clinicians and their team of health-care providers face in translating research results and comprehensive data sets into the clinic in order to improve patient management. A major challenge is still the classification of variants into pathogenic or disease-causing versus benign. Often variants are defined as "uncertain," which makes the application for clinical purposes even more difficult [9]. Additionally, when a pathogenic variant has been identified, there can be substantial variation in penetrance, age of onset, and clinical expression of the phenotype, also within the same family. Here, modifying factors such as lifestyle,

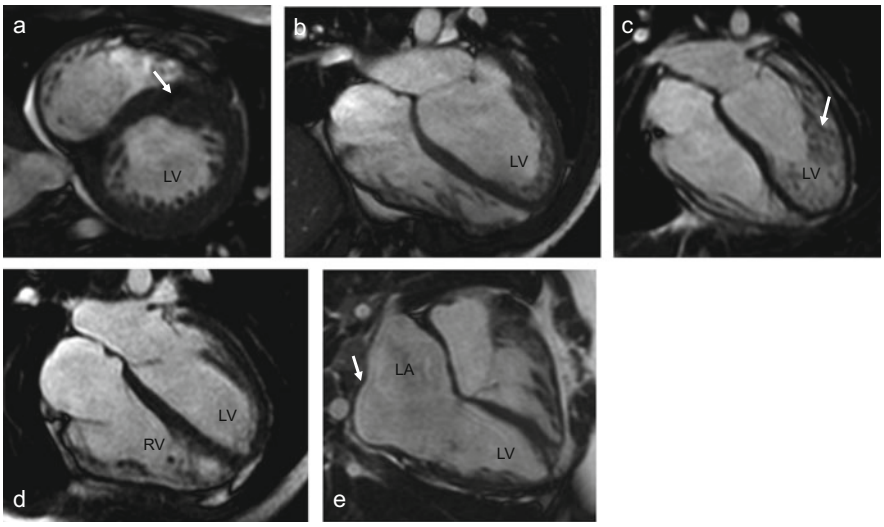

Fig. 2.1 Examples of cardiac magnetic resonance imaging (MRI) pictures of cardiomyopathy subtypes. (**a**) Short-axis two-chamber view of hypertrophic cardiomyopathy (HCM). Note the thick septal wall of the left ventricle (LV) (*white arrow*). (**b**) Long-axis four-chamber view of dilated cardiomyopathy (DCM). Note the enlarged left ventricle. (**c**) Long-axis four-chamber view of left ventricular noncompaction (LVNC). Note the noncompacted, trabeculated layer of the LV (*white arrow*). (**d**) Long-axis four-chamber view of arrhythmogenic cardiomyopathy (ACM). Note the enlarged right ventricle (RV). (**e**) Long-axis four-chamber view of restrictive cardiomyopathy (RCM). Note the massively enlarged left atrium (LA) (*white arrow*)

other genetic and epigenetic factors, pregnancy, and many still unknown entities are playing a role—an ongoing field of research. Moreover, different mutations in the same genes can cause variable clinical entities and even lead to the opposite phenotype (dilated vs. hypertrophic cardiomyopathy). Given the complexity, today the question arises how much a particular genetic diagnosis may help guiding diagnosis and clinical management? There are potential benefits such as differentiating a genetic etiology from other causes of CMPs or allowing the identification of at-risk individuals early, in a preclinical stage. But more importantly, the understanding of the molecular pathways in a translational setting will help to further understand these diseases and dissect more complex disease pathways toward targeted therapies.

This chapter summarizes current knowledge about clinical and molecular genetics of the five main subtypes of inherited cardiomyopathies in a bench-to-bedside approach.

2.2 Hypertrophic Cardiomyopathy (HCM)

Definition Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder affecting clinically about 1 in 500 individuals [10]. The pathological sign is an unexplained left ventricular hypertrophy which is not caused by abnormal loading conditions (Fig. 2.1a). Classically, HCM is characterized by asymmetric septal hypertrophy; however there can be any pattern of left ventricular hypertrophy associated with the disease [11–13].

Clinical Manifestations Clinically, the disease is highly variable in presentation and includes diastolic dysfunction, left ventricular outflow tract obstruction (in about 25%), ischemia, and atrial fibrillation. In about 5% of cases, end-stage HCM shows progression to systolic impairments. Many patients are asymptomatic and are diagnosed incidentally, and others may manifest shortness of breath, chest pain, palpitations, or syncope [11]. Disease-related mortality is most often attributable to sudden cardiac death, heart failure, and embolic stroke. However, early data about high mortality rates from tertiary centers from the 1970s and early 1980s, with annual death rates of 2–4% in adults and 4.2–5.9% in children, have been revised. Disease-related mortality in adults is today about 0.5% similar to that of the general population. Decreased mortality is an achievement of more effective risk stratification and the use of the implantable cardioverter-defibrillator for primary prevention of sudden death [14–16].

Inheritance HCM is mainly inherited as an autosomal dominant trait with incomplete penetrance and variable expression of the clinical phenotype. Some cases are explained by de novo mutations, and other apparently sporadic cases can arise due to autosomal recessive, compound heterozygous, or digenic mode of inheritance [17–19]. Furthermore, genetic modifiers and environmental and epigenetic factors are likely to influence the phenotype. Consequently, even identical mutations may show distinct degrees and morphology of hypertrophy, pattern of fibrosis, age of onset, and risk for arrhythmias and sudden death [20, 21]. On the other hand, population-based studies looking for variants in HCM-associated sarcomere genes indicated that changes in cardiac morphology and function may also occur without causing overt or typical HCM [22].

Disease Genes HCM was the first primary cardiomyopathy for which a genetic cause was identified back in 1990. Ever since over thousand mutations in numerous genes have been described. The most common eight genes encoding sarcomere proteins of the thick and thin filaments are beta-myosin heavy chain (*MYH7*) [2], alpha-tropomyosin (*TPM1*), cardiac troponin T (*TNNT2*) [23, 24], cardiac myosin-binding protein C (*MYBPC3*) [25], myosin regulatory light chain (*MYL2*), myosin essential light chain (*MYL3*) [26], cardiac troponin I (*TNNI3*) [27], and cardiac α-actin (*ACTC1*) [28]. Two major genes, *MYH7* and *MYBPC3*, account together for up to 75% of all identified mutations, whereas other genes including *TNNT2*, *TNNI3*, *TPM1*, *MYL2*, *MYL3*, and *ACTC1* each account for a small proportion of

cases (1–5%) [29, 30]. Furthermore, rare variants have been described in additional genes encoding proteins of the sarcomere apparatus (MYH6, TNNC1, TTN) and the adjacent Z-disc (ACTN2, CSRP3, TCAP, VCL, NEXN, LDB3, MYOZ2, FLNC, MYPN, ANKRD1) or are involved in calcium homeostasis pathways (PLN, CASQ2, JPH2, CALR3). Some of these genes are less evident for direct pathogenicity and may function as modifiers (Table 2.1, Fig. 2.2a) [31–33].

Genotype-Phenotype Correlation The penetrance of expressing the phenotype when carrying a mutation appears to be highly variable and can be delayed or incomplete. Often left ventricular hypertrophy (LVH) does not develop until the third decade of life or even after. In addition, penetrance may also differ according to gender with males showing earlier clinical signs than females [21, 34]. Early genotype-phenotype studies described some genes (or particular mutations) with a higher degree of sudden cardiac death (*TNNT2*, *MYH7* p.Arg403Gln) and other genes (*MYBPC3*) with milder LVH and later age of onset [20, 24]. More recently, reports from the UK suggest a higher risk of sudden death in TNNT2 vs. MYBPC3 families (0.93% vs. 0.46% per year). Overall, currently available phenotypic data could not show clear correlations for specific genes and most of the mutations. Therefore, genotype data have only minor influence on current risk stratification [21, 35, 36].

Despite inherited as an autosomal dominant disease, complex phenotypes with patients carrying more than one mutation or variant exist, and they usually show more severe or earlier phenotypic expression. Such complexity has been reported in 5–7% of cases by Sanger sequencing and is even higher using next-generation sequencing (8–9%). Here, different scenarios have been seen including compound heterozygosity (different heterozygous mutation in each allele of the same gene), digenic cases (heterozygous mutations in two different genes), and also rare homozygosity [37, 38].

Lastly, mutations in classical HCM genes can result in divergent clinical features, also mimicking other forms of cardiomyopathy, in particular LVNC or RCM. Sometimes in the same family, different clinical manifestations may occur [39].

Genetic Counselling and Testing As indicated above, the majority of HCM cases is inherited as an autosomal dominant trait with a 50% risk for first-degree relatives. Current guidelines of the European Society of Cardiology (ESC) recommend genetic counselling for all patients with HCM, unless an acquired cause is demonstrated. Counselling should be performed by trained health-care professionals working within multidisciplinary teams to help patients understand and manage the psychological, social, professional, ethical, and legal implications of genetic disease [11].

If genetic testing is considered, genetic counselling should be performed to fully inform patients about the benefits and limitations of genetic testing and consequences for them and their families. In patients fulfilling the diagnostic criteria for HCM, genetic testing identifies a pathogenic mutation in up to 65% of cases. Although, nowadays, there is no direct benefit in most of the clinically affected cases having a genetic diagnosis in regard to treatment options and a dedicated prognosis,

Table 2.1 Overview about genes associated with HCM

Gene symbol	Encoded protein	Subcellular location/ function	Frequency (%)	First description
Main disease-causing genes[a]				
MYBPC3	Cardiac myosin-binding protein C	Sarcomere, thick filament associated	30–40	1995
MYH7	β-myosin heavy chain	Sarcomere, thick filament	20–30	1990
MYL2	Regulatory myosin light chain	Sarcomere, thick filament	2–4	1996
MYL3	Essential myosin light chain	Sarcomere, thick filament	1–2	1996
TNNI3	Cardiac troponin I	Sarcomere, thin filament	5–7	1997
TNNT2	Cardiac troponin T	Sarcomere, thin filament	5–10	1994
TPM1	α-tropomyosin	Sarcomere, thin filament	<1	1994
ACTC1	Cardiac α-actin	Sarcomere, thin filament	<1	1999
Rare potentially associated genes[a,b]				
ACTN2	α-Actinin 2	Z-disc	Rare	2010
MYOZ2	Myozenin 2	Z-disc	Rare	2007
CSRP3	Cardiac LIM protein	Z-disc	Rare	2003
MYPN	Myopalladin	Z-disc	Rare	2012
FLNC	Filamin C	Z-disc	Rare	2014
TTN	Titin	Sarcomere	Rare	1999
TNNC1	Cardiac troponin C	Sarcomere, thin filament	Rare	2001
MYH6	α-Myosin heavy chain	Sarcomere, thick filament	Rare	2005
NEXN	Nexilin	Z-disc	Rare	2010
TCAP	Telethonin	Z-disc	Rare	2004
ANKRD1	Cardiac ankyrin repeat protein	Z-disc	Rare	2009
LDB3	LIM domain-binding protein 3	Z-disc	Rare	2006
VCL	Vinculin	Z-disc, intercalated disc, sarcolemma	Rare	2006
JPH2	Junctophilin 2	Sarcolemma, Ca^{2+} handling	Rare	2007
CAV3	Caveolin-3	Sarcolemma, repair	Rare	2004
PLN	Phospholamban	SR, Ca^{2+} handling	Rare	2007
CALR3	Calreticulin 3	SR, Ca^{2+} handling	Rare	2007
CASQ2	Calsequestrin	SR, Ca^{2+} handling	Rare	2007

[a]Autosomal dominant inheritance
[b]Evidence for pathogenicity unclear
SR sarcoplasmic reticulum

it is more important for pre-symptomatic testing in the family and reproductive advice. Generally speaking, predictive genetic testing can be performed in asymptomatic relatives of a patient with HCM when a definitive disease-causing mutation has been determined to initiate cascade family screening.

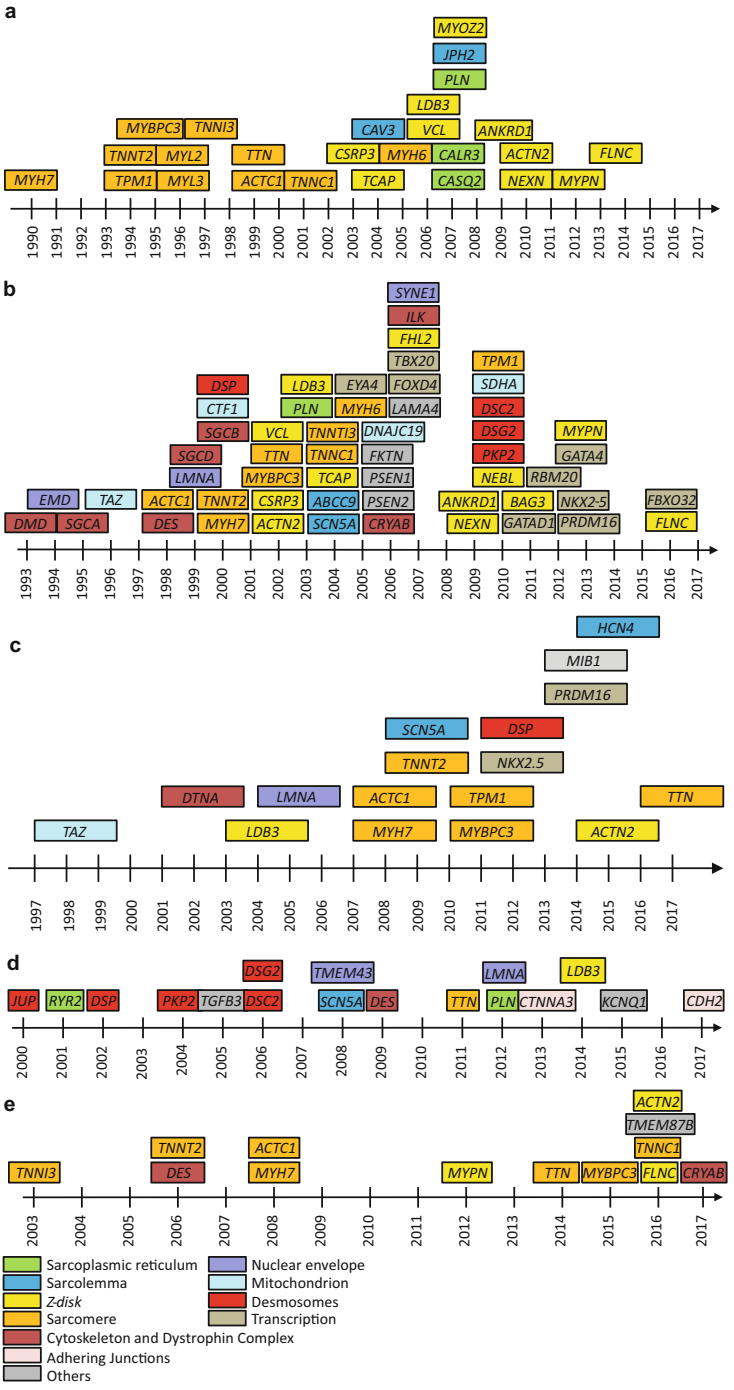

Fig. 2.2 Genes associated with different subtypes of cardiomyopathies according to the year of discovery. Colors indicate the subcellular location and/or functional association. (**a**) Hypertrophic cardiomyopathy. (**b**) Dilated cardiomyopathy. (**c**) Left ventricular noncompaction. (**d**) Arrhythmogenic cardiomyopathy. (**e**) Restrictive cardiomyopathy

However, in situations where predictive genetic testing is either not available or not considered, first-degree relatives should be offered clinical screening with an ECG and echocardiogram starting at an age of 10 years [40]. Individuals who have nondiagnostic clinical features that are consistent with early disease should be seen initially at intervals of 6–12 months and potentially less frequent depending on progression. As indicated above, age-dependent penetrance requires repeat screening even in individuals with no clinical features, unless a predictive genetic test has been performed and was "negative" for a proven disease-causing mutation [3, 11, 41].

Today, new high-throughput sequencing technologies are more and more used for genetic testing in diseases such as HCM by analyzing the whole exome with the potential identification of a large number of variants of unknown clinical significance (VUS). In contrast to other cardiomyopathies, broader genetic testing has shown only a modest increase in the diagnostic yield in HCM (45–72%) while producing more uncertainty. No matter what sequencing technology is used, for clinical practice, genetic testing should include the eight most commonly implicated sarcomere genes and may also consider genes of potential phenocopies of sarcomeric HCM, in particular when additional or atypical phenotypic signs are present [42, 43].

Other Genetic Etiologies There are phenocopies of HCM which can mimic sarcomeric HCM on the basis of cardiac imaging (Table 2.2). In adults, the main non-sarcomeric etiologies are metabolic storage disease such as Danon disease (LAMP2), LVH and Wolff-Parkinson-White syndrome (PRKAG2), Anderson-Fabry disease (GLA), familial TTR amyloidosis (TTR), and some mitochondrial cardiomyopathies. Others are more prevalent in children such as Pompe disease (GAA), Noonan syndrome and Leopard syndrome (PTPN11), or Friedreich ataxia (FXN). To distinguish these diseases from sarcomeric HCM is quite important as an early diagnosis ensures an appropriate management in particular in metabolic diseases [44, 45].

Functional Consequences Although the genetic basis for HCM is well established, the biochemical and biophysical mechanisms how sarcomere mutations lead to disease remain only partially understood. The majority of mutations described are missense mutations that result in mutant dominant-negative acting "poison" peptides, which are incorporated into the sarcomere and potentially have an adverse effect on sarcomere function [46]. The exception for the "poison" protein thesis is mutations in MYBPC3, which often result in truncated proteins. Here, mutant proteins are often cleared by cell surveillance mechanisms, which leads to a reduced amount of full-length protein resulting in haploinsufficiency and consequently an inadequate amount of functional proteins [47, 48].

Mechanistically, there is substantial evidence that myofilament mutations increase calcium sensitivity and Ca^{2+} affinity and thereby actin-dependent ATPase activity [49, 50]. Enhanced Ca^{2+} sensitivity and subsequent defects in calcium homeostasis such as intracellular calcium cycling, sarcoplasmic reticulum

Table 2.2 Other rare genes associated with cardiac hypertrophy

Gene symbol	Encoded protein	Subcellular location/ function	First description	Associated phenotypes/ disease	Inheritance
GLA	α-Galactosidase A	Lysosomes	1989	Fabry disease	X-linked
LAMP2	Lysosome-associated membrane protein 2	Lysosomes	2000	Danon disease	X-linked
PRKAG2	AMP-activated protein kinase, γ2-subunit (noncatalytic)	Energy sensor, cellular energy metabolism	2001	PRKAG2 cardiomyopathy	AD
GAA	α-Glucosidase	Lysosomes, extracellular	1991	Pompe disease	AR
TTR	Transthyretin	Lysosomes, extracellular	1989	Amyloidosis	AD
PTPN11	Protein tyrosine phosphatase, non-receptor 11	Cytosolic, nucleus, signaling molecule	2001	Noonan syndrome	AD
FXN	Frataxin	Mitochondria	1996	Friedreich ataxia	AR

AD autosomal dominant, *AR* autosomal recessive

[SR] Ca^{2+} reuptake, and CaMKII-mediated phosphorylation of proteins, including phospholamban, are likely to contribute to the pathogenesis of HCM [51]. A consequence of increased sarcomeric Ca^{2+} sensitivity is also an enhanced cross-bridge turnover and higher actin-activated ATPase activity. Subsequently, this generates higher energy need to produce a given tension. In accordance with this explanation, several studies have shown mitochondrial abnormalities and an impaired myocardial energy metabolism. Altered Ca^{2+} handling and energy deficiency appear to be major pathways leading to pathological changes such as hypertrophy and myofibrillar disarray as well as functional features such as impaired relaxation [52, 53].

More recently, understanding of fundamental mechanisms arises hope of more specific, substrate-modulating therapy ranging from metabolic modulators to small molecule effectors and gene therapy rescuing HCM at the mechanistic and biochemical level. Targets are energy utilization and oxidative stress, increased calcium sensitivity, sarcomere function (hypercontractility), and the action potential of the myocytes. However, the challenge exists that different mutations even at the same locus can lead to opposite functional consequences. For example, different mutations in MYH7 exert opposing effects on myofilament calcium sensitivity and contractility [54]. In silico models, such as motility assays using purified recombinant sarcomeric protein constructs containing dedicated mutations, are a way to investigate individual mutations [53]. Mutations in the myosin head region domain

lead to hypercontractility and impaired relaxation by assessing the chemo-mechanical cycle in ex vivo preparations of mutated sarcomeric proteins. A small molecule, MYK-461, that decreases sarcomeric power due to inhibition of the myosin adenosine triphosphatase (ATPase) counteracts the effects of the mutation. In mice with hypercontractile mutations in myosin heavy chain, early chronic administration of MYK-461 prevented the development of LVH, myocyte disarray, and fibrosis and normalized expression of profibrotic and mitochondrial genes involved in energy utilization [55].

2.3 Dilated Cardiomyopathy (DCM)

Definition Dilated cardiomyopathy (DCM) is characterized by left or biventricular dilatation and systolic dysfunction that are not explained by abnormal loading conditions or coronary artery disease (Fig. 2.1b). The disease is a common cause of heart failure leading to heart transplantation and sudden death [1]. Causes of DCM can be genetic, estimated as high as 35–50% [56, 57]; however even non-genetic etiologies may predisposed by genetic factors and interact with extrinsic and environmental factors. Lately, there are suggestions for an updated definition of DCM recognizing a broader clinical spectrum of the disease, in particular in the setting of familial disease and before overt clinical manifestations are present. This includes criteria defining preclinical phases of the disease that may occur in mutation carriers without clinical expression, cases with isolated ventricular dilation, arrhythmic cardiomyopathy, or hypokinetic non-dilated cardiomyopathy [58].

Prevalence data based on echocardiography estimated unexplained DCM at 1:2500; more recently epidemiological and next-generation sequencing data suggest a much higher prevalence, possibly as high as 1:250. The disease incidence is 7 per 100,000, and males are more frequently affected than females (3:1) [59, 60].

Clinical Manifestations DCM can present as a clinical syndrome of systolic heart failure with reduced ejection fraction (HFrEF) but also with arrhythmias that may lead to sudden death or thromboembolic events. Management of HFrEF should be performed according to current heart failure guidelines; however, despite optimal therapy, the prognosis remains poor for patients showing heart failure symptoms with a 5-year mortality of up to 20%. Cardiac transplantation or other advanced therapies should be considered with progressive DCM, advanced heart failure, or otherwise refractory disease [61–63].

Another spectrum of the disease represents unidentified cases without clinical symptoms in early phases of the disease. Genetic approaches offer the possibility to identify individuals at risk in the setting of familial disease. Although not proven by placebo-controlled trials, early medical management may be beneficial, even in symptom-free mutation carriers with only minor cardiac abnormalities [58, 64, 65].

Inheritance DCM can be inherited as an autosomal dominant, recessive, or X-linked trait; however chromosomal abnormalities or even matrilineal inheritance may also be present.

Most cases of isolated DCM follow autosomal dominant inheritance with age-dependent penetrance and variable clinical expression, which can be delayed until the fifth or sixth decade. This indicates a role for potential modifying genetic, epigenetic, and environmental factors [66, 67]. However, these factors also contribute to the fact that familial DCM is often not recognized, as other more common etiologies are attributed. When compared to other cardiomyopathies, the genetic etiology of DCM is even more heterogenous, which became more obvious since the introduction of next-generation sequencing [68]. To date, more than 50 disease-related genes have been reported, although relatively few are supported by robust segregation analyses or experimental data (Table 2.3; Fig. 2.2b).

Genes Involved in DCM Pathogenic variants have been reported for a heterogenous group of genes encoding proteins with different functions involved in sarcomere integrity and force transmission, cytoskeletal architecture, cell-cell contacts, nuclear organization, transcription, and ion channel activity. Although extensive genetic heterogeneity is present, titin (*TTN*) is the most common disease gene accounting for 20–25% of the genetic causes [69–71]. The second most prevalent gene is lamin A/C (*LMNA*) with about 6%, followed by beta-myosin heavy chain (*MYH7*) [72–74]. Several other genes account for 1–2% of familial cases, while many others are less frequent or even reported once. Alterations, such as copy number variations (CNVs), have been reported in association with DCM but also with a low frequency. The most important genes and their role in subcellular systems will be discussed in more detail.

Titin and the Sarcomere Mutations in the titin gene (*TTN*) are the main cause of DCM accounting for about 20–25% in familial cases and even up to 18% of sporadic DCM cases. In particular, mutations that truncate the protein have been found to cause disease, although such variants have been also found in 1–2% of the control population [69–71]. Titin, the biggest protein in nature, provides the external scaffold interacting with the thin and thick filaments. It is important for sarcomere assembly and provides passive force and elasticity to maintain diastolic and systolic function, respectively. TTN is composed of different domains according to the sarcomere structure (Z-disc, I-band, A-band, M-band). In addition, *TTN* undergoes extensive alternative splicing and therefore produces many isoforms. Current data suggest that truncating variants in exons that are incorporated into all expressed isoforms, and are part of the final transcript in the heart, are more likely to cause disease (90%), whereas exons, e.g., of the I-band, which are not included in the mature transcript, may not be disease-causing and have been found more frequently in the control population [75].

Mutations in other proteins of the sarcomere are also associated with autosomal dominant DCM such as ACTC1, MYBPC3, MYH6, MYH7, TNNC1, TNNI3, TNNT2, and TPM1, with MYH7 as the most common one [73]. The frequency of

Table 2.3 Overview about genes associated with DCM

Gene symbol	Encoded protein	Subcellular localization/ function	Frequency (%)	First description	Associated phenotypes/ disease	Inheritance
Predominant DCM disease genes						
TTN	Titin	Sarcomere, molecular spring	20–25	2002	None	AD
LMNA	Lamin A/C	Nuclear envelope	6–10	1999	CD, EDMD2, EDMD3, LGMD1B	AD, AR
MYH7	β-myosin heavy chain	Sarcomere, thick filament	5	2000	None	AD
TNNT2	Cardiac troponin T	Sarcomere, thin filament	2	2000	None	AD
BAG3	Bcl2-associated athanogene 3	Z-disc, co-chaperone	2	2011	MFM	AD
RBM20	RNA-binding protein 20	Regulator of RNA splicing	2	2012	None	AD
SCN5A	Voltage-gated sodium channel type V, α-subunit	Ion channel/electrolyte imbalances	2	2004	CD, arrhythmias	AD
ACTC1	Cardiac α-actin	Sarcomere, thin filament	1	1998	None	AD
TPM1	Alpha-tropomyosin	Sarcomere, thin filament	1	2010	None	AD
TNNI3	Cardiac troponin I	Sarcomere, thin filament	1	2004	None	AR, AD
PLN	Phospholamban	SR, Ca^{2+} handling	1	2003	None	AD
TNNC1	Cardiac troponin C	Sarcomere, thin filament	1	2004	None	AD
Rare potentially associated genes						
MYBPC3	Cardiac myosin-binding protein C	Sarcomere, thick filament	Rare	2002	None	AD
MYPN	Myopalladin	Z-disc	Rare	2013	None	AD
DES	Desmin	IF protein, intercalated disc, Z-disc	Rare	1998	MFM	AD, AR
DMD	Dystrophin	Cytoskeleton, force transduction	Rare	1993	Duchenne, Becker muscular dystrophy	X-linked
DNAJC19	DNAJ (Hsp40) homolog	Mitochondrial chaperone	Rare	2006	Dilated cardiomyopathy with ataxia	X-linked

EMD	Emerin	Inner nuclear membrane	Rare	1994	EDMD1	X-linked
TAZ	Tafazzin	Mitochondrial chaperone	Rare	1996	Barth syndrome	X-linked
ANKRD1	Cardiac ankyrin repeat protein	Transcription co-inhibitor	Rare	2009	None	AD
LDB3	LIM domain-binding protein 3	Z-disc, structural integrity	Rare	2003	Myofibrillar myopathy	AD
NEXN	Nexilin	Z-disc, actin-binding protein	Rare	2009	None	AD
SGCD	Delta-sarcoglycan	Transmembrane protein	Rare	1999	LGMD2F	AR, AD
EYA4	Eyes absent homolog 4	Transcriptional coactivator	Rare	2005	Sensorineural hearing loss	AD
PSEN1	Presenilin 1	Catalytic component of gamma-secretase	Rare	2006	None	AD
FBXO32	F-box protein 32/atrogin 1	Ubiquitin ligase	Rare	2016	None	AR
GATAD1	GATA zinc finger domain containing 1 protein	Transcription factor	Rare	2011	None	AR
GATA4	GATA-binding protein 4	Transcription factor	Rare	2013	Congenital heart disease	AD
MYH6	α-Myosin heavy chain	Sarcomere, thick filament	Rare	2005	None	AD
ACTN2	α-Actinin 2	Z-disc, actin-binding protein	Rare	2002	None	AD
CSRP3	Cardiac LIM protein	Z-disc, stretch sensing	Rare	2002	None	AD
TCAP	Telethonin	Z-disc, stretch sensing	Rare	2004	LGMD2G	AD
ABCC9	Sulfonylurea receptor 2	Subunit of the cardiac K(ATP) channel	Rare	2004	Cantú syndrome	AD
TBX20	T-box 20	Transcription factor	Rare	2007	Congenital heart disease	AD
NKX2-5	NK2 homeobox 5	Transcription factor	Rare	2013	Congenital heart disease	AD
CTF1	Cardiotrophin 1	Cytokine, hypertrophy	Rare	2000	None	AD
VCL	Vinculin	Cell-ECM and cell-cell adhesion	Rare	2002	None	AD
SGCB	β-Sarcoglycan	Transmembrane protein	Rare	2000	LGMD2E	AR
SGCA	α-Sarcoglycan	Transmembrane protein	Rare	1995	LGMD2D	AR
FHL2	Four and a half limb domains 2	Z-disc, focal adhesions	Rare	2007	Myopathy	X-linked
FKTN	Fukutin	Transmembrane protein, Golgi apparatus	Rare	2006	Fukuyama-type muscular dystrophy	AR

(continued)

Table 2.3 (continued)

Gene symbol	Encoded protein	Subcellular localization/ function	Frequency (%)	First description	Associated phenotypes/ disease	Inheritance
FOXD4	Forkhead box protein D4	Transcription factor	Rare	2007	Obsessive-compulsive disorder	AD
LAMA4	Laminin subunit alpha-4	ECM	Rare	2007	None	AD
ILK	Integrin-linked kinase	Focal adhesions, ECM connection	Rare	2007	None	AD
PSEN2	Presenilin 2	Catalytic component of γ-secretase	Rare	2006	None	AD
SDHA	Succinate dehydrogenase subunit A	Mitochondrial inner membrane	Rare	2010	None, neonatal DCM	AR
CRYAB	αB-Crystallin	Z-disc, small heat-shock protein	Rare	2006	MFM, cataract	AD, AR
SYNE1	Nesprin 1	Cytoskeleton, nuclear lamina	Rare	2007	EDMD4	AD
PRDM16	PR domain containing 16	Transcription factor	Rare	2013	1p36 deletion syndrome	AD
DSC2	Desmocollin 2	Desmosomes, intercalated disc, cell adhesion	Rare	2010	None	AD
DSG2	Desmoglein 2	Desmosomes, intercalated disc, cell adhesion	Rare	2010	None	AD, AR
DSP	Desmoplakin	Desmosomes, intercalated disc, cell adhesion	Rare	2000	Palmoplantar keratoderma	AD
PKP2	Plakophilin 2	Desmosomes, intercalated disc, cell adhesion	Rare	2010	None	AD
FLNC	Filamin C	Z-disc, actin cross-linking protein	Rare	2016	MFM	AD
NEBL	Nebulette	Z-disc	Rare	2010	10p14-p13 deletion	AD

AD autosomal dominant, *AR* autosomal recessive, *CD* conduction disorder, *ECM* extracellular matrix, *EDMD* Emery-Dreifuss muscular dystrophy, *LGMD* limb-girdle muscular dystrophy, *RNA* ribonucleic acid, *SR* sarcoplasmic reticulum, *IF* intermediate filament

sarcomere gene mutations to be associated with DCM is much lower compared to HCM and LVNC. Mechanistically, and in contrast to HCM, mutations are suggested to decrease Ca^{2+} sensitivity causing a hypocontractile state that leads to systolic dysfunction. For example, mice carrying a HCM-associated mutation (delGlu160) in TNNT2 showed increased Ca^{2+} sensitivity, whereas a DCM-associated mutation (delLys210) in the same gene showed the opposite, decreased Ca^{2+} sensitivity [53].

Nuclear Envelope Proteins DCM-associated mutations are also involving proteins of the nuclear envelope such as lamin A/C (LMNA) located in the nuclear lamina and emerin (EMD), a protein of the inner nuclear membrane. Dominant *LMNA* mutations account for 6–10% of genetic causes and are frequently associated with arrhythmias and conduction system disturbances [72]. In addition, limb-girdle myopathies are a variable feature. Lamins are involved in nuclear structure support, DNA repair, cell signaling pathway mediation, and chromatin organization. There are two major hypotheses how mutations in LMNA may lead to cardiac dysfunction: (1) disruption and uncoupling of structural proteins at the nuclear lamina that lead to mechanical instability and to an increased susceptibility to mechanical stress and (2) disrupted chromatin organization that impacts directly on gene transcription [76, 77].

EMD is a LEM-domain protein located in the nuclear lamina and has a role in assembly of the nuclear lamina and structural organization of the nuclear envelope. EMD mutations are X-linked and often associated with a skeletal muscle phenotype of Emery-Dreifuss muscular dystrophy [78].

Gene Expression Genes regulating transcription are also important in the pathogenesis of DCM. Rare mutations have been described in *TBX20*, *NKX2-5*, *GATA4*, *GATA6*, *FOXD4*, *PRDM16*, *EYA4*, *GATAD1*, and *RBM20*. Other associated phenotypes such as congenital heart defects, hearing loss, or more complex syndromic features are often observed (Table 2.3). Variants in most of those genes lead to decreased transcriptional activity influencing a set of genes important for cardiac development and structural remodeling [79–83].

A very interesting gene is *RBM20*, which encodes a spliceosome protein that regulates pre-mRNA splicing for many genes, including *TTN*. Interestingly, a mutational hotspot causing highly penetrant DCM alters an arginine-serine-rich region of RBM20, which influences binding with other splicing factors and changes transcript processing [84, 85].

Calcium Handling and Ion Imbalances Mutations in phospholamban (*PLN*) are predicted to alter Ca^{2+} homeostasis. The protein regulates Ca^{2+} uptake by the SR Ca^{2+} ATPase (SERCA2a) and inhibits Ca^{2+} cycling when dephosphorylated [86]. In its phosphorylated state by protein kinase A (PKA), muscle relaxation is enhanced, and beta-agonist activates PKA and enhances relaxation. Mutations in PLN blunt beta-adrenergic activation of PKA and control of Ca^{2+} cycling leading to decreased contractility [87].

Another important gene is the voltage-gated, type V alpha-subunit of the cardiac sodium channel (*SCN5A*) which is involved in the cardiac action potential. The channel is responsible for rapid depolarization of the myocardium and the maintenance of impulse conduction. Mutations lead to a variety of arrhythmic disease and also DCM by modifying electrical excitability of the channel leading to disturbances of currents and different ions which are also involved in contraction [88].

The ABCC9 protein is predicted to form ATP-sensitive potassium channels in cardiac and other muscles. Variants in this gene have been also associated with DCM [89].

Z-Disc-Associated Proteins The sarcomeric Z-disc defines the lateral borders of the sarcomere and consists of actin filaments coming from adjacent sarcomeres which are cross-linked by α-actinin molecules. The Z-disc serves as a nodal point with multiple functions such as intracellular signaling, mechanosensation and mechanotransduction. The Z-disc also links to the T-tubular system and the sarcoplasmic reticulum; moreover, several E3 ubiquitin ligases localized to the Z-disc link this structure to protein turnover and autophagy [32]. To date, mutations in multiple Z-disc proteins or Z-disc-related proteins have been reported to be associated with DCM including ACTN2, ANKRD1, BAG3, CRYAB, CSRP3, LDB3, MYPN, NEBL, NEXN, TCAP, FLH2, FLNC, and DES; however the evidence for clear pathogenicity is variable (Table 2.3) [90]. A typical sarcomeric Z-disc protein is α-actinin 2 (ACTN2), which is important for actin filament localization. The cardiac LIM protein CSRP3 is a protein with multiple interaction partners and is involved in various signal transduction cascades, including mechanosensation and mechanotransduction, calcium metabolism, and myofibrillogenesis. Mutations in *CSRP3* can either cause DCM or HCM [91, 92].

A protein, which is present at the sarcomeric Z-disc but also as an intermediate filament, is desmin (DES). It provides the link to the desmosomes and to other compartments such as the nucleus [93].

An interesting protein is the co-chaperone BAG3 (Bcl2-associated athanogene 3), which acts as a multifunctional adaptor protein responsible for cell survival, apoptosis, migration, proliferation, macro-autophagy, and proteasomal processes. Mutations causing DCM may influence BAG3-interacting proteins such as HSP70 responsible for protein folding and quality control of newly synthetized proteins [94].

Overall, the Z-disc-associated proteins are diverse and are becoming a "hotspot" for cardiomyopathy-causing mutations; however the spectrum of functional disturbances is various and depending on their specific location and behavior.

Desmosomes Desmosomes are located at the intercalated discs and part of a junctional structure called "area composita." Mutations in desmosomal proteins can cause DCM-like phenotypes but are more frequently involved in ACM (see chapter ACM). There is a substantial overlap, in particular in phenotypic features of more left-sided ACM phenotypes and DCM with pronounced arrhythmic features,

as seen mainly with mutations in desmoplakin (*DSP*), but also in other desmosomal proteins [95, 96].

DCM Associated with Other Pathologies As indicated in Table 2.3, DCM is sometimes associated with other non-cardiac phenotypic features, in particular myopathies. In addition, DCM can also occur as part of a syndrome that often affects children.

Interestingly, there are frequent associations of DCM with either myofibrillar myopathy (MFM), Emery-Dreifuss muscular dystrophy (EDMD), or limb-girdle muscular dystrophy (LGMD). Genetic variations in the same genes can cause isolated DCM and associations with those types of skeletal muscle diseases. Often, but not always, isolated DCM is inherited as an autosomal dominant disease, whereas associated myopathies are X-linked or autosomal recessive.

MFMs are chronic neuromuscular disorders. The morphologic changes in skeletal muscle and sometimes in cardiac muscle result from disintegration of the sarcomeric Z-disc and the myofibrils, followed by abnormal ectopic accumulation of multiple proteins (myofibrillar cytoplasmic inclusions). Mutations in genes encoding desmin (DES), alpha-B-crystallin (CRYAB), dystrophin (DMD), filamin C (FLNC), LIM domain-binding protein 3 (LDB3), and BAG3 [97] are causing MFM and/or DCM.

The two other common myopathies are limb-girdle muscular dystrophy (LGMD) and Emery-Dreifuss muscular dystrophy (EDMD), which are mainly inherited as recessive disorders. EDMD is characterized by myopathic changes in certain skeletal muscles and early contractures at the neck, elbows, and Achilles tendons, as well as cardiac conduction defects. Disease genes for EDMD are emerin (EMD), lamin A/C (LMNA), and nesprin-1 (SYNE1) [98]. Autosomal recessive LGMDs are a heterogenous group of disorders affecting primarily skeletal muscle in various forms; in some, DCM is part of the clinical spectrum such as in LGMD2F, LGMD2E, LGMD2D, and LGMD2G, whereas dominant mutations in LMNA can cause LGMD1B [99].

DCM is an important part of the disease spectrum in Duchenne and Becker muscular dystrophies caused by mainly truncating mutations in the dystrophin gene (DMD). In Duchenne or Becker with a later onset, cardiac features are present in about 95% of cases by the last years of life. Also, female carriers of these X-linked diseases develop DCM in about 15% of cases [100].

Lastly, DCM is also part of inherited syndromes. Some of them are listed in Table 2.3. They are usually associated with a congenital onset, inherited as a recessive or X-linked trait, and affect proteins that play a role in the heart and other tissues.

Genetic Testing and Counselling The increasing understanding of the genetic basis of DCM and the availability of comprehensive and cost-effective next-generation sequencing technologies have highlighted the importance of considering genetic testing in all patients with DCM, not just those with an obvious family history or a particular phenotype. Today, cardiomyopathy multi-gene panels or even whole-exome sequencing (WES) is available to perform genetic testing. In clinical settings,

as opposed to research testing, the focus should be on known genes associated with DCM [101]. The major challenge occurs in interpreting genetic test results to be used in a clinical setting.

Moreover, not only the interpretation of genetic test results but also proper communication to the patients and their families require a clinician specifically trained in medical genetics and cardiology, who is embedded in a team of experts including genetic counsellors, psychologists, and specialized cardiologists. Expert knowledge of advances in testing, emerging data on newly identified variants and clinical correlations, and an understanding of the complex allelic heterogeneity and complicated scenarios such as multiple variants that may influence the disease are particularly important in DCM.

In the scenario that genetic testing results in a pathogenic/likely pathogenic mutation, the mutation can be considered to be tested in relatives at risk for cascade screening in order to facilitate prompt diagnosis, surveillance, and in selected cases preventative treatment. Furthermore, relatives who do not carry the mutation may be discharged from clinical surveillance which has long-range consequences for families and requires a correct review and classification of genetic variants identified by genetic testing.

Strict variant classification according to the ACMG criteria [9] can facilitate a highly accurate diagnostic yield in DCM, with a pathogenic/likely pathogenic variant detection rate of 35.2%, with 47.6% in familial DCM and 25.6% in sporadic cases [102]. However, even with these restrictions, many variants of uncertain significance (VUSs) are identified mainly in genes with weak evidence of being associated with DCM. For example, the interpretation of *TTN* variants is a big challenge, and pathogenicity depends on additional information and resources, as *TTN* truncating variants are apparently also present in healthy individuals. There are additional online tools available indicating details in the exon composition of the major *TTN* transcripts; information whether an exon is constitutively expressed, and other structural features for each exon; as well as the distribution of TTN variants in large published studies of cohorts of DCM patients and controls [71, 75].

Overall, genetic testing is challenging and takes an expert panel to draw the right conclusions. Likewise, there is no doubt about the importance of genetic counselling and clinical surveillance of first-degree relatives of individuals with DCM.

Genotype-Phenotype Correlation DCM is characterized by marked genetic heterogeneity and variable disease penetrance, which make direct applications to clinical management difficult. Additionally, clinical variability in the phenotype development with the influence of other contributing factors impedes the prediction for a certain genotype [8]. Only few genes such as *TTN* and *LMNA* as well as some founder mutations in *PLN* or *MYBPC3* are more common for comprehensive investigations to allow genotype-phenotype studies.

Mutations in *LMNA* are highly suggestive for progressive conduction disease and ventricular arrhythmias with an increased risk for sudden death. Risk assessment also involves a gender-specific risk with a higher mortality in men compared to women. LMNA-associated DCM demonstrates an age-related penetrance with onset

in the third and fourth decades, so that by the seventh decade, penetrance is considered greater than 90–95%. Management implications are to assess for prophylactic implantable cardioverter-defibrillator placement to treat malignant ventricular arrhythmias for patients receiving a pacemaker for LMNA-associated conduction system disease, independent of ejection fraction [76, 103–105].

More recently, genotype-phenotype studies for *TTN* truncation variants suggested a milder phenotype compared to non-*TTN*-related cardiomyopathies, although the comparison was driven by a direct comparison to *LMNA* cardiomyopathy which has, as indicated above, a severe phenotype [106, 107]. First findings also suggest a gender-specific difference with regard to median age of onset and prognosis which was more preferable for woman compared to man. In terms of age-dependent penetrance, current data suggest a late age of onset, ranging between about 30% and 50% at the age of 50 and between 80% and 100% at the age of 70 [102, 106].

Severe phenotypes may also appear when additive genetic effects appear, for example, in cases carrying compound heterozygous variants [108].

2.4 Left Ventricular Noncompaction (LVNC)

Definition and Classification Left ventricular noncompaction (LVNC) is a rare disorder characterized by hypertrophic segments that consist of a thin compacted epicardial layer and a thick noncompacted endocardial layer. The noncompacted layer contains numerous prominent trabeculations and deep intertrabecular recesses [109, 110]. LVNC may be an isolated finding in the absence of any coexisting cardiac anomaly (isolated LVNC) or may be associated with other congenital heart anomalies such as complex congenital heart disease (non-isolated LVNC).

LVNC is a relatively new clinicopathologic condition, first described as such by Chin et al. in 1990 [109]. Based on the predominant myocardial involvement and genetic etiology, LVNC was classified by the American Heart Association (AHA) as a distinct primary cardiomyopathy [1]. The European Society of Cardiology (ESC) recognizes LVNC as an unclassified cardiomyopathy [41]. The ESC questions whether LVNC is a distinct cardiomyopathy or merely a congenital or acquired morphological trait shared by many phenotypically distinct cardiomyopathies [111, 112].

Clinical Manifestation LVNC presents with a unique congenital cardiac morphology, variable clinical features, and a diverse natural history. The heterogeneity of the clinical features includes both asymptomatic and symptomatic patients with progressive deterioration in cardiac function resulting in congestive heart failure, arrhythmias, thromboembolic events, and sudden cardiac death [113–115].

There was a prevalence of 0.014% in patients referred to an echocardiography laboratory in a tertiary referral center [115]. Lately, due to improved imaging techniques, increased awareness, and family screening, the rare entity LVNC is recognized with growing frequency [116, 117]. A substantial proportion of individuals is asymptomatic, suggesting that the true prevalence of LVNC may be

higher. Greater extent of, and even excessive, LV trabeculation measured in end-diastole in asymptomatic population-representative individuals by cardiac magnetic resonance imaging (MRI) appeared benign and was not associated with deterioration in LV volumes or function during an almost 10-year period [MESA (Multi-Ethnic Study of Atherosclerosis)] [118]. LVNC was identified as the most frequent cardiomyopathy after DCM and HCM in childhood, with an estimated prevalence of 9% [119] in an Australian cohort and 5% in the US Pediatric Cardiomyopathy Registry [120].

The clinical diagnosis is performed with two-dimensional echocardiography and/or cardiac MRI on the basis of the prominent appearance of LV trabeculae and the ratio between the compacted and noncompacted LV wall (Fig. 2.1c). The diagnosis of LVNC in the symptomatic patient is made at any age, ranging from fetus to old age. Heart failure symptoms are the most common reason for hospital admission. Both systolic and diastolic cardiac dysfunctions have been described. Ventricular tachycardia with a significant risk of cardiac sudden death is frequently found (20–40%). The formation of thrombi in the extensive intertrabecular recesses leading to systemic thromboembolic events is another, although less common, presentation of patients with LVNC. The natural history of LVNC is largely unresolved. As in other cardiomyopathies, index cases represent the most severe spectrum of the disease [114]. LVNC has a high mortality rate and is strongly associated with arrhythmias in children. Preceding cardiac dysfunction or ventricular arrhythmias are associated with increased mortality. Children with normal cardiac dimensions and normal function are at low risk for sudden death [121].

Morphology and Pathogenesis The noncompacted endocardial layer of the myocardium comprises numerous, excessively prominent ventricular trabeculations with deep intertrabecular recesses. The recesses extend deeply into the trabecular meshwork and end at the thin compacted outer layer. In contrast to "persisting myocardial sinusoids" which were first observed in patients with left or right ventricular outflow tract obstruction, recesses in LVNC have no connection with the coronary circulation and are covered by endocardium throughout the ventricular cavity. The most widely used method for the morphologic diagnosis of LVNC is two-dimensional echocardiography and was established by Jenni et al. [110]. The diagnosis of LVNC is made irrespective of the presence of left ventricular systolic dysfunction or dilatation (DCM) due to hypokinetic segments in the altered LV myocardium. Given the common localization of the noncompacted areas in the apex and the common localization of septal hypertrophy in HCM, the two diagnoses of HCM and LVNC can coexist. LV dilation/dysfunction and LV hypertrophy can therefore be present or absent and do not influence LVNC diagnosis. There may be biventricular noncompaction, but criteria for the diagnosis of noncompacted myocardium involving the right ventricle have not been established. Imaging criteria for the assessment of LVNC are still evolving. A significant proportion of an asymptomatic population free from CVD satisfy all currently used cardiac magnetic resonance imaging diagnostic criteria for LVNC, suggesting that those criteria have poor specificity for LVNC [112].

There is evidence that LVNC can originate during embryonic development or be acquired later in life. The de novo LV trabeculations in a significant proportion (>25%) of pregnant women suggest that these may occur as a consequence of increased LV loading conditions or other physiological adaptation mechanisms related to pregnancy. Moreover, the general assumption that LVNC is caused by incomplete myocardial compaction during embryogenesis has been questioned [122, 123]. During fetal development, compaction of the ventricular myocardium normally progresses from epicardium to endocardium, from the base to the apex, and from the septum to the lateral wall. An arrest in this process of myocardial morphogenesis would explain the predominant localization of noncompacted myocardium in LVNC. If not reflecting compaction of pre-existing trabeculations, it is certainly possible that noncompaction relates to defects of proliferation of the compacted myocardium. Mutation of *PRDM16* causes LVNC in patients, and PRDM16 zebrafish mutants show impaired cardiomyocyte proliferation [79]. Genome editing of *PRDM16* leads to proliferation defects in iPSC-CMs, and abnormal TGF-β signaling was suggested as pathological mechanism [124]. Mouse embryos lacking Notch1, systemically or in the endocardium, show defective trabeculation. Molecular analysis of these mutants reveals that expression of endocardial and myocardial trabecular differentiation markers is impaired and ventricular cardiomyocyte proliferation is inhibited. These findings imply that endocardial Notch1 signaling is required for proliferation and differentiation of trabecular myocardium [125].

Disease Genes and Inheritance Among many sporadic cases, familial recurrence has already been observed in the first reports of isolated LVNC. In familial cases, autosomal dominant inheritance is more common than X-linked inheritance [126]. LVNC has been associated with mutations in almost 20 different genes (Table 2.4 and Fig. 2.2c). Defects in sarcomere genes are the most prevalent genetic cause occurring in 30% of adult patients with isolated LVNC. *MYH7* is the most frequent LVNC-associated gene in adult patients with isolated LVNC [127]. Mutations in the sarcomere genes encoding thick (MYH7) [128–131], intermediate/thick filament associated (MYBPC3) [127, 129, 132], and thin filaments (TNNT2, TPM1, ACTC1) [127, 129, 130, 133] have been described. *TTN*, encoding for the giant protein Titin that serves as a molecular spring of the sarcomere, has recently been added to the list of sarcomere genes in LVNC [134].

However, mutations in other genes are only rare causes of LVNC in single families. *TAZ* was the first gene shown to be associated with isolated LVNC by genetic linkage analysis in a family with X-linked inheritance [135]. *TAZ* encodes for taffazin, a protein involved in the biosynthesis of cardiolipin, an essential component of the inner mitochondrial membrane. A small proportion of familial autosomal dominant LVNC can be explained by mutations in genes encoding proteins of the Z line of the sarcomere, LDB3/ZASP [129, 136] and *ACTN2*/α-actinin 2 [137]. Two cardiac ion channels *HCN4*/hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 [138, 139] and *SCN5A*/cardiac sodium channel alpha-subunit gene [140] lead to LVNC with sinus node dysfunction and arrhythmias, respectively. A component of the nuclear lamina,

Table 2.4 Overview about genes associated with LVNC

Gene symbol	Encoded protein	Subcellular location	Frequency (%)	First description	Associated phenotype/ disease
Predominant LVNC disease genes					
MYH7	β-Myosin heavy chain	Sarcomere, thick filament	<15	2007	Congenital heart defects
MYBPC3	Cardiac myosin-binding protein C	Sarcomere, thick filament associated	<10	2010	Congenital heart defects
ACTC1	Cardiac α-actin	Sarcomere, thin filament	<5	2007	Congenital heart defects
TNNT2	Cardiac troponin T	Sarcomere, thin filament	<5	2008	None
TPM1	α-Tropomyosin	Sarcomere, thin filament	<5	2010	None
PRDM16	PR domain-containing protein 16	Transcription factor	<5	2013	1p36 deletion syndrome
TAZ[a]	Taffazin	Mitochondrial chaperone	Rare	1997	Barth syndrome
DTNA	α-Dystrobrevin	Cytoskeleton, contractile force transduction	Rare	2001	Congenital heart defects
LDB3	LIM domain-binding protein 3	Z-disc	Rare	2003	None
MIB1	Mindbomb drosophila homolog 1	Cell-cell signaling, ubiquitin ligase	Rare	2013	None
ACTN2	α-Actinin 2	Z-disc	Rare	2014	Ventricular fibrillation, sudden death
HCN4	Hyperpolarization-activated cyclic nucleotide-gated potassium channel 4	Ion channel	Rare	2014	Sinus node dysfunction/ bradycardia
Rare, potentially associated genes					
LMNA	Lamin A/C	Nuclear envelope	Rare	2004	Cardiac conduction disease
SCN5A	Voltage-gated sodium channel type V, α-subunit	Ion channel	Rare	2008	Arrhythmia
NKX2-5	NK2 homeobox 5	Transcription factor	Rare	2011	Congenital heart defects, sudden death

DSP[b]	Desmoplakin	Desmosomes, intercalated disc, cell adhesion	Rare	2011	Acantholytic palmoplantar keratoderma
TTN	Titin	Sarcomere, molecular spring	Rare	2016	None

[a]X-linked inheritance
[b]Autosomal recessive; all other disorders are autosomal dominant

lamin A/C (*LMNA*) [141] causes LVNC with cardiac conduction disease. Mutations in the gene *MIB1* segregated with autosomal dominant LVNC in two families, and a conditional loss-of-function allele in a mouse model, also led to LVNC [142]. The hypertrabeculation and noncompaction seen in the MIb1 mouse was mimicked in a mouse with inactivation of Jagged1 in the myocardium or Notch1 in the endocardium, suggesting that the Notch1 signaling pathway was involved.

Genetic Syndromes and/or Other Disorders LVNC is present in a number of neuromuscular disorders, metabolic and mitochondrial disease, congenital malformations, and chromosomal syndromes. Some of these disorders may share pathogenetic mechanisms with LVNC. Alternatively, LVNC might be secondary to other cardiac malformations or even vice versa.

LVNC can occur as part of a syndrome in combination with dysmorphic features and other congenital malformations. Chromosomal deletions have been found on chromosomes 1p36, 1q43, and 5q35 [79]. Left ventricular noncompaction is known to be a part of various syndromes, including the Barth, Noonan, Roifman, Melnick-Needles, Nail-Patella, Toriello-Carey, and other uncommon syndromes [143]. *TAZ* mutation typically results in Barth syndrome, which is characterized by cardiomyopathy (frequently LVNC), skeletal myopathy, cyclic neutropenia, and 3-methylglutaconic aciduria (a marker of mitochondrial dysfunction) [144]. *DSP*, encoding for desmoplakin, a gene known for the first recessive human mutation that causes a generalized striate keratoderma particularly affecting the palmoplantar epidermis, woolly hair, and dilated left ventricular cardiomyopathy (Carvajal syndrome), also leads to LVNC with acantholytic palmoplantar keratoderma with autosomal recessive inheritance [145].

The co-occurrence of congenital heart defects (CHD) and noncompaction is seen in children and in adults [144, 146]. *DTNA*, encoding for α-dystrobrevin, a cytoskeletal component responsible for force transduction, is mutated in patients with hypoplastic left heart syndrome and LVNC [144]. Septal defects and Ebstein anomaly are the most prevalent congenital heart defects in LVNC. Mutations in the cardiac transcription factor *NKX2-5* were identified in children with LVNC and atrial septal defects [147]. Noncompaction associated with Ebstein anomaly, a rare type of CHD, has been shown to result from mutations in *MYH7* [131]. The association of sarcomere gene defects, cardiomyopathy, and structural CHD still requires further investigation. Very much like HCM and DCM, LVNC has been linked to neuromuscular disorders such as dystrophinopathies and with mitochondrial disease. In a number of muscular dystrophies, "left ventricular hypertrabeculation" was identified [148]. In a study of 113 pediatric patients with mitochondrial disease, LVNC was identified in 13% [149].

Genetic Counselling and Testing Since extensive family studies showed that the majority of affected relatives are asymptomatic, cardiologic evaluation should include all first-degree relatives irrespective of medical history. Other cardiomyopathies may co-occur within families, like HCM and DCM, so cardiac screening should aim at identifying all cardiomyopathies. Cardiac screening of

relatives may show minor abnormalities not fulfilling LVNC criteria. Genetic testing, preferably with a targeted cardiomyopathy gene panel, may lead to the identification of a molecular defect in over 40% of isolated LVNC patients [129].

Molecular studies of LVNC have thus far shown that there are few recurrent mutations. Therefore, it is difficult to establish genotype-phenotype correlations. Additionally, intrafamilial phenotypic variability complicates predictions based on an identified mutation. Compound heterozygous or homozygous truncating sarcomere gene mutations appear to result in a more severe phenotype with childhood onset [132]. Whereas TAZ mutations have been reported in pediatric patients often diagnosed with LVNC during infancy, heterozygous mutations in autosomal dominant LVNC were mainly identified in adult patients.

Probst et al. [127] reported a cohort of 63 LVNC probands, previously studied by Klaassen et al. [130], in which 8 sarcomere genes were analyzed and heterozygous mutations found in 18 (29%) of the probands: 8 mutations were in the MYH7 gene, 5 in MYBPC3, 2 in ACTC1, 2 in TPM1, and 1 in TNNT2. There were no significant differences between mutation-positive and mutation-negative probands in terms of average age, myocardial function, or presence of heart failure or tachyarrhythmias at initial presentation or at follow-up. Probst et al. [127] noted that although 8 of the 15 distinct mutations were novel in this cohort, they were likely not specific to LVNC, because the other 7 mutations had previously been described in patients with other forms of cardiomyopathy, including hypertrophic and dilated forms. In conclusion, molecular analyses of LVNC support the concept of a shared molecular etiology of the different cardiomyopathic phenotypes.

For further reading: Left Ventricular Noncompaction [143] in Clinical Cardiogenetics, Springer International Publishing, H.F. Baars et al. (eds), 2016.

2.5 Arrhythmogenic Cardiomyopathy (ACM)

Definition Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary cardiomyopathy characterized by progressive fibro-fatty replacement of the right and left ventricular myocardium (Fig. 2.1d) [150]. In the early eighteenth century, the clinical phenotype of ARVC was first reported by Giovanni Maria Lancisi in a four-generation family, where patients presented with right ventricular dilation or aneurysms and suffered from sudden cardiac death, both typical signs of the disease [151]. During the 1980s, clinical features were systematically described by Marcus and colleagues [152]. Particularly, the central involvement of the right ventricle was described. However, today there is growing evidence that the left ventricle is also affected leading to the term "arrhythmogenic cardiomyopathy" (ACM), which will be also used in this chapter. The estimated disease prevalence ranges from 1:2000 to 1:5000 considering ACM as a rare disease [153].

Clinical Manifestation Clinical features of the disease are highly variable ranging from unaffected mutation carriers to patients suffering from sudden cardiac death or requiring heart transplantation. Classical symptoms include palpitations, cardiac

syncope, and aborted cardiac arrest due to ventricular arrhythmias. Heart failure is rare and may develop in later stages. ACM is a progressive disease which typically manifests in the second to fourth life decade. However, about 20% of cases develop the disease after the age of 50 [154]. Penetrance is age and gender dependent, and clinical manifestations and progression of the disease are highly variable. Men are clinically more often affected than women. The influence of sex hormones and higher physical activity of men may contribute to the disease expression. The clinical diagnosis is challenging, because of the lack of a specific diagnostic test. Hence, the diagnosis is based on fulfilling a set of major and minor criteria proposed by an international task force initially in 1994 [155]. This set of Task Force Criteria (TFC) was highly specific but lacked sensitivity for early forms of ACM and has been revised in 2010 to incorporate new findings and diagnostic modalities [150]. The TFC include evaluation of findings from six different diagnostic categories including cardiac imaging, assessment of electrical alterations, and family history. Management is individualized and focused on prevention of sudden death through use of antiarrhythmic medication and implantable cardioverter-defibrillators and rarely heart transplantation.

Inheritance An autosomal dominant trait is the most common inheritance pattern for non-syndromic forms of the disease. Today about 40–60% of the genetic causes are known, and plakophilin 2 (*PKP2*) is the most prevalent disease gene [4]. However, there have been reports of autosomal recessive patterns of almost all desmosomal disease genes; with and without additional syndromic features. For example, mutations in genes like plakoglobin (*JUP*) and desmoplakin (*DSP*) lead to ACM, palmoplantar keratoderma, and abnormalities of the hair structure. Carriers with homozygous mutations in desmocollin 2 (*DSC2*) show an isolated cardiac phenotype (Table 2.5). As seen in other cardiomyopathies, incomplete penetrance and variable clinical expression are also common; even in the same family, the severity of phenotypes demonstrates a wide range. In some cases, different family members develop DCM or ACM [156]. Besides cases with one mutation, there are several reports about compound heterozygous mutations or two or more variants in different genes [157]. Of note, there are also rare cases of de novo mutations [158]. Besides the main genetic drivers, also modifiers such as environmental (e.g., athletic activity) and epigenetic factors might influence the phenotype.

Disease Genes At the beginning of the 2000s, it was recognized that about 50% of ACM patients carry mutations in five different genes encoding desmosomal proteins: *JUP* [5], *DSP* [159], *PKP2* [4], *DSC2* [160, 161], and *DSG2* [162]. Desmosomes are cell-cell junctions, which have important functions for the nano-mechanical coupling of cells [96]. In organs exposed to high mechanical stress like the skin or the heart, cells are connected by these multi-protein complexes. Desmosomes are linked to the intermediate filament system, which is mainly formed in the heart by desmin (*DES*). Besides cardiac desmosomes, also adhering junctions are important for mechanical coupling of cardiomyocytes. Adhering junctions are linked to actin filaments [163]. Interestingly, ACM-associated mutations were also

Table 2.5 Overview about genes associated with ACM

Gene symbol	Encoded protein	Subcellular location	Frequency (%)	First description	Inheritance
PKP2	Plakophilin 2	Desmosomes, intercalated disc, cell adhesion	20–40	2004	AD, AR
DSP	Desmoplakin	Desmosomes, intercalated disc, cell adhesion	5–10	2002	AR[a], AD
DSC2	Desmocollin 2	Desmosomes, intercalated disc, cell adhesion	5–10	2006	AR, AD
DSG2	Desmoglein 2	Desmosomes, intercalated disc, cell adhesion	5–10	2006	AD; AR
JUP	Plakoglobin	Desmosomes, intercalated disc, cell adhesion	<5	2000	AR[b]
RYR2	Ryanodine receptor 2	SR, Ca^{2+} channel	Rare	2001	AD
TGFB3	Transforming growth factor β3	Cytokine	Rare	2005	AD
TMEM43	Luma	Nuclear envelope, endoplasmic reticulum	Rare	2008	AD
DES	Desmin	IF protein, intercalated disc, Z-disc,	Rare	2009	AD[c]
TTN	Titin	Sarcomere, molecular spring	Rare	2011	AD
PLN	Phospholamban	SR, Ca^{2+} handling	Rare	2012	AD
LMNA	Lamin A/C	IF protein, nuclear lamina	Rare	2012	AD
SCN5A	Voltage-gated sodium channel, type V, α-subunit	Intercalated disc, T-tubules system, sodium channel	Rare	2008	AD
CTNNA3	αT-Catenin	Intercalated disc, cell adhesion	Rare	2013	AD
LDB3	LIM domain-binding protein 3	Z-disc, structural integrity	Rare	2014	AD
KCNQ1	Voltage-gated potassium channel Q1	T-tubules system, potassium channel	Rare	2014	AD
CDH2	N-Cadherin	Intercalated disc, cell adhesion	Rare	2017	AD

[a]Carvajal syndrome
[b]Naxos disease
[c]Skeletal myopathy
AD autosomal dominant, *AR* autosomal recessive, *SR* sarcoplasmic reticulum, *IF* intermediate filament

identified in *CTNNA3* and *CDH2*, which encode two structural proteins of adhering junctions [164, 165]. Therefore, it is suggested that ACM is mainly a disease of the cardiac intercalated disc, as both desmosomes and adhering junctions are located there. In 40–60% of ACM patients, one or more mutations in genes encoding proteins involved in cell adhesion could be identified (Table 2.5; Fig. 2.2d) [158, 166]. In addition to genes, encoding structural proteins involved in cell adhesion of cardiomyocytes, there are some reports about mutations in other genes like *RYR2* [167], *TGFB3* [168], *TMEM43* [169], *SCN5A* [170], *TTN* (M [171]), *PLN* [156], *LMNA* [172], *LDB3* [173], and *KCNQ1* [174]. However, mutations in those genes are rare and account for less than 10% (Fig. 2.2d; Table 2.5).

Cell-Cell Adhesion McKoy et al. identified the first homozygous 2 bp deletion mutation in *JUP* in families from the Greek island Naxos [5]. Patients developed ACM in combination with keratosis and woolly hair. The typical triad of features is known in the literature as "Naxos disease" [175]. *JUP* encodes plakoglobin, a member of the armadillo protein family, which is a structural cytoplasmic component of the desmosome. Nonsense-mediated mRNA decay (NMD) is linked to the pre-mRNA splicing process, and the exon-junction complexes are necessary for the degradation of mRNA carrying a premature termination codon (PTC) [176]. Zhang et al. generated two *Jup* knock-in mouse models with the same deletion mutation. In one of them, the authors deleted additionally the introns to block NMD. Remarkably, the knock-in mice without the introns were completely healthy [177]. Those findings suggest that potentially "loss of function" mediated by NMD may explain the mechanism due to *JUP* mutations.

Similar to Naxos disease, Carvajal syndrome is characterized by striate keratoderma, woolly hair, and left ventricular arrhythmic cardiomyopathy. It is caused by mutations in *DSP* [178]. Rampazzo et al. described the first *DSP* mutation in dominant ACM [159]. Desmoplakin is a cytolinker protein and connects the cardiac desmosomes with the desmin intermediate filaments. The C-terminal tail domain is responsible for this protein-protein interaction. Desmoplakin forms dimers by the formation of a coiled coil of the Rod domains [179]. Autosomal recessive as well as autosomal dominant *DSP* mutations were reported in 5–10% of ACM patients (Table 2.5).

In 2004, Gerull et al. identified *PKP2* mutations in a large cohort of ACM patients [4]. *PKP2* is the most common gene for autosomal dominant ACM, and it accounts for about 20–40% of the known mutations. Most mutations are small deletions, insertions, nonsense, or splice site changes leading to the truncation of the protein. *PKP2* encodes plakophilin 2, which is also a member of the Armadillo protein family. Plakophilin 2 binds to the desmosomal cadherins and mediates the molecular interaction with the cytolinker protein desmoplakin [180]. Plakophilin 2 is necessary for the vesicle transport of the desmosomal cadherin desmocollin 2 to the plasma membrane [181]. It is suggested that haploinsufficiency could be the main genetic mode of action. Presumably, NMD and protein degradation pathways are involved in *PKP2* haploinsufficiency [182].

Different groups described also mutations in the genes *DSC2* [160, 161] and *DSG2* [162] encoding for desmosomal cadherins. The extracellular domains of both cadherins mediate the protein-protein interactions in a Ca^{2+}-dependent way by homophilic and presumably also by heterophilic trans-interaction [183]. Besides the description of heterozygous missense and nonsense variants in *DSC2* with, so far, lack of clear pathogenicity, there have also been homozygous truncation mutations reported causing a severe biventricular form of ACM without skin and hair features [184, 185]. Interestingly, Wong et al. investigated the clinical phenotype of a founder population with 28 heterozygous and 11 homozygous *DSC2*-p.Q554X mutation carriers. Almost all of the heterozygous carriers were healthy or presented only with mild clinical symptoms, whereas all homozygous mutation carriers developed ACM [186].

Besides the desmosomal genes, ACM-related mutations were also identified in desmin (*DES*) [158, 187]. Desmin is the major component of the intermediate filaments in cardiomyocytes, which provides the connection to different cellular organelles like the desmosomes and the costameres. Interestingly, ACM-associated *DES* mutations disturb the intermediate filament assembly [188].

Recently, mutations in αT-Catenin (*CTNNA3*) and in N-cadherin (*CDH2*) have been described [164, 165, 189]. Both proteins are structural components of the adhering junctions. Adhering junctions are cell-cell junctions which are connected to F-actin filaments. However, further studies are required to investigate the frequency and the pathogenic impact of variants/mutations in those genes.

Other Genetic Contributors Besides mutations affecting cell-cell adhesion proteins, there are also rare mutations reported in genes involved in Ca^{2+} handling like the *RYR2* [167] or *PLN* [156]. *RYR2* encodes the cardiac ryanodine receptor 2 which is mediating the Ca^{2+} release from the sarcoplasmic reticulum [190], whereas phospholamban (*PLN)* is a regulator of the sarco(endo)plasmic reticulum Ca^{2+} ATPase (SERCA), which transports Ca^{2+} into the sarcoplasmic reticulum [191]. Rare variants were also identified in the 5′- and 3′-untranslated regions of *TGFB3*, a cytokine from the transforming growth factor family [168]. TGF-β cytokines are involved in fibrotic remodeling process by upregulation of expression of extracellular matrix proteins like different collagens [192]. Merner et al. identified a missense mutation in *TMEM43* in a founder population from Newfoundland [169]. Remarkably, this specific mutation leads to nearly complete penetrance [169] and was also identified in ACM patients from different other countries [193]. *TMEM43* encodes the nuclear envelope protein luma [194]. The exact biochemical functions and the molecular structure of luma are widely unknown. Additionally, mutations were also identified in *LMNA* [172], which encodes the nuclear intermediate filament lamin A/C involved in the structural stabilization of the nuclei. Other rare variants were identified in *SCN5A* [170], encoding the α-subunit of the voltage-gated sodium channel 5, and in *KCNQ1* [174], encoding the voltage-gated potassium channel Q1. Mutations in both genes cause inherited arrhythmias like Brugada syndrome or long and short QT syndrome, indicating a genetic overlap of ACM with channelopathies.

Genetic Counselling and Testing Clinical genetic testing in ACM is in particular challenging and requires to be performed in dedicated cardio-genetic centers, with pre- and post-counselling possibilities. As indicated above, the inheritance pattern of ACM is more complex than previously thought, with frequent requirement for more than one "hit" for fully penetrant disease. More frequent than in other CMPs, patients carry homozygous or compound heterozygous variants in the same gene or digenic/oligogenic variants in a cluster of desmosomal genes. The broad use of large gene panels or whole-exome sequencing often results in a high number of variants of unknown clinical significance (VUSs), which should be carefully classified according to guidelines as suggested by the ACMG [9]. Additionally, genetic testing should be performed with the consideration that even a positive genetic test result assigned as a pathogenic or likely pathogenic mutation may not be the only genetic contributor to the phenotype in the patient and/or family.

However, genetic counselling should be done in all families with a confirmed case of ACM, and first-degree relatives should be screened according to the TFC by ECG, echocardiography, Holter ECG, and signal-averaged ECG starting at the age of 10 years, and this should be regularly repeated [40]. In case there is a reliable genetic test result (pathogenic or likely pathogenic mutation) available, this may be used for cascade family screening, although cardiologic evaluation may still continue at a lower level as a negative genetic result may not exclude any genetic predisposition. Lifestyle advice and reproductive counselling on the risk of transmission to offspring should be also provided. Restriction from competitive sports activity and strenuous physical exercise is strongly recommended to prevent disease onset and progression.

Despite some progress in the understanding of the functional impact of certain mutations, there is still a gap of knowledge of all contributing factors resulting in the clinical picture of ACM. Hopefully, the increasing genetic knowledge will also lead to more profound biochemical and cellular understanding of the pathomechanisms toward the development of more efficient molecular therapies.

2.6 Restrictive Cardiomyopathy (RCM)

Definition Restrictive cardiomyopathy (RCM) is characterized by an abnormal left ventricular filling pattern, diastolic dysfunction but normal wall thickness, and usually preserved systolic function. The restrictive filling pattern is caused by an increased muscle stiffness leading to atrial enlargement and an increase of ventricular end-diastolic blood pressure (Fig. 2.1e). RCM can be classified as a rare primary cardiomyopathy, often affecting children but also adults. However, there are also secondary causes known, such as storage or infiltrative disorders [41, 195].

Clinical Manifestation and Inheritance Patients typically develop heart failure symptoms such as dyspnea and fatigue [196]. Preserved LV ejection fraction, normal or mildly increased left and right ventricular wall thicknesses, restrictive diastolic filling patterns and severe atrial enlargement are common echocardiographic findings. The general prognosis is poor, patients often requiring heart

Table 2.6 Overview about genes associated with RCM

Gene symbol[a]	Encoded protein	Subcellular location	First description
TNNI3	Cardiac troponin I	Sarcomere, thin filament	2003
TNNT2	Cardiac troponin T	Sarcomere, thin filament	2006
DES	Desmin	IF protein, intercalated disc, Z-disc	2006
ACTC1	Cardiac actin	Sarcomere, thin filament	2008
MYH7	β-Myosin heavy chain	Sarcomere, thick filament	2008
TTN	Titin	Sarcomere	2014
MYPN	Myopalladin	Sarcomere, Z-band	2012
MYBPC3	Cardiac myosin-binding protein C	Sarcomere, thick filament associated	2015
TNNC1	Cardiac troponin C	Sarcomere, thin filament	2016
FLNC	Filamin C	Cytoskeleton, intercalated disc	2016
TMEM87B	Transmembrane protein 87 B	Membrane	2016
ACTN2	α-Actinin 2	Z-disc	2016
CRYAB	αB-Crystallin	IF protein, intercalated disc, Z-disc,	2017[b]

[a]Autosomal dominant inheritance
[b]Phenotype associated with skeletal myopathy
IF intermediate filament

transplantation. Clinically, the differentiation between RCM and constrictive pericarditis imposed by external pericardial constraint can be challenging. Secondary RCM can be part of systemic diseases, e.g., a mineralization disorder called pseudoxanthoma elasticum (PXE), caused by *ABCC6* mutations [197] or of cardiac amyloidosis associated with *TTR* mutations [198]. Additionally, metabolic diseases such as Pompe, Fabry, and Danon disease as well as Friedreich ataxia can be associated with LVH (Table 2.2) but can also present as RCM. Primary RCM is mainly a familial disease and inherited as an autosomal dominant trait (Table 2.6).

Disease Genes RCM is a rare disease and the proportion of genetic etiology remains unknown. However, Kostareva et al. investigated 24 non-related index patients using broad next-generation sequencing panels and identified in about 54% of them a pathogenic or likely pathogenic mutation [199]. Overall, mutations in 13 different genes have been reported (Fig. 2.2e, Table 2.6). Most of those genes encode for sarcomeric or cytoskeletal proteins. Of note, there is also a genetic overlap with other primary cardiomyopathies, in particular with HCM.

Sarcomeric Proteins Sarcomeres are the essential contracting units of striated muscle cells consisting of thick and thin filaments, which are connected by Z-bands. First mutations associated with familial RCM were identified in the *TNNI3* gene, encoding cardiac troponin I (cTnI) [200]. cTnI inhibits the ATPase function of the actin-myosin complex during the contraction cycle [201]. Mutations

in cardiac troponin C (*TNNC1*, cTnC) and troponin T (*TNNT2*, cTnT), encoding the two other cardiac components of the troponin complex, were also identified in RCM patients [202, 203]. cTnC is the Ca^{2+}-binding and cTnT is the tropomyosin-binding subunit of the troponin complex, mediating the molecular interaction of thin and thick filaments during the contraction cycles [204]. Other sarcomeric disease genes are *ACTC1* and *MYH7* [205, 206]. Recently, Wu et al. identified a family with three affected patients carrying a nonsense mutation in *MYBPC3*, which encodes the myosin-binding protein C and binds to the thick filaments [207]. Peled and colleagues identified a de novo missense mutation (p.Y7621C) in titin (*TTN*) causing RCM [208]. Furthermore, other RCM-associated mutations were found in genes encoding myopalladin (*MYPN*) and α-actinin 2 (*ACTN2*) [199, 209]. α-Actinin 2 is the major structural component of the Z-bands, and myopalladin is a binding partner. Myopalladin is involved in the regulation and maintenance of sarcomeres close to the Z-disc [210].

Cytoskeletal Proteins The second group of RCM-associated disease genes includes different cytoskeletal structural proteins like desmin (*DES*) [211], filamin C (*FLNC*) [212], and αB-Crystallin (*CRYAB*) [213]. *DES* mutations cause besides RCM a wide spectrum of different other cardiac and skeletal myopathies including myofibrillar myopathy (MFM). Desmin is the major component of the cardiac intermediate filaments and connects different cell organelles like desmosomes, Z-bands, costameres, and presumably also the nuclei with the cytoskeleton [214]. αB-Crystallin is a member of the small heat-shock protein family and binds directly to the intermediate filaments suggesting a stabilizing function, and filamin C is an actin cross-linking protein, which is involved in the integrin-mediated cell-extracellular matrix adhesion [215]. Interestingly, mutations in those three genes cause also myofibrillar myopathy (MFM), characterized by toxic protein aggregation within the skeletal myocytes [216]. There is some evidence that an abnormal protein aggregation and accumulation in the myocardial tissue might contribute to the increased stiffness of the ventricular walls in RCM.

Genetic Counselling and Testing Because RCM is less common than other primary cardiomyopathies, the knowledge about prevalence and genetic associations are currently limited or even missing. Most reports about disease genes are based on single families or patients. As indicated above, there is substantial overlap in the genetic etiology, but also clinical presentation with other cardiomyopathies. Moreover, some genes are also involved in skeletal muscle disease, in particular MFM. Formal genetic counselling should be performed in all familial cases, and repeated clinical screenings of first-degree relatives are recommended using ECG, Holter ECG, and echocardiogram [40]. Secondary forms of RCM and constrictive pericarditis should be considered as a differential diagnosis as some metabolic and systemic diseases may lead to instituting specific therapy. As indicated for other cardiomyopathies, genetic testing should be performed for clinical purposes using NGS panels focusing on known genes. Broader approaches such as whole-exome analysis should be considered for research studies. However, in single patients, the

classification of novel variants will be challenging and often leading to VUS. Over time more genetic and phenotypic data on bigger cohorts, genotype-phenotype studies, and further functional validation are required to provide more certain recommendations.

2.7 Translational Perspectives

Classical genetic approaches such as linkage analysis and positional cloning in combination with newer technologies such as next-generation sequencing have provided dramatic progress in unraveling the genetic causes of cardiomyopathies but have also demonstrated the complexity of human disease. What we previously thought are monogenic diseases are now much more complex diseases where the primary mutation appears to be a "more or less" important contributor. Despite making some progress in the understanding of disease mechanisms and the gain of knowledge about molecular changes of specific genes and mutations, there are still a lot of unknowns in the pathogenesis of cardiomyopathies—to understand how a mutated gene leads to clinical expression. Prospectively, this inspiring field of research provides remarkable opportunities to dissect what are the genetic and non-genetic contributors in the early and late disease process, how does different disease expression develop, and how to disrupt disease progression or even prevent full clinical expression.

From the clinical and translational perspective, many more questions should be answered to translate research findings to the benefit of patient care. We still have a "genetic gap"—overall about 50% of the genetic causes of CMPs remain unknown. How do we handle the increasing number of variants of unknown significance? Is there a way to translate research information about specific mutations and how they alter protein function directly to the benefit of patients to improve health care, rather than identifying just family members at risk?

Last but not least, someday there is the hope that genetic cardiomyopathies are not only treated but may also be cured. Given the current advances in genome editing technologies and other personalized genetic and molecular approaches, also outlined in other chapters, this day may be not so far away.

Compliance with Ethical Standards

Conflict of Interest Brenda Gerull declares that she has no conflict of interest. Sabine Klaassen declares that she has no conflict of interest. Andreas Brodehl declares that he has no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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