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REVIEW

Translating emerging molecular genetic insights into clinical practice in inherited cardiomyopathies

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Abstract

Cardiomyopathies are primarily genetic disorders of the myocardium associated with higher risk of life-threatening cardiac arrhythmias, heart failure, and sudden cardiac death. The evolving knowledge in genomic medicine during the last decade has reshaped our understanding of cardiomyopathies as diseases of multifactorial nature and complex pathophysiology. Genetic testing in cardiomyopathies has subsequently grown from primarily a research tool into an essential clinical evaluation piece with important clinical implications for patients and their families. The purpose of this review is to provide with a contemporary insight into the implications of genetic testing in diagnosis, therapy, and prognosis of patients with inherited cardiomyopathies. Here, we summarize the contemporary knowledge on genotype-phenotype correlations in inherited cardiomyopathies and highlight the recent significant achievements in the field of translational cardiovascular genetics.

Keywords Cardiomyopathy · Genetics · Arrhythmia · Sudden cardiac arrest · Sudden death · Genetic test

Abbreviations

AAV	Adeno-associated virus
ACCF	American College of Cardiology Foundation
AHA	American Heart Association
ARVC	Arrhythmogenic right ventricular cardiomyopathy
AV	Atrioventricular
CPVT	Catecholaminergic polymorphic ventricular tachycardia
DCM	Dilated cardiomyopathy
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
HCM	Hypertrophic cardiomyopathy
HRS	Heart Rhythm Society
ICD	Implantable cardioverter defibrillator
LBBB	Left bundle branch block
LDAC	Left-dominant arrhythmogenic cardiomyopathy
LVNC	Left ventricular non-compaction cardiomyopathy
MRI	Magnetic resonance imaging
PPCM	Peripartum cardiomyopathy
PVC	Premature ventricular contraction
RCM	Restrictive cardiomyopathy
RV	Right ventricle
SCD	Sudden cardiac death
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WPW	Wolff-Parkinson-White
XLCM	X-linked forms of dilated cardiomyopathy

Introduction

Inherited cardiomyopathies are primarily genetic diseases caused by mutations in myocardial structural genes, which lead to electrophysiological and morphological alterations in the myocardium, predisposing affected individuals to life-threatening cardiac arrhythmias, heart failure, and sudden cardiac death (SCD) [1, 2]. These diseases usually follow Mendelian inheritance; however, complex inheritance have also been found. The penetrance is often incomplete and the disease expression may be variable, even in the same family. The pathogenesis is complex, involving genetic, epigenetic, and environmental factors [3]. Causative mutations may occur in an affected individual for the first time within the family (de novo mutation) or affect more than one family member (familial cardiomyopathy) [4]. The recent advances in next-generation sequencing technologies have spread light into

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our understanding of the genetic determinants of cardiomyopathies, allowing to detect multiple cardiomyopathy phenotypes stemming from identical mutations in extended pedigrees [5] and to identify asymptomatic mutation carriers at risk to develop cardiomyopathy and/or SCD [1]. Genetic testing thus is currently an important tool for evaluation, management, and risk stratification of affected patients [1]. In this paper, we summarize the fundamental pathogenetic mechanisms and current knowledge on genotype-phenotype correlations in inherited cardiomyopathies, with a focus on important clinical implications of the genetic test in management of affected individuals and family members.

Hypertrophic cardiomyopathy

Clinical description of HCM

Hypertrophic cardiomyopathy (HCM) is characterized by asymmetrical myocardial hypertrophy with a predilection for the interventricular septum and high degree of myocyte disarray in the absence of hemodynamic stressors sufficient to account for the degree of hypertrophy and systemic conditions associated with HCM phenocopies [4]. HCM is the most common monogenic cardiovascular disease (1:500) [6], as well as the most common cause of SCD in competitive athletes in the USA [7]. The disease often has a subclinical course, and patients are diagnosed incidentally; nevertheless, a sizeable proportion presents with angina, dyspnea, palpitations, and syncope. SCD in HCM is primarily mediated by ventricular fibrillation (VF), but asystole and pulseless electrical activity have also been reported [8]. In hypertrophic obstructive cardiomyopathy (HOCM), nearly 70% of all deaths are sudden. The annual risk of cardiac arrest is estimated to be 1% in general HCM population, while patients with prior ventricular tachycardia (VT), VF, or aborted cardiac arrest have 10% annual risk for cardiac arrest and mortality rate of 4.7% [9].

Diagnosis

HCM is diagnosed in the presence of left ventricular (LV) wall thickness ≥ 15 mm in one or more myocardial segments (or ≥ 13 mm in a first degree relative of an index patient with HCM) measured by any imaging technique (echocardiography, CT scan, magnetic resonance imaging (MRI)), in the absence of secondary causes of hypertrophy [10]. Other typical findings include systolic anterior motion of the mitral valve with associated LV outflow tract (LVOT) obstruction and mitral regurgitation, mid-ventricular obstruction due to systolic LV obliteration, diastolic dysfunction (including restrictive type), and arrhythmias largely attributed to the electrical inhomogeneity in the disorganized myocardium [11].

Genetic bases of HCM

At least half of HCM victims have a family history of HCM or premature sudden death [11]. HCM is mostly transmitted as an autosomal dominant trait (Table 1). Causative mutations have been detected in genes encoding myocardial contractile proteins, particularly, in genes critical to the cardiac sarcomere (myofilaments) (Fig. 1). Approximately 70% of genetically-confirmed HCM cases stem from mutations in genes that encode myosin heavy chain-β (*MYH7*) [27, 28] and cardiac myosin-binding protein C (*MYBPC3*) [19]—components of thick and intermediate filaments, respectively [11]. Mutations in other genes encoding thick filament proteins (*MYL2*, *MYL3*) [33], components of thin filaments (*TNNT2*, *TNNI3*, *TNNC1*, *TPM1*, *ACTC1*), and Z-disk proteins (*ACTN2*, *MYOZ2*) each explain less than 5% of HCM cases [6]. The vast majority of mutations are random; however, several "hot spots" such as Arg403Gln, Arg453Cys and Arg663His in *MYH7*, Arg92Gln, Arg92Trp and Arg104Val in *TNNT2*, and Arg495Gln, Arg502Trp, and c.1928-2A>G in *MYBPC3* have been recognized [201, 202]. Other genes are involved in less than 5% of HCM cases each (Table 1) [6]. Approximately 5% of HCM patients have multiple sarcomeric mutations, most commonly involving *MYBPC3* [203]. Sequential alterations in *MYH6* (myosin heavy chain-α), *TTN* (titin), *PLN* (phospholamban), *JPH2* (junctophilin 2), *CALR3* (calreticulin 3), *TCAP* (theletonin), *VCL* (vinculin/metavinculin), *NEXN* (nexilin), *CSRP3* (cysteine and glycine-rich protein 3), and *SRI* (sorcin) have been suggested as likely causes of HCM phenotype, but there is subtle evidence supporting their pathogenicity [6].

Pathophysiology of HCM

While large gaps in the understanding of HCM pathophysiology still demand profound investigation, the mechanisms implicated in sarcomeric HCM have been partly unraveled. Mutations in the myosin heavy chain-β (*MYH7*) head have been shown to lead to enhanced myocardial contraction and impaired relaxation because of inefficient energy utilization and interaction with functionally related proteins [204]. Impaired LV relaxation has been reported as the first sign in asymptomatic carriers of sarcomeric mutations who have normal LV wall thickness [205]. In experimental studies, chronic administration of MYK-461, inhibitor of myosin adenosine triphosphatase (ATPase) and sarcomere contractility, suppressed the development of HCM features in mice harboring heterozygous human mutations in *MYH7* [206]. Interestingly, the ultimate phenotype seems to depend on the topology of sarcomeres and the background in which the mutant proteins

Table 1 Molecular and genetic characteristics and genotype-dependent phenotype variability in inherited cardiomyopathies

Gene	Locus	Inheritance	Encoded protein	Associated cardiomyopathy phenotype (s)	Other cardiac or muscular phenotypes
Sarcomeric protein genes					
ACTC1	15q14	AD	Actin, α cardiac muscle 1	DCM [12]; HCM [13]; LVNC [14, 15]; RCM [16]	ASD [17]
MYBPC3	11p11.2	AD	Myosin-binding protein C, cardiac	DCM [18]; HCM [19]; LVNC [20]	SIDS [21]
MYH6	14q11.2	AD	Myosin heavy chain 6 (α-myosin heavy chain)	DCM [22]; HCM [22]	ASD [23]; SSS [24]
MYH7	14q11.2	AD	Myosin heavy chain 7 (β-myosin heavy chain)	DCM [25, 26]; HCM [27, 28]; LVNC [14]; RCM [29]	SPM [30]; MSMA; MSMB (AR) [31] Ebstein's anomaly [32]
MYL2	12q24.11	AD	Myosin light chain 2	HCM [33]; RCM [34]	Infantile type I muscle fiber disease with DCM (AR) [35]
MYL3	3p21.31	AD	Myosin light chain 3	HCM [33]; RCM [34]	–
TNNC1	3p21.1	AD	Cardiac troponin C	DCM [36]; HCM [37]; RCM (AR) [38]	–
TNNI3	19q13.42	AD	Cardiac troponin I3	DCM (AR) [39]; HCM [40]; RCM [41]	–
TNNT2	1q32	AD	Cardiac troponin T2	DCM [25]; HCM [42]; LVNC [14]; RCM [43]	–
TPM1	15q22.2	AD	Tropomyosin 1	DCM [44]; HCM [42]; LVNC [20]; RCM [34]	Ebstein's anomaly (with LVNC) [45]
TTN	2q31.2	AD	Titin	ARVC [46]; DCM [47]; HCM [48]; RCM [49]	HMERF [50]; LGMD (AR) [51]; SALMY (AR) [52]; TMD [53]
Z-disk protein genes					
ACTN2	1q43	AD	Actinin α 2	DCM [54]; HCM [55]; LVNC [56]	–
ANKRD1	10q23.31	AD	Ankyrin repeat domain 1	DCM [57, 58]; HCM [59]	TAPVR [60]
CSRP3	11p15.1	AD	Cysteine and glycine-rich protein 3	DCM [61]; HCM [62]	–
CTNNA3	10q21.3	AD	Catenin alpha 3 (αT-catenin)	ARVC [63]	–
FLNC	7q32.1	AD	Filamin C	DCM [64]; HCM [65]; RCM [66]	MFM [67]; MPD [68]
LDB3 (*Cypher/ZASP*)	10q23.2	AD	LIM domain binding 3	DCM [69]; HCM [55]; LVNC [69]	MFM [70]
MYOZ2	4q26	AD	Myozenin 2	HCM [71]	–
MYPN	10q21.3	AD	Myopalladin	DCM [72]; HCM [73]; RCM [73]	NEM (AR) [74]
NEBL	10p12.31	AD	Nebulette (Actin-binding Z-disk protein)	DCM [75]	EFE [76]
NEXN	1p31.1	AD	Nexilin	DCM [77]; HCM [78]	ASD [79]
TCAP	17q12	AD	Titin-cap (telethonin)	DCM [80]; HCM [80]	LGMD (AR) [81]
VCL	10q22.2	AD	Vinculin	DCM [82]; HCM [83]	–
Cytoskeletal protein genes					
CRYAB	11q23.1	AD	Crystallin α B	DCM [84]	MFM [85]
DES	2q35	AD	Desmin	ARVC [86]; DCM [87]; RCM [88]	AVB [88]; LGMD (AR) [89]; MFM (AD or AR) [90]; SCPNK [91]

Table 1 (continued)

Gene	Locus	Inheritance	Encoded protein	Associated cardiomyopathy phenotype (s)	Other cardiac or muscular phenotypes
DMD	Xp21.2–21.1	XL	Dystrophin	DCM [92]	DMD (XLR) [93]; BMD (XLR) [94]
DTNA	18q12.1	AD	Dystrobrevin-α	LVNC with or without congenital heart defects [95]	–
FKRP	19q13.32	AR	Fukutin-related protein	DCM [96]	MDD [97]
FKTN	9q31.2	AR	Fukutin	DCM [98]	LGMD [99]
FXN	9q21.11	AR	Frataxin, mitochondrial	HCM [100]	FRDA [101]
LAMA4	6q21	AD	Laminin subunit α4	DCM [102]	–
MTTL1	mtDNA	Maternal	Mitochondrially encoded tRNA leucine 1 (UUA/G) ($tRNA^{Leu\text{-}UUR}$)	HCM [103]	–
PDLIM3	4q35.1	AD	PDZ and LIM domain 3	DCM [104]	–
PLEC	8q24.3	AR	Plectin	DCM [105]; LVNC [106]	LGMD [107]
SGCB	4q12	AR	B-Sarcoglycan	DCM [108]	LGMD [109]
SGCD	5q33.2-q33.3	AD	δ-Sarcoglycan	DCM [110]	LGMD [111]
Membrane protein genes					
HFE	6p22.2	AR	Hereditary hemochromatosis protein	DCM (AR) [112]; RCM (AR) [113]	Hemochromatosis (AR) [114]
TMEM43	3p25.1	AD	Transmembrane protein 43	ARVC [115]	EDMD [116]
Cochaperone (heat shock protein)					
BAG3	10q26.11	AD	BCL2-associated athanogene 3	DCM [117]	MFM [118]; prolonged QT interval [119]
Lysosomal protein/enzyme genes					
GLA	Xq22.1	XL	Galactosidase α	HCM [120]	Fabry disease [121]
LAMP2	Xq24	XLD	Lysosome-associated membrane protein 2	HCM [122]; DCM [123]; LVNC with severe myopathy [124]	Danon disease [125]
Cellular enzyme genes					
DOLK	9q34.11	AR	Dolichol kinase (endoplasmatic reticulum enzyme)	DCM (AR) [126]	Dolichol kinase deficiency (AR) [126]
MYLK2	20q11.21	AD	Myosin light chain kinase 2	HCM [127]	–
PRKAG2	7q36.1	AD	5'-AMP-activated protein kinase subunit γ2	HCM [128]	WPW [129]
PTPN11	12q24.13	AD	Protein tyrosine phosphatase, non-receptor type 11	HCM [130]	LEOPARD syndrome [131]; Noonan syndrome [132]
RAF1	3p25.2	AD	Raf-1 proto-oncogene, serine/threonine kinase	HCM [133]; DCM [134]	LEOPARD syndrome [133]; Noonan syndrome [133]
Desmosomal protein genes					
DSC2	18q12.1	AD/AR	Desmocollin-2	ARVC [135]	–
DSG2	18q12.1	AD/AR	Desmoglein-2	ARVC [136]; DCM [137]	–
DSP	6p24	AD/AR	Desmoplakin	ARVC [138]; DCM [139]	Carvajal syndrome [139]
FHL1	Xq26.3	XLD/XLR	Four and a half LIM domains protein 1	HCM [140, 141]	EDMD [142]

Table 1 (continued)

Gene	Locus	Inheritance	Encoded protein	Associated cardiomyopathy phenotype (s)	Other cardiac or muscular phenotypes
FHL2	2q12.2	AD?	Four and a half LIM domains protein 2	DCM [143]	–
JUP	17q21	AD/AR	Junction plakoglobin	ARVC [144]	Naxos disease (AR) [145, 146]
PKP2	12p11	AD/AR	Plakophilin-2	ARVC [147]; DCM [148]	BrS [149]
Mitochondrial protein/enzyme genes					
Mitochondrial genes (e.g. *MTND1*, *MTRNR1*; $tRNA^{Ala}$)	mtDNA	Maternal	e.g., NADH dehydrogenase subunit 1; rRNA; tRNA	DCM [150]	–
SDHA	5p15	AR	Succinate dehydrogenase [ubiquinone] flavoprotein subunit, mitochondrial	DCM [151]	–
TAZ (*G4.5*)	Xq28	XLR	Zinc finger and BTB domain-containing protein 18	DCM [152]; LVNC [153]	Barth syndrome [154]
TSFM	12q14.1	AR	Ts translation elongation factor, Mitochondrial	DCM [155]; HCM [156]	–
mRNA splicing protein genes					
RBM20	10q25.2	AD	RNA-binding protein 20	DCM [157]	–
Nuclear envelope protein genes					
EMD	Xq28	X-linked	Emerin	DCM [158]	EDMD [159]
GATAD1	7q21-q22	AR	GATA zing finger domain-containing protein 1	DCM [160]	–
LMNA	1q22	AD/AR	Lamin A/C	ARVC [161]; DCM [162]; LVNC [163]	CCD [162]; EDMD [164]; LGMD [165]
NKX2-5	5q35.1	AD	NK2 Homeobox 5 (transcription factor)	DCM [166]; LVNC [167]	ASD [168]; HLHS [169]; TOF [170]; VSD [171]
NSD1	5q35.3	AD	Nuclear receptor-binding SET domain protein 1 (histone methyltransferase)	LVNC [172]	–
TMPO	12q22	AD	Thymopoietin (lamina-associated polypeptide 2, isoforms β/γ)	DCM [173]	–
Cell proliferation protein genes					
MIB1	18q11.2	AD	Mindbomb E3 ubiquitin protein ligase 1	LVNC [174]	–
PRDM16	1p36.32	AD	PR/SET domain 16	DCM [175]; LVNC [175]	–
TGFB3	14q24	AD	Transforming growth factor β3	ARVC [176]	LDS [177]
YWHAE	17p13.3	AD	14-3-3 Protein epsilon	LVNC [178]	–
Calcium/sodium-handling genes					
CALR3	19p13.13	AD	Calreticulin	HCM [179, 180]	–
JPH2	20q13.12	AD	Junctophilin-2	HCM [181]	AF [182]
PLN	6q22.31	AD	Cardiac phospholamban	ARVC [183]; DCM [184]; HCM [185]	–
PSEN1	14q24.3	AD	Presenilin-1	DCM [186]	–
PSEN2	1q31-q42	AD	Presenilin-2	DCM [186]	–
RYR2	1q43	AD	Ryanodine receptor 2	ARVC [187]	CPVT [188]; prolonged QT interval [189]

Table 1 (continued)

Gene	Locus	Inheritance	Encoded protein	Associated cardiomyopathy phenotype (s)	Other cardiac or muscular phenotypes
SCN5A	3p22.2	AD	Nav1.5 (sodium voltage-gated channel alpha subunit 5)	DCM [190]	LQTS [191]; BrS [192]; PCCD [193]; IVF [194]; CCD [195]; SIDS [196]; SSS (AR) [197], AF [198]
Other genes					
TP63	3q28	AD	Tumor protein p63	ARVC [199]	–
Unknown	11p15	AD	–	LVNC [200]	–

Exceptions in inheritance pattern are provided in brackets

AD autosomal dominant, *AF* atrial fibrillation, *AR* autosomal recessive, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *ASD* atrial septal defect, *AVB* atrioventricular block, *BMD* Becker muscular dystrophy, *BrS* Brugada syndrome, *CCD* cardiac conduction disease, *DCM* dilated cardiomyopathy, *DMD* Duchenne muscular dystrophy, *EDMD* Emery-Dreifuss muscular dystrophy, *EFE* endocardial fibroelastosis, *FRDA* Friedreich's ataxia, *HCM* hypertrophic cardiomyopathy, *HLHS* hypoplastic left heart syndrome, *HMERF* hereditary myopathy with early respiratory failure, *LDS* Loeys-Dietz syndrome, *LVNC* left ventricular non-compaction, *LQTS* long QT syndrome, *MDD* muscular dystrophy-dystroglycanopathy, *MPD* distal myopathy, *MSMA* myosin storage myopathy autosomal dominant, *MSMB* myosin storage myopathy, *NEM* nemaline myopathy, *SALMY* Salih myopathy (also known as early-onset myopathy with fatal cardiomyopathy (EOMFC)), *SCPNK* scapuloperoneal syndrome neurogenic Kaeser type, *SPM* scapuloperoneal syndrome myopathic type, *TAPVR* total anomalous pulmonary venous return, *TMD* tibial muscle dystrophy, *TOF* tetralogy of Fallot, *WPW* Wolf-Parkinson-White syndrome, *XLD* X-linked dominant, *XLR* X-linked recessive

operate [207]. As such, mutations disrupting a force-generating domain of myofilament components seem to result in HCM whereas those disrupting a force-generating domain result in dilated cardiomyopathy (DCM). Other studies proposed that inefficient energy utilization by the sarcomere may lead to energetic depletion of cardiomyocytes and consequently disturb homeostatic functions. Studies on transgenic murine models of *TNNT2* or *MYH7*-mediated HCM, and patients and non-penetrant carriers of HCM-associated mutations in *MYH7*, *TNNT2*, or *MYBPC3* have revealed a decrease in the concentration of phosphocreatine and increased ATP utilization, and consequent impaired force-generating capacity of the heart [208–210]. This hypothesis is also supported by the evidence that HCM phenotype is a common feature in syndromic diseases that are caused by impaired mitochondrial energetics [211]. These hypotheses, however, do not explain the susceptibility to arrhythmias in some HCM patients, particularly in the absence of robust phenotype. It may rather be explained by the fact that specific mutations cause perturbed calcium cycling in HCM [212, 213] because of altered expression and/or phosphorylation of calcium handling proteins or increased calcium sensitivity of the myofilament [214, 215]. Increased calcium sensitization results in more tension generation in the mutant sarcomere at the same calcium concentration (hypercontraction) and/or less relaxation of mutant sarcomere (diastolic dysfunction). In patient-specific induced pluripotent stem (IPS) cells, calcium dysregulation has been reported as the central mechanism for *MYH7*-HCM pathogenesis, and restoration of calcium homeostasis prevented the development of hypertrophy and electrophysiological irregularities [216]. Moreover, high calcium sensitization has been shown to create increased spatial dispersion of activation times during rapid heart rates that is capable of generating functional reentry, even in phenotypically normal hearts [217]. In transgenic mice with HCM expressing calcium-sensitizing troponin I or troponin T mutants, treatment with a calcium channel blocker attenuated the HCM phenotype, and VT could be reproduced by calcium-sensitizing agents and prevented with blebbistatin, a medication that decreases calcium sensitivity [217].

The alterations in different physiological mechanisms initiate pathologic cascades (e.g., alterations in transcription and expression of RNAs, activation of signal transduction pathways, expression of trophic and mitotic factors) which eventually lead to myocardial hypertrophy and fibrosis (secondary). Coronary microvascular ischemia because of intimal hyperplasia, medial hypertrophy of intramyocardial arterioles, decreased capillary density and increased energy demand of the hypertrophied myocardium [218, 219], and the myocardial fibrosis resulting from replacement of necrotic cardiomyocytes create electrical inhomogeneity and contribute to the arrhythmogenic milieu in HCM.

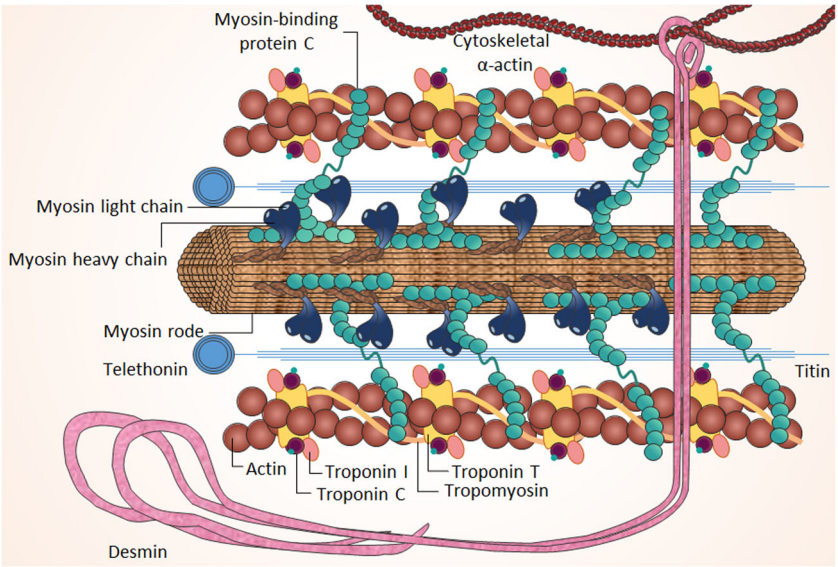

Fig. 1 Main structural elements of the cardiac sarcomere, involved in the pathogenesis of hypertrophic cardiomyopathy

Implications of the genetic test in HCM

Diagnostic value

A genetic substrate can be identified in approximately 60% to 70% of HCM patients with a family history of HCM and in 10% to 50% without [1, 11]. The genetic nature of HCM, however, cannot be ruled out in patients with negative test since its genetic architecture is not completely known. Diagnosis of HCM during early childhood-adolescence is associated with a significantly higher yield of genetic test and a more severe phenotype [220].

Genetic testing in all HCM patients is recommended for confirmation of the diagnosis (class I) [10, 11]. Construction and analysis of family pedigree allows to note specific features, such as familial history of SCD, unexplained heart failure, cardiac transplantation, pacemaker and defibrillator implants, and evidence for systemic disease, which may assist in diagnosis and help to determine the mode of inheritance in the family. When a mutation is identified in the index patient, cascade screening should be offered to family members to ascertain their genetic status. Because HCM mutations are highly penetrant, carriers have a substantial lifetime risk (> 95%) to develop the phenotype [11]. In general, the penetrance (proportion of mutation carriers with clinically detectable disease) of HCM increases with age. Regular follow-up in genotype-positive/phenotype-negative individuals with serial ECG, transthoracic echocardiography (TTE), and clinical assessment at periodic intervals (every 12 to 18 months in children and adolescents and every 5 years in adults) is recommended for early detection of clinical expression of the disease and timely initiation of therapy [11]. Patients and carriers of an autosomal dominant HCM mutation have a 50% risk to transmit the disease-causing mutation to their offspring.

Genotype-phenotype correlation

Studies have suggested that HCM patients with mutations in *MYBPC3* or *MYH7* have similar structural phenotype [203]. Those who host mutations in sarcomeric genes usually present at younger age and have higher rate of familial history of HCM and SCD, than those without a mutation [221]. This population also tends to have more severe microvascular dysfunction, LV hypertrophy, and fibrosis [222].

Mutations in thick filament protein genes commonly result in enhanced ATPase activity and accelerated actomyosin binding and are associated with late-onset HCM [223], whereas those in thin filaments predominantly lead to increased calcium sensitivity of the myofilaments and frequently produce life-threatening arrhythmias in the absence of marked LV hypertrophy [224]. Increased calcium sensitivity, previously reported for *TNNT2* and *TNNT3*, and suggested for many HCM mutations in *MYH7* [225], *MYBPC3* [226], and *MYL2* [227], is associated with life-threatening cardiac arrhythmias and SCD regardless of the displayed phenotype.

The genetic findings differ in HCM morphologic subtypes. Nearly 80% of HCM patients with reverse curvature septum have been found to have an identifiable HCM-associated mutation, whereas only 25% of patients with apical and 8% of patients with a sigmoid-shaped septum HCM were genotype-positive [228, 229]. Furthermore, mutations in Z-disk genes have been commonly associated with a sigmoidal shaped septal contour, whereas myofilament mutations preferentially produced reverse septal curvature or apical variant HCM [55, 229, 230].

HCM phenocopies have been reported in patients with infiltrative diseases, such as Fabry disease (*GLA*), Danon disease (*LAMP2*), Pompe's disease (*GAA*), hereditary transthyretin-related amyloidosis (*TTR*), and

PRKAG2-mediated disease (Wolff-Parkinson-White (WPW) syndrome in association with HCM phenotype) [231]. Among these, Fabry disease is relatively common and is seen in 1–3% of adult males with HCM phenotype [232]. Age at presentation is a key to diagnosis, since inborn errors of metabolism usually present in infancy.

Patients with *PRKAG2*-disease have a variable combination of glycogen storage cardiomyopathy, cardiac conduction disease, including sinus bradycardia and progressive and infra-Hisian AV block, ventricular arrhythmias, and SCD [233]. The preexcitation phenotype (WPW) in this patients has been explained by the structural disruptions of the annulus fibrosus by glycogen-laden myocytes [233]. WPW syndrome and HCM have also been reported in Danon disease (*LAMP2*) [234].

HCM is a common feature in cardio-facio-cutaneous syndrome, a rare genetic disorder caused by mutations in the RAS-mitogen activated protein kinase (MAPK) pathway genes [235]. HCM phenocopies in LEOPARD, Noonan and Costello syndromes, commonly referred as RASopathies, are commonly present in affected children; the phenotype may be less evident in adulthood, which, in turn, can explain some unexplained cardiac arrests in adults [236].

HCM is also a part of the phenotype spectrum of Friedreich's ataxia, an inherited disease caused by expansion of an intronic GAA sequence in the frataxin (*FXN*) gene. The disease usually starts with peripheral muscle weakness and visual and hearing impairment at childhood and progresses more rapidly in males [237].

Prognosis value

Although genotyping does not allow to precisely predict the load of arrhythmic events or risk for SCD, a positive HCM genetic test involving any of the myofilament genes increases the likelihood of developing systolic and diastolic dysfunction and propensity to develop symptoms [238]. In a multivariable analysis, a positive mutation status has been shown to be the strongest predictor of an adverse outcome [221].

Patients with sarcomere mutations have been reported to have younger age at the time of diagnosis, higher prevalence of family history of HCM and SCD (high penetrance), higher prevalence of asymmetric septal hypertrophy, greater maximum LV wall thickness, and increased incidence of cardiovascular death [239]. Maron et al. have documented a correlation between the severity of ventricular hypertrophy and the risk for SCD in patients with *MYH7*-mediated HCM [240]. Patients with multiple sarcomeric mutations have more severe phenotype and higher rate of SCD than patients with a single or no mutation, indicating that gene-dosage may be a contributor to disease severity [240, 241].

Therapeutic implications

Symptomatic mutation carriers should be warned about the effect of rigorous physical exercise, which can trigger fast development of the phenotype, ventricular arrhythmias, and SCD. The risk of SCD in asymptomatic HCM mutation carriers with insignificant clinical and family history is likely to be no different from the risk in the healthy general population of the same age; therefore, participation in competitive athletics is reasonable [242].

Pharmacotherapy with blebbistatin, diltiazem, and ranolazine, which are known to alter the myofilament calcium sensitivity and calcium homeostasis, is currently being investigated to target the increased calcium sensitivity of myofilaments [217]. Data from a small, randomized study suggests that modifiers of myocardial energetic substrates may be useful for increasing the exercise tolerance in symptomatic HCM patients [243]. Preliminary studies on animal models of Noonan and LEOPARD syndromes showed promising results by reversing the HCM phenotype in response to MEK and mTOR inhibition, respectively [235, 244]. However, much remains to study before translation of these methods to patients affected with RASopathies. In the field of gene therapy, intravenous injection of adeno-associated virus (AAV) rh10 vector expressing human frataxin in mice with complete frataxin deletion in cardiac and skeletal muscle fully prevented the onset of Friedreich's ataxia cardiomyopathy, completely reversed the cardiomyopathy in the mice within few days [245]. A single systemic administration of AAV9-Mybpc3 in homozygous *Mybpc3*-targeted knock-in mice prevented the development of cardiac phenotype and increased Mybpc3 messenger RNA and cardiac myosin-binding protein C levels in a dose-dependent manner [246]. With precise CRISPR–Cas9-based targeting accuracy and high homology-directed repair efficiency by activating a germline-specific DNA repair mechanism, a targeted correction of germline heterozygous *MYBPC3* mutation was recently performed in human preimplantation embryos [247], demonstrating the great therapeutic potential of genome editing for the prenatal correction of heritable cardiac conditions. Although gene therapy has several obstacles to overcome, it represents a very promising field.

Dilated cardiomyopathy

Clinical description of DCM

DCM is a myocardial disorder characterized by ventricular chamber dilation and progressive systolic dysfunction that frequently result in congestive heart failure [248, 249]. The incidence of DCM rises steadily with age: in children < 18 years of age, it is approximately 0.57 case per 100,000/year [250] and reaches up to 5.5 cases per 100,000/year in adults

[251]. DCM is a common final phenotype for multiple etiologic influences including heritable factors, congenital and acquired heart disease, excessive alcohol intake, vitamin deficiency, toxins, and infections. The prevalence of idiopathic DCM has been estimated to be 36 per 100,000 population [251], but the revisited estimations show it can be as high as 1:250 [252].

A common feature of DCM regardless of etiology is its propensity to thromboembolic disease, ventricular arrhythmias, and SCD. The arrhythmic load is particularly high in idiopathic DCM and is explained by subendocardial scarring in the LV and multiple patchy areas of myocardial fibrosis [253], which act as reentry sites and generate a VT with progression to VF, a common mechanism of death in DCM patients. Infrequently, SCD may be precipitated by bradycardia, electromechanical dissociation, atrioventricular (AV) block, pulmonary embolism, electrolyte imbalances, or myocardial ischemia, secondary to acute coronary thrombi or emboli [254].

Diagnosis of DCM

DCM is defined by the presence of LV dilation and dysfunction. Diagnosis is usually made by a two-dimensional transthoracic echocardiogram (TTE) or other imaging methods (e.g., cardiac MRI, CT) in the presence of LV ejection fraction < 45% and/or an end-diastolic diameter > 2.7 cm/m^2.

Genetic bases of DCM

A genetic factor can be identified in about 50% of patients and in higher proportion in individuals presenting with disease in childhood [255]. Familial DCM has autosomal dominant inheritance in 90% of cases and autosomal recessive, X-linked or mitochondrial inheritance in the remaining cases [256]. More than 30 autosomal and X-linked genes have been associated with idiopathic DCM (Table 1), majority of which encode structural elements of cardiac sarcomere or dystrophin-associated glycoprotein complex [257]. The most common genes associated with DCM are *TTN*, *LMNA*, *MYH7*, and *MYH6*. *TTN* mutations are responsible for 25% of familial and 18% of sporadic DCM cases [258]. *TTN* is the largest gene known in the human genome; therefore, it has been possible to better understand its variants only with the development of next-generation sequencing (NGS) technologies. Titin filaments contribute to myofibril assembly, stabilization, maintenance, and force transmission at the Z-line and are essential for the passive stiffness of the sarcomere. *TTN* is not a conserved gene; several missense variants have been reported. Vast majority of missense variants are nonpathogenic, and therefore, only nonsense, frameshift, and splice-site variants are considered pathogenic (with few exceptions). In DCM patients, *TTN* truncating mutations showed clustering in the A-band region and were absent from the Z-disk and M-band regions, whereas in healthy individuals, *TTN* variants were less enriched for the A-band region [258].

Nearly 40% of DCM patients with a truncating *TTN* variant have at least one additional mutation in the known DCM-associated genes; therefore, titin variants may serve as modifiers in the DCM pathogenesis [148].

The role of mutations in *MYH7*, *MYBPC3*, *TNNT2*, *ACTC 1*, *CSRP3*, and *LDB3* in the DCM pathogenesis suggests a genetic overlap with HCM and left ventricular noncompaction (LVNC). Cytoskeletal genes including α-, β-, and δ-sarcoglycans and dystrophin have been associated with DCM [259]. Mutations in the β-sarcoglycan (*SGCB*) and δ-sarcoglycan (*SGCD*) genes cause DCM with or without limb-girdle muscular dystrophy [109, 110, 260].

Mitochondrial DCM usually manifests in children or young adults. Both mitochondrial DNA and nuclear DNA-encoded mitochondrial proteins and enzymes have been associated with DCM. Syndromic or non-syndromic cardiomyopathies, including DCM, HCM, restrictive cardiomyopathy (RCM), and LVNC, have also been reported in association with defects in electron transport chain complexes (*MTND1*, *SDHA*, etc.), mitochondrial tRNAs (*MTTK*, *MTTL1*), rRNAs (*MTRNR1* and *MTRNR2*), translation elongation factors (*TSFM*), ribosomal proteins, mtDNA maintenance (*TYMP*), and CoQ_{10} biosynthesis (*COQ2*, *COQ4*, and *COQ9*) (reviewed in ref. [261]). An evident cardiomyopathy has been reported in one-third of children with mitochondrial diseases, and correlated with poor outcome [262].

Several X-linked forms of DCM (XLCM) have been described: XLCM in adolescents and young adults [263], Danon syndrome, which frequently presents with HCM in boys and later progresses to DCM and with late-onset DCM in female carriers [264], Emery-Dreifuss muscular dystrophy, and Barth syndrome, which is commonly identified in infancy [265, 266]. Mutations in dystrophin (*DMD*) also cause either XLCM (isolated) or Duchenne and Becker types of muscular dystrophy—skeletal muscle dystrophies before teenage years and DCM before the age of 20 in male patients [267]. Patients with isolated XLCM, similar to patients with dystrophin-mediated muscular dystrophy, have elevated serum creatinine kinase muscle isoforms, which is due to muscular expression of mutant dystrophin. In both XLCM and muscular dystrophies, carrier females develop DCM phenotype at an older age.

Laminopathies are caused by pathogenic variants in *LMNA* and exhibit different combinations of clinical features, such as cardiomyopathy (mainly DCM, less frequently ARVC), conduction defects, atrial and ventricular arrhythmias, neuropathy, and skeletal muscular dystrophy. These disorders can present isolated or together [268].

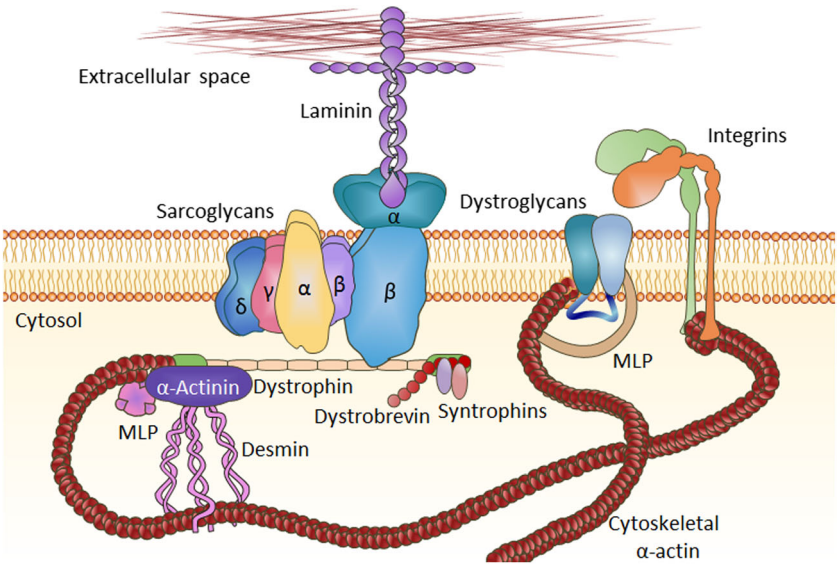

Fig. 2 Schematic representation of cytoskeletal elements of cardiomyocytes, implicated in the pathogenesis of dilated cardiomyopathy. MLP indicates muscle LIM [Lin-11, Islet-1, Mec-3] protein (also known as cysteine and glycine-rich protein 3)

Pathophysiology of DCM

Genetically heterogeneous substrates of DCM are likely to create the final DCM phenotype through different pathophysiological cascades [269]. The phenotypical overlaps with other cardiomyopathies and the incomplete penetrance suggest that multiple pathogenetic mechanism may be involved. Though the impact of many genes is currently controversial, plausible pathogenetic mechanism has been identified. DCM-related mutations disturb the functional link between the cytoskeleton and the sarcomere (Fig. 2). Mutations in the Z-disk protein genes have been implicated in destabilization of cardiac Z-disks, impaired functional interaction with binding proteins, myofibrinogenesis, and cardiac remodeling [77]. Titin has domains that can accommodate passive stiffness and participate in sarcomere contraction and signaling [270]. Functional analysis of DCM-associated *TTN* variants showed decreased interaction with actinin (*ACTN2*) and titin-cap (Tcap, *TCAP*) [80, 271]. Similarly, DCM-associated mutations in *TCAP* resulted in decreased interaction of the mutant protein with titin, calsarcin-1, and MLP [80]. In an animal model of *CSRP3*-DCM, Z-disks appeared wide, and the stretch response was impaired [61]. These observations generated the "loose sarcomere" hypothesis. Cypher/ZASP (*LDB3*) connects calsarcin (which binds to serine-threonine phosphatase calcineurin) and actinin and is also known to bind to protein kinase C (protein phsophorylase) and hosphoglucomutase-1; therefore, mutations in *LDB3* may alter the activation/deactivation of stretch response and/or molecule signaling pathways of cardiac hypertrophy and impair the energy metabolism at the Z-disk [272, 273]. Nebulette, an actin-binding protein localized to the Z-disk, interacts with a large number of proteins associated with thin filaments and the Z-disk [274]. Mutant nebulette (*NEBL*), a component of the Z-disk and a regulator of the length of actin thin filaments, has been shown to produce different phenotypes including DCM and endocardial fibroelastosis, dependent on the functional interaction of the mutant protein with its binding partner [76]. Other Z-disk-associated proteins were shown to affect different mechanisms: *VCL* mutations resulted in decreased binding to actin, desmin (*DES*) mutations resulted in changes in the cytoplasmic desmin meshwork, and myopalladin (*MYPN*) mutations caused defective myofibrinogenesis and possibly pathological cardiac remodeling due to its interaction with transcriptional factor CARP [275].

Mutations in conserved regions of RNA-binding motif 20 (*RBM20*)—a splicing factor that controls tissue-specific gene isoform expression—caused aberrant splicing of titin [276], myomesin 1, as well as calcium and other ion handling genes, resulting in arrhythmogenic DCM [277]. Mutations in lamins A and C gene (*LMNA*) impair its multiple physiological functions in various processes such as regulation of gene expression, mechanotransmission, DNA replication, and nuclear–cytoplasmic transport. Loss of nuclear lamina proteins disrupted its interactions with the muscle-specific desmin network, which led to loss of cytoskeletal tension and defective force transmission, ultimately resulting in DCM [278]. Mutations in *PLN*—an inhibitor of sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2)—have been identified in patients with DCM, often with overlapping features of ARVC [279]. Mutant phospholamban was associated with aberrant calcium handling, a higher percentage of irregular calcium transients, and abnormal cytoplasmic distribution of protein product [280]. In three-dimensional human-engineered cardiac tissue model, these abnormalities resulted in reduced force development that was improved after targeted correction of *PLN*-R14del mutation [281].

Sarcomeric gene mutations cause DCM through a dominant negative mechanism of action. Mutations in the actinin interacting domain of cardiac muscle alpha actin (*ACTC1*) were found in patients with DCM [12], while HCM-associated mutations were at the myosin heavy chain-interacting domain [13]. Similarly, functional studies revealed calcium desensitization of force generation in sarcomere in DCM-associated cardiac troponin T (*TNNT2*) mutations and increased calcium sensitivity in HCM-associated mutations [282]. It is therefore thought that domain-specific alterations in function and structure of the mutant protein underlie the variable phenotype in sarcomeropathies.

The dystrophin-associated protein complex links the sarcomeric contractile apparatus to the sarcolemma and the surrounding extracellular matrix through the cell membrane and protects the cardiomyocytes from contraction-induced injury. Malfunction of dystrophin (*DMD*) or associated proteins renders the cardiomyocytes and skeletal muscle myocytes susceptible to contraction-mediated damage and sarcolemmal instability [283]. Mutations in desmin (*DES*) cause accumulation of desmin aggregates within the cytoplasm and result in myofibrillar myopathy with DCM and other cardiomyopathy phenotypes [284]. A similar mechanism explains the DCM caused by mutations in α-crystallin B (*CRYAB*), a chaperone that in normal conditions prevents the aggregation of misfolded proteins [285].

Mutations in *SCN5A* were shown to result in a disruption of the voltage-sensing mechanism of the voltage-gated sodium channel subunit $Na_V1.5$, which conducts the I_{Na} current [286]. Defective $Na_V1.5$ results in a combination of electrical and myocardial dysfunction, but the determinants of variable phenotype features remain poorly studied.

The main mechanism of mitochondrial cardiomyopathies is insufficient energy production by the mitochondria to meet the high energy requirements of the heart [287]. Manifestation of a cardiomyopathy might be precipitated by stressors, such as febrile illnesses or surgery that cause metabolic decompensation [288]. Concomitant involvement of other high energy demand organs is possible but not always present.

Implications of the genetic test in DCM

Diagnostic value

The diagnosis of DCM is evidently clinical; however, DCM genetic testing allows to identify population at risk to develop DCM and, moreover, allows the close monitoring of those DCM cases associated with high risk of SCD [1]. Overall, the yield of the genetic test is 30 to 40% [266]. Results of genetic testing should be interpreted in the context of complete cardiac and systemic evaluation. Comprehensive evaluation in the index patient with DCM should ideally include family pedigree for at least 3–4 generations to identify potential familial occurrence of disease. Notably, symptoms of heart failure in the peripartum period can be indicative of peripartum cardiomyopathy (PPCM), which shares common genetic background with DCM [289].

Genotype-phenotype correlation

Several genotype-phenotype studies in DCM are currently being performed. Based on current knowledge, few important associations can be highlighted: *LMNA*- and *SCN5A*-mediated DCM usually presents in conjunction with cardiac conduction disturbances (Fig. 3) [162], and *ABCC9* is frequently identified in patients with DCM and concomitant atrial fibrillation (AF) [290]. Mutations in *LMNA* and X-linked *EMD* (emerin) cause Emery-Dreifuss muscular dystrophy, characterized by skeletal muscular dystrophy and cardiac phenotype, including but not limited to DCM [159, 164]. *LMNA*- and *EMD*-mediated DCM show age-dependent penetrance with early onset of atrial arrhythmias, cardiac conduction disease, progression to end-stage heart failure, high incidence of potentially fatal ventricular arrhythmias and SCD [291]. In patients with *LMNA*-mediated disease, neuromuscular involvement may precede the development of cardiac phenotype; however, some patients may exhibit no neuromuscular disease, SCD may occur with subtle or no systolic dysfunction, and is often the presenting manifestation. *LAMP2* mutations in females (X-linked disease, highly lethal in males) can be difficult to recognize in early stages and have also been associated with high risk of SCD.

Desmin (*DES*) mutations have been associated with restrictive cardiomyopathy (RCM), DCM, ARVC, and SCD [87, 90, 292, 293]. Affected patients often exhibit heart failure and advanced AV block requiring pacemaker implantation and/or implantable cardioverter defibrillator (ICD) due to non-sustained VT [294]. It has been recently shown, that mutations in *DES* and other cytoskeleton Z-disk genes are associated with a lower rate of LV reverse remodeling at follow-up, suggesting milder structural myocardial damage and a higher probability of better response to treatment [295].

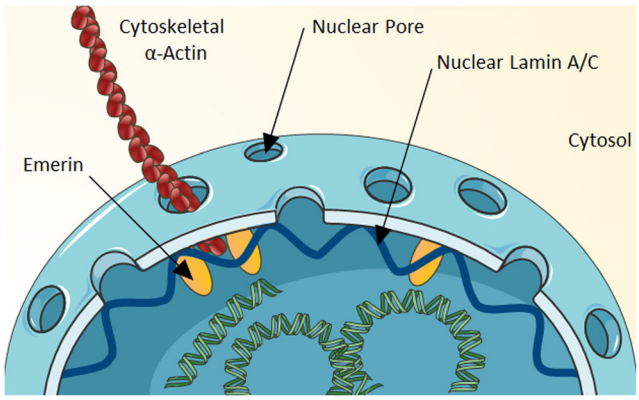

Fig. 3 Nuclear envelop proteins implicated in inherited cardiomyopathies

Since these aggressive forms of DCM are often hard to recognize at early stages, it seems useful to perform genetic testing in young individuals with early symptoms of idiopathic DCM.

Prognosis value

Patients with *LMNA*-related cardiac disease have a poor prognosis compared to patients with non-*LMNA*-DCM, as evidenced by higher incidence of SCD, appropriate ICD therapy, or end-stage heart failure with a need for transplantation [296]. The risk of SCD in *LMNA*-DCM patients does not differ between subjects with predominantly cardiac or neuromuscular disease [297]. A recent meta-analysis on more than 8000 DCM patients revealed that the frequency of ventricular arrhythmias in *PLN* and *RMB20*-mediated DCM is lower than in *LMNA*-DCM, but significantly higher than in sarcomeric DCM. Additionally, it has been shown that DCM patients with mutations in *PLN*, *MYH7*, or *TNNT2* have a more progressive disease with a need for heart transplantation [296]. Although *LAMP2* is has not been analyzed in large cohorts, but it has been also proposed that both men and women with *LAMP2*-cardiomyopathy manifest an aggressive cardiomyopathy phenotype with rapid progression to end-stage heart failure and with high risk for sudden death [298].

Among *DES* mutation carriers, 74% show cardiac involvement, including 22% who have isolated DCM or conduction disease with no evident muscular disease [299]. These patients may experience conduction disturbances and confer high risk for SCD at all stages of disease [294]. Decisions for device implantation in these patients should be individualized and guided by cardiac evaluation findings and examination of potentially related phenotypes in family members.

Therapeutic implications

Genetic diagnosis in presymptomatic patients with *LMNA*- or *DES*-mediated DCM allows to prevent fatalities through prophylactic ICD implantation prior to the progression to end-stage heart failure, conduction disturbances, or ventricular arrhythmias [1, 300]. Similarly, genetic testing can have therapeutic implications for patients with muscular dystrophy, arrhythmias, and/or cardiac conduction disease, as it may identify *LMNA* and *DES* mutation carriers and enable the consideration of surveillance and prophylactic pacemaker and/or ICD implantation [301]. Asymptomatic *LMNA* mutation carriers can be offered cardiac evaluation with medical history, ECG, and TTE annually or biannually and upon manifestation of new symptoms. *LMNA* patients who experience a symptomatic bradyarrhythmia or high-grade AV block can receive an implantable electronic pacemaker. However, given that conduction disturbances in these patients is highly associated with occurrence of life-threatening arrhythmias regardless of ejection fraction [302], the use of ICD should be strongly considered [303]. Other risk factors for malignant ventricular arrhythmias are non-sustained VT, LV ejection fraction < 45% at the first clinical contact, male sex, and non-missense mutations (ins-del/truncating or mutations affecting splicing) [291]. These risk factors assist to identify *LMNA* mutation carriers who would most benefit from ICD. Additionally, familial history of cardiac arrest and of unexpected SCD (particularly in the absence of preceding symptoms) should be given appropriate attention as it may warrant early ICD implantation in genetically affected family members.

Encouraging results have been achieved in preclinical studies of DCM gene therapy. Transgene expression of δ-sarcoglycan by using recombinant AAV vector in δ-sarcoglycan-deficient mouse and hamster models of DCM led to amelioration of sarcolemmal permeability, reduced histological lesions in the heart, normalized the myocardial function, and extended the lifespan [304, 305]. Gene therapy with AAV targeting numerous pathogenic mechanisms improved the outcomes in rodent models of dystrophic cardiomyopathy [306]. For many of muscular dystrophies, gene therapy has been a successful therapeutic method in rodent models [306].

Restrictive cardiomyopathy

Clinical description of RCM

RCM is a rare myocardial disease with a very poor prognosis, characterized by restrictive filling and reduced diastolic volume of either or both ventricles in the presence of normal or near-normal systolic function and normal ventricular wall thickness [307]. The exact prevalence is unknown, but is thought to be less than 20 per 100,000 [308]. The hallmark feature of RCM is the abnormal rigidity of ventricular walls that impede ventricular filling. The etiology of RCM can be genetic, acquired, or related to systemic disease [2]. Familial forms of both isolated and systemic RCM have been described. When all the secondary causes such as AL-amyloidosis, hemochromatosis, and irradiation are excluded, RCM is likely to have a genetic origin.

Diagnosis of RCM

RCM is typically diagnosed by TTE, which demonstrates the characteristic (yet non-specific) morphologic constellation of a non-hypertrophied, non-dilated ventricle with preserved ejection function and dilated atria [307]. Doppler techniques reveal restrictive filling dynamics of the LV and RV, with an abnormally high E/A ratio, indicating accentuated early filling with diminished late filling [309]. Cardiac MRI is used for detailed assessment of myocardial wall composition and endomyocardial biopsy may be useful to exclude specific

myocardial and systemic diseases. Primary (idiopathic) RCM is a rare condition and a diagnosis of exclusion, as many secondary causes can lead to the restrictive cardiac physiology.

Genetic basis of RCM

Due to its rare incidence, the genetic characteristics of RCM have been confined to evaluation of a limited number of genes in small cohorts, and consequently, its genetic spectrum remains poorly understood. Familial RCM is usually transmitted as an autosomal dominant trait, although autosomal recessive and compound heterozygous forms have been described [90]. RCM has been associated with mutations in genes encoding sarcomeric elements (*MYH7*, *TPM1*, *ACTC1*, *TNNI2*, *TNNT3*, *MYBPC3*, *MYL3*, and *MYL*), Z-disk proteins (*TTN*, *MYPN*, and *BAG3*), *DES* and *CRYAB* [34, 41, 88, 310, 311]. *MYH7* and *TNNI3* are relatively more frequently affected and each explains nearly 5% of cases [1].

Additionally, several systemic diseases that affect the heart can mimic RCM phenotype, including hereditary amyloidosis (primary caused by mutations in *TTR* gene, but also *CST3*, *FGA*, *LYZ*, *GSN*, *APOA2*, and *APOA1*), metabolic disorders such as glycogen storage diseases, Fabry disease (*GLA*), hemochromatosis (*HFE*), cystinosis, as well as sarcoidosis, lymphoma, Danon's disease (*LAMP2*), and *PRKAG2*-mediated heart disease [312].

Pathophysiology of RCM

The restrictive pattern can be caused by multiple different cardiovascular diseases and systemic conditions. Secondary causes of RCM are categorized into myocardial (infiltrative and storage disorders) or endomyocardial pathologies (diabetic cardiomyopathy, endomyocardial fibroelastosis, scleroderma, carcinoid heart disease, radiation, hypereosinophilic syndrome, anthracycline-induced cardiotoxicity, drug-induced fibrous endocarditis). The most common causes of secondary RCM are infiltrative diseases, particularly amyloidosis.

The pathophysiology of primary (idiopathic) RCM is poorly understood. The disease shares genetic substrates (sarcomeric mutations) [16], histological (interstitial fibrosis and myofiber disarray), and clinical characteristics with HCM [310, 313]. Molecular mechanisms overlapping with or primarily based on those proposed for HCM have been suggested as the cause of the impaired myocardial relaxation and increased ventricular filling pressures, but remain poor speculations. Moreover, identical sarcomeric mutations manifested with HCM and RCM in different subjects within the same family [41], indicating that RCM may represent a spectrum of manifestations of a familial cardiomyopathy. The mechanisms underlying the variable penetrance in RCM remain unclear, but epigenetic factors, modifier genes, and environmental influences have been proposed as potential determinants of the ultimate phenotype.

Implications of the genetic test in RCM

Diagnostic value

The yield of genetic test in RCM remains undetermined. Genotyping success rate of 60% has been reported in one study which screened > 200 cardiac genes in 29 RCM patients [314]; however, the yield was ≤ 30% in other cohorts [16, 41, 88]. According to the Heart Rhythm Society/European Heart Rhythm Association Expert Consensus Statement, RCM genetic testing may be considered (class IIb) when RCM is suspected based on the clinical and family history and electrocardiographic/echocardiographic phenotype [1]. Mutation-specific genetic testing is recommended (class I) for appropriate relatives following the identification of a RCM-causative mutation in the index case [1].

Genotype-phenotype correlation

Currently known genotype-phenotype associations in RCM are limited because of small number of genotyped patients and lack of long-term follow-up studies reported so far. In a study by Kubo et al., restrictive phenotype in HCM patients was associated with progression to moderate to advanced heart failure, paroxysmal or persistent AF, as well as fivefold higher risk for cardiac death, transplantation, or ICD discharge, compared to patients with non-restrictive HCM [310]. Non-sarcomeric RCM often occurs with mild to severe concomitant skeletal myopathy and cardiac conduction disease [312]. The combination of RCM with elevated serum creatine kinase suggests a mutation in *DES* or *LMNA*.

Prognosis value

So far, genetic testing has no role in risk stratification for patients with isolated RCM, but can be important when evaluating patients with syndromic RCM, such as *TTR*-amyloidosis [1]. It is important to ascertain the genetic status in asymptomatic members to determine their potential risk for developing RCM or other cardiomyopathy phenotype later in life.

Therapeutic implications

Genetic testing has limited impact on management of patients with RCM; however, it can identify genotypes associated with high arrhythmic risk and can assist in the early detection of syndromic causes of RCM in patients with subtle syndromic manifestations. Because *DES*- and *LMNA*-mediated RCM is associated with relatively high rates of SCD, identification of a mutation in *DES* or *LMNA* in an RCM patient should prompt

consideration of a prophylactic ICD, particularly in the setting of conduction defects [315]. Early recognition of an underlying cause may allow for disease-specific therapy, such as transplantation in *TTR*-amyloidosis, or enzyme replacement therapy in some storage diseases.

Arrhythmogenic right ventricular cardiomyopathy

Clinical description

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically determined heart muscle disease, characterized by necrosis and fatty or fibrofatty replacement of the right ventricular (RV) and less frequently left (LV) myocardium, which leads to progressive heart failure and increased susceptibility to malignant ventricular arrhythmias and SCD at young age [316]. The prevalence of ARVC in the general population is estimated 1:2000 to 1:5000, with three times higher occurrence and more severe course in men [317]. Arrhythmias in ARVC can range from premature ventricular contractions (PVCs) to sustained VT usually of left bundle branch block (LBBB) morphology and eventually VF. Patients with ARVC typically present between the second and fourth decade of life with palpitations, light-headedness, or syncope. Nonetheless, cardiac arrest or SCD can be the first clinical manifestation in up to 50% of cases [318].

Left-dominant arrhythmogenic cardiomyopathy (LDAC) is an under-recognized clinical entity, and its prevalence is unknown. The disease has a phenotypical overlap with dilated cardiomyopathy (DCM); however, patients with LDAC often present with arrhythmias or chest pain but not heart failure, thus distinguishing LDAC from DCM, in which arrhythmias typically occur in the setting of ventricular dysfunction [319].

Diagnosis

The diagnosis of ARVC relies on the combination of structural, functional, and electrophysiological abnormalities, family history, and results of genetic test, according to the modified Task Force criteria [316]. Criteria included in the diagnostic scheme are combined in the following categories: global or regional dysfunction and structural alterations, tissue characterization of wall, repolarization and depolarization/conduction abnormalities, arrhythmias, and family history (including genetic findings) [316]. Based on the strength of the phenotype and the criteria met, the diagnosis can be "definite ARVC," "borderline ARVC," or "possible ARVC" [316].

Genetic bases of ARVC

Nearly 60% of all ARVC cases are caused by mutations in desmosomal genes that encode plakophillin-2 (*PKP2*), desmoplakin (*DSP*), junctional plakoglobin (*JUP*), desmoglein-2 (*DSG2*), and desmocollin-2 (*DSC2*) (Table 1, Fig. 4) [320]. ARVC predominantly follows autosomal dominant inheritance with incomplete penetrance, except for the Naxos disease (triad of autosomal recessive ARVC, palmoplantar keratoderma, and woolly hair) [145, 146], and Carvajal syndrome (a variant of Naxos disease with LDAC, associated with early morbidity), caused by recessive mutations in *JUP* and *DSP*, respectively. Additionally, a single case of autosomal recessive ARVC caused by homozygous mutations in *DSG2* has been reported [321]. The majority of ARVC mutations are insertions/deletions or nonsense mutations, which lead to premature termination of the encoded proteins [322]. Nearly 75% of genotype-positive ARVC cases in American cohorts, and nearly 60% of genotype-positive index cases and up to 90% of familial cases in European cohorts are caused by single mutations in *PKP2* [320, 323, 324]. Nearly 45% of genetically positive ARVC patients have been reported to have an affected relative [324]. A polygenic nature of the disease has been described in nearly 10% of patients, which might explain part of the sporadic cases [325, 326]. However, this proportion may increase with identification of new genes.

Several non-desmosomal genes have been implicated in ARVC or overlapping phenotypes (Table 1) [115, 322, 327]. Mutated desmin (*DES*), titin (*TTN*), lamin A/C (*LMNA*), αT-catenin (*CTNNA3*), transmembrane protein 43 (*TMTM43*), and transforming growth factor β3 (*TGFB3*) lead to functional impairment on proteins interacting with desmosomal constituents [266]. Mutations in *PLN* are associated with DCM, ARVC, and SCD at young age [183]. Diseases associated with titin mutations include ARVC, HCM, DCM, and skeletal muscle myopathy. Mutations in *RyR2*, which usually cause catecholaminergic polymorphic ventricular tachycardia (CPVT), have been also identified in patients with clinical and morphological characteristics of ARVC [187, 328–330], but the pathophysiological role of *RyR2* mutations in ARVC is controversial and needs profound investigation.

Pathophysiology of ARVC

ARVC has been originally considered a disease of cardiac desmosome [321, 331]. Later, many desmosome-associated and non-associated genes were linked to the disease. Cardiac desmosomes are composed of proteins such as plakoglobin, plakophilin, desmoglein, desmocollin, desmoplakin, and associated proteins. Desmosomes anchor intermediate filaments to the cytoplasmic membrane in adjacent cardiomyocytes, thereby forming a three-dimensional scaffolding and providing mechanical strength. They are responsible for

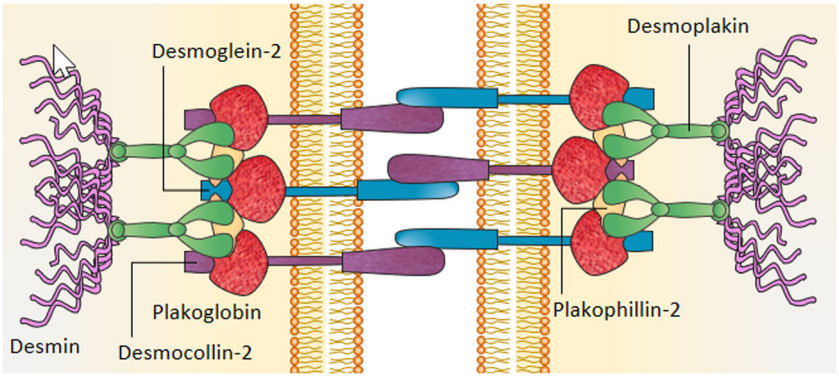

Fig. 4 Main structural proteins of the cardiac desmosome. Desmosomal mutations are the main genetic substrate for arrhythmogenic right ventricular cardiomyopathy

cardiomyocyte resistance to mechanical stress, regulate the transcription of genes involved in adipogenesis and apoptosis, and also play a major role in myocardial electrical conduction through regulation of gap junctions and calcium homeostasis.

Two disease mechanisms/features are noteworthy in ARVC pathogenesis: the fibrofatty degeneration of the myocardium and the electrical instability leading to arrhythmias. While the mechanisms of disease are largely unclear, ARVC appears to result from a final common pathologic pathway which leads to disturbance in normal structure and function of the cardiac desmosome and the intercalated disk [266]. It is currently considered that mutant desmosomal proteins (or interacting proteins) promote impairment of mechanical coupling and thereby weaken the cell-to-cell adhesions during exposure to physical stress, eventually resulting in cardiomyocyte detachment and degeneration with subsequent inflammation, apoptosis, and fibrofatty replacement of the affected cardiomyocytes [331, 332]. Mutations in *TMEM43*, which encodes for an inner nuclear membrane protein that contains a response element for PPARγ, could explain the fibrofatty replacement of the myocardium in ARVC [115]. This hypothesis however does not explain the increased myocardial fibrosis in ARVC. Additionally, mutations in *TGFB3* have been shown to induce myocardial fibrotic response by promoting the expression of extracellular matrix genes and inhibiting extracellular matrix degradation by suppressing the activity of matrix metalloproteinases [176, 333].

The mechanisms of arrhythmogenesis in ARVC are likely multifactorial. Alterations in macroscopic structures (fibrofatty infiltration), microstructure (interstitial fibrosis; loss of cell–cell mechanical and electrical coupling), and/or nanostructure (dysfunction of macromolecular complexes responsible for cardiomyocyte electrical activity) can precipitate arrhythmias in patients with ARVC. These factors, and the myocardial bundles within the fibrofatty tissue, contribute to conduction delay, electrical heterogeneity and instability—a potential substrate for reentry arrhythmias. This electrophysiological instability is further increased by impairing ability of affected desmosomes on intercellular conductance by altering expression of gap junctions [334] and ion channels [335, 336].

Ventricular dysfunction can later result in more stress-induced progressive myocyte detachment, death, and fibrofatty replacement, eventually resulting in profound deterioration of systolic and diastolic function and rendering the end-stage disease hardly distinguishable from DCM.

Implications of the genetic test in ARVC

Diagnostic value

The diagnostic yield of genetic testing in ARVC is around 60% [1]. In the 2010 revised Task Force criteria, identification of an ARVC-associated or probably associated pathogenic mutation is considered a major diagnostic criterion [316]. When the test is positive, in an ARVC proband, cascade screening is recommended for family members, because early identification of asymptomatic individuals at risk can give the opportunity to recommend lifestyle changes (limitation in vigorous exercise) which may delay the phenotype development [320].

Genotype-phenotype correlation

In a study by Bhonsale et al., ARVC patients with *PKP2* mutations exerted a more severe phenotype with VT/VF earlier in life, compared to those with other ARVC genotypes [323]. The presence of multiple pathogenic mutations in major desmosomal genes (oligogenic inheritance) has been associated with earlier manifestation of disease, higher prevalence of arrhythmic events, and higher likelihood of LV dysfunction [323]. Nearly 86% of mutation carriers relatives of ARVC patients were asymptomatic at the time of diagnosis, but 8% had sustained VT/VF or an appropriate ICD intervention during a mean follow-up of 4 ± 5 years, with no significant differences among gene groups [323].

An asymptomatic carrier of an ARVC-associated gene mutation is at risk, but may or may not develop the disease. Low penetrance has been reported, particularly in missense mutations. Studies have documented nearly 16% prevalence of missense mutations in ARVC susceptibility genes in healthy

controls, whereas radical mutations were almost exclusively identified in ARVC subjects [325]. However, few controls were checked and large databases were not available for screening, which may have led to an overestimation of presumed pathogenic variants in controls. It has been proposed that the development of ARVC phenotype depends on several factors, such as the presence of an additional gene abnormality or > 1 abnormalities within the same class of genes such as *PKP2* (so called "gene-dose effect" or "more than one hit"), exposure to certain viruses, and athletic lifestyle. Interestingly, the majority of patients with "definite" ARVC phenotype host mutations in desmosomal genes, whereas patients with weaker ARVC phenotypes based on the Task Force criteria host mutations in non-desmosomal genes, associated previously with DCM and result in a disease spectrum, including DCM or phenocopies of ARVC [337].

Young (< 20 years), asymptomatic mutation carrier relatives of ARVC patients frequently exhibit prolonged terminal activation duration (measured from the nadir of the S wave to the end of all depolarization deflections in V_1–V_3 leads, considered prolonged when ≥ 55 ms) as an early marker of ARVC [324]. Individuals with mutations in *LMNA* present with severe ARVC phenotype, frequently in combination with atrial fibrillation and cardiac conduction disease [161]. These cases are probably not truly ARVC cases and misclassification can be attributed to the high sensitivity and low specificity of the Task Force criteria, particularly in possible or borderline phenotypes.

The genetic bases of LDAC are less studied. Sen-Chowdhry et al. identified *DSP*, *DSG2*, and *PKP2* mutations in 8 of 24 families with LDAC (33%) [319]. Four out of the 8 causative mutations were previously linked to ARVC. *DSG2* mutations alone have been associated with high likelihood of developing LV involvement [321]. Additionally, relatives of ARVC patients, who carried *DSP* mutations, had a higher rate of LV involvement and SCD without preceding symptoms [338]. In general, patients with LDAC or biventricular disease are known to have worse outcomes than those with spared LV [339].

Prognosis value

Rare autosomal recessive ARVC syndromes have the poorest outcome [331, 340]. Desmosomal mutations usually predispose to younger onset, higher incidence of T-wave inversion in V_1–V_3 leads, and a strong family history of ARVC [341]. Multiple mutations are associated with higher risk of unexplained SCD [339].

Therapeutic implications

Studies have revealed that endurance sports activities increases the age-related penetrance, risk of VT/VF, and occurrence of heart failure in asymptomatic desmosomal mutation carriers [342, 343]. Therefore, asymptomatic ARVC mutation carriers should consider restraining from athletic activities beyond recreational, low-intensity sports (class IIa) [344].

Left ventricular non-compaction cardiomyopathy

Clinical description of LVNC

LVNC cardiomyopathy is a predominantly congenital condition characterized by numerous prominent LV trabeculations and deep intertrabecular recesses, as well as diminished systolic function with or without associated chamber dilation [345, 346]. The prevalence of LVNC is estimated between 0.05 and 0.25% per year in the general population [347, 348]. The disease can either present in an isolated form (iLVNC) or coexist with cardiomyopathy, cardiovascular malformation, and/or systemic (mainly neuromuscular) conditions. iLVNC has a widely variable clinical course, ranging from lifelong latent course to life-threatening ventricular arrhythmias, congestive heart failure, thromboembolic complications, and SCD [347]. Approximately 40% of children with LVNC manifest life-threatening ventricular arrhythmias. The severity of arrhythmias in LVNC has no correlation with the systolic dysfunction, as nearly 20% of LVNC patients with VT or VF show normal systolic function [349]. SCD is the most common cause of mortality in LVNC patients [350] and can occur in up to 23% at 15 years, surpassing the SCD incidence in DCM (5%), HCM (6%), and RCM (12%) at the same age [351].

Diagnosis of LVNC

Diagnosis of LVNC is based on demonstration of imaging pattern of hypertrabeculations in the ventricular myocardium considered as non-compacted-to-compacted myocardium ratio ≥ 2 in end-systole [352]. Color Doppler allows for good visualization of the intertrabecular space. Contrast echocardiography can help to better visualize trabeculations. Cardiac MRI may reveal fibrosis and be useful for distinguishing LVNC from myocarditis.

Genetic bases of LVNC

LVNC is a genetically heterogeneous disorder. Mutations are identified in 35 to 45% of cases [345], and familial occurrence is detected in 30% of cases [353]. LVNC usually follows an autosomal dominant inheritance with incomplete penetrance and variable expressivity, but X-linked and mitochondrial inheritance have also been

documented [354]. So far, mutations in more than 15 genes encoding sarcomeric (*MYH7*, *MYBPC3*, *ACTC1*, *TNNT2*, and *TPM1*) [14, 95, 355, 356], ion channel (*HCN4*, *SCN5A*) [357, 358], and other proteins have been linked to LVNC (Table 1) [69, 163, 359, 360]. Bleyl et al. were the first to map LVNC to Xq28, where *TAZ* (tafazzin) gene is located [153]. Tafazzin is a phospholipid transacylase that has an important role in maintenance of normal cell membrane function. Abnormal tafazzin typically leads to different combinations of clinical abnormalities, including a cardiomyopathy (LVNC, less frequently DCM), skeletal myopathy, cyclic neutropenia, 3-methylglutaconic aciduria (a marker of mitochondrial dysfunction), and deficiency of cardiolipin (a key membrane phospholipid of cardiomyocytes and mitochondria for energy production), collectively called Barth syndrome [345].

Sarcomeric mutations account for nearly 30% of genotype-positive LVNC cases [1], and show marked phenotypical variability and pleiotropy even within the same family [361]. A missense 109A>G mutation in tropomyosin α-1 (*TPM1*) gene has been identified in three relatives with isolated LVNC who demonstrated endocardial and subendocardial fibrosis with prominent elastin deposition, and adipose tissue between muscle layers [356]. Causative mutations in dystrobrevin-α gene (*DTNA*) have been identified in patients with hypoplastic left heart syndrome and LVNC [360], in Homeobox protein Nkx-2.5 gene (*NKX2-5*) in children with LVNC and atrial septal defects [167], and in *MYH7* and in *TPM1* gene in patients with combination of LVNC and Ebstein's anomaly [32, 45, 345, 362]. In LVNC with congenital heart disease, disturbance of the NOTCH signaling pathway seems part of a final common pathway [174]. Different studies also established a link between LVNC and mitochondrial genome mutations, chromosomal abnormalities, including Edwards, Patau, Coffin-Lowry, DiGeorge, Sotos, and Turner syndromes, Pierre Robin sequence, as well as Charcot-Marie-Tooth disease type 1A [345, 354]. Isolated LVNC is also part of the phenotypic spectrum of Danon disease (*LAMP2*) and cardiac laminopathies (*LMNA*) [163]. Mutations in the HCN4 channel (*HCN4*), that mediates the I_f pacemaker current, were previously associated with autosomal dominant LVNC, mitral valve prolapse, sinus node dysfunction, familial and non-familial sick sinus syndrome, bradycardia, and dilation of the ascending aorta ascendens [363].

The genetic background of iLVNC and its role in phenotype are less understood. In a recent study, cardiomyopathy panel testing in pediatric population with iLVNC in the absence of a family history of cardiomyopathy revealed no relevant mutations, indicating that in the absence of family history of cardiomyopathy iLVNC may represent a benign anatomic variant [364].

Pathophysiology of LVNC

The pathophysiology of LVNC is currently unclear. There are two competing theories on the etiology of LVNC. According to the embryological theory, LVNC is caused by an arrest in the process of normal, gradual compaction (trabeculation) of the myocardial during development [365]. Association of LVNC with mutations in the NOTCH pathway and regulator genes is consistent with this theory, as this pathway, controls multiple cell differentiation processes during embryogenesis [174]. Recently, an LVNC-associated stop-gain mutation in *TBX20* has been studied on IPS cells [366]. TBX20 transcription factor normally controls the expression of TGF-β signaling modifiers including *PRDM16*, a known genetic cause of LVNC [175]. The iPS cell-derived cardiomyocytes with a mutation in the *TBX20* displayed proliferation defects associated with perturbed transforming growth factor beta (TGF-beta) signaling. These alterations recapitulated a key aspect of LVNC pathophysiology at the single-cell level and could be corrected with inhibition of TGF-β signaling and genome correction of the TBX20 mutation [366].

The non-embryogenic hypothesis is based on the reported cases of acquired and potentially reversible forms of LVNC in athletes [367], in pregnant women [368], and in patients with sickle cell disease [369], myopathies [370], and chronic renal failure [371]. These findings expand the variety of potentially implicated mechanisms from arrested maturation of the ventricular trabeculations during embryogenesis to acquired mechanisms, including hemodynamics, phenotype-driven trabecular gene expression, or epigenetic factors [372].

Little is known about the arrhythmia susceptibility in patients with LVNC, but possible substrates for electrical instability have been proposed, such as the subendocardial ischemia due to prominent trabeculations and intratrabecular recesses, microcirculatory dysfunction and subendocardial fibrosis within the non-compact myocardium, and the presence of myocardial tissue around deep intratrabecular recesses, which can serve as slow conducting zones and initiate reentry arrhythmias [346, 373].

Implications of the genetic test in LVNC

Diagnostic value

The role of genotyping in clinically diagnosed LVNC patients is confirmation of diagnosis and, whenever positive, identification of asymptomatic relatives at risk. It is important to remember that the age of manifestation and the displayed phenotype may be different in families with an LVNC-associated variant [345]. Additionally, genetic testing is inevitable for early diagnosis of syndromic forms of LVNC in the absence of other typical features (e.g., in Danon disease), which allows for early medical interventions and family planning.

Interestingly, some patients in the same family can exhibit different phenotypes with same the mutation (variable expression of the disease), varying from LVNC to HCM or DCM.

Genotype-phenotype correlation

One study reported that patients with LVNC who develop systolic heart failure and those with arrhythmias were more likely to carry mutations in *SCN5A* [357]. Recently, we showed that, in addition to previously described phenotypes, *HCN4* mutations can also lead to VF in patients with LVNC [358].

Prognosis value

One recent study reported higher rate of atrial and ventricular arrhythmias and need for cardiac transplantation due to progressive LV dysfunction in carriers of pathogenic *TTN*, *LMNA*, and *RBM20* variants [374], but larger cohorts are required for more reliable analysis.

Therapeutic implications

Genetic testing so far provides no therapeutic repercussions in patients with LVNC.

Important considerations in inherited cardiomyopathies

Variable phenotype

Earlier reports described severe phenotypes; however, subsequent studies have revealed that classic disease forms are not as common as previously thought and identified mild and atypical manifestations of disease [316]. It also became apparent that identical mutations may produce different cardiomyopathy phenotypes even within families [163], consistent with the complex, heterogeneous pathophysiology. The mechanisms involved in phenotype expression in cardiomyopathies are poorly understood. It has been proposed that epigenetic, environmental, and behavioral factors can modulate gene expression and lead to different clinical traits [3]. Evaluation of such mechanisms is currently difficult to examine in clinical trials because of inadequacy of sample size, costs of genetic testing, non-standardized evaluation records, and other limitations.

For high risk genotypes, such as certain *LMNA* variants, knowledge gained from the clinical profile of the proband may be useful for decision making in mutation carrier family members regardless of their displayed phenotype. Whether other genotypes increase the susceptibility to SCD at similar extent in relatives with different cardiomyopathy phenotypes, or whether they will benefit from similar therapy, remain uncertain and need evaluation in prospective studies. The presence of family history of SCD should however warn about high risk for arrhythmic events in mutation carrier relatives regardless of phenotype.

Interestingly, the expressed phenotype may also evolve over time. Evident examples of cardiomyopathy phenotype remodeling include the development of LV dilation and systolic dysfunction in certain HCM patients [375], progression of ARVC to biventricular disease [376], and disappearance of trabeculations in LVNC. Most commonly the end result is a DCM phenotype with irreversible heart failure, once again suggesting that it is not only a distinct cardiomyopathy but also a common outcome for distinct pathophysiological pathways.

Incomplete penetrance

The penetrance appears to increase with age, but remains < 100% for all cardiomyopathies (incomplete penetrance). For example, in HCM, the cardiac hypertrophy usually becomes apparent from adolescence, whereas the age of onset of sarcomeric DCM is bimodal, with peaks during childhood (severe course) and middle age (mild course) [377]. Therefore, identifying family members with subtle phenotype is difficult, as development of measurable, robust phenotype may take decades. Moreover, increasingly more data suggest that certain cardiomyopathy mutations confer high arrhythmogenic risk regardless of the phenotype, making cascade genetic screening the key tool for identifying high risk individuals in affected families [378]. Genetic testing allows preimplantation diagnosis, for oocyte or embryo selection. These techniques are controversial particularly in mild diseases and not approved in many countries. Since inherited cardiac diseases exhibit incomplete penetrance and variable expression of the disease, each case/family has to be evaluated separately by an expert team.

Choice of the mode of genetic test

The progress in NGS technologies made large-scale genome-wide sequence analysis possible, allowing for shorter times of the test and larger volumes of screened genes. Screening of a panel of cardiomyopathy-associated genes is the current standard of practice, as it is the most cost-efficient and precise approach to the diagnosis of complex traits and overlapping phenotypes. The utility of whole genome sequencing, whole exome sequencing [379–381], and clinical exome sequencing is currently being evaluated mostly in the research setting. These techniques provide efficient means to discover common polymorphisms (modifiers) and new candidate genes responsible for different cardiomyopathy traits and have the potential to enhance the yield of molecular diagnostics. Currently, the

added diagnostic yield of these tests is insignificant but the techniques are costly and therefore not suitable for routine diagnostic testing.

Defining an actionable gene/variant

Over the years, more than 70 genes have been associated with one or more inherited cardiomyopathies or syndromes; however, some have only been identified in one proband with no segregation, or in one family. While in certain cases a modifier effect cannot be excluded, the evidence on *causality* is often limited and insufficient for application to clinical practice. It is therefore important to review the strength of phenotypes associated with the gene/variant, segregation of the variant with cardiac phenotype, the available functional characterization, and whether or not the association was replicated over time. This approach is currently pursued by investigators of Clinical Genome Resource (ClinGen; http://www.clinicalgenome.org) for curating the genes related to inherited cardiomyopathies and will optimistically allow to implement evidence-based expert consensus for clinical actionability of genes and variants.

Conclusions

The enormous progress in NGS technologies over the last two decades have generated an essential role for genetic testing in evaluation of patients with cardiomyopathies. The genetic test now is used for diagnosis and risk stratification and often helps to define the therapeutic strategy or suggest lifestyle recommendations. When a genetic cardiomyopathy is confirmed in a proband, extension of targeted genetic testing to the relatives often allows to define the segregation of the mutation with phenotype in the family and identify and initiate preventive therapy and sometimes necessary lifestyle changes in genetically affected, asymptomatic family members at risk of developing a cardiomyopathy and/or SCD. Preimplantation and prenatal screening of causal mutation are new advancing technologies that allow to avoid from inheriting the mutant gene to the successive generations.

Many knowledge gaps however still exist in our understanding of cardiomyopathies. Establishing clear genotype–phenotype correlations remains a challenge, as the presently known heritable factors only partially explain the multiple cardiomyopathy phenotypes and the variable expression of an identical mutation even within the same family. Many ongoing studies that investigate the potential role of modifier genes, environmental and epigenetic factors in arrhythmogenesis, and disease progression and expression of phenotype may soon unravel novel pathogenetic mechanisms. Recent advances in cellular reprogramming of somatic cells have made it possible to perform studies on patient-specific IPS cells derived toward the cardiac lineage, which is actively used for studies of the molecular mechanisms underlying genetic cardiomyopathies and screens of novel patient-specific therapies in vitro cardiomyopathy models. The growing knowledge gained from genetically specific pathophysiological mechanisms and gene therapy on cardiomyopathy animal models will optimistically pave the way of human clinical trials and eventually provide novel preventive and therapeutic measures much needed for these life-threatening diseases.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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