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MYOCARDIAL DISEASE (A ABBATE, SECTION EDITOR)

Genetics of Dilated Cardiomyopathy: Clinical Implications

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Abstract

Purpose of Review This review aims to summarize the current knowledge on the genetic background of dilated cardiomyopathy (DCM), with particular attention to the genotype-phenotype correlations and the possible implications for clinical management.

Recent Findings Next generation sequencing (NGS) has led to the identification of an increasing number of genes and mutations responsible for DCM. This genetic variability is probably related to the extreme heterogeneity of disease manifestation. Important findings have associated mutations of *Lamin A/C (LMNA)* and *Filamin C (FLNC)* to poor prognosis and the propensity to cause an arrhythmic phenotype, respectively. However, a deeper understanding of the genotype-phenotype correlation is necessary, because it could have several implications for the clinical management of the patients. Furthermore, the correct interpretation of pathogenicity of mutations and the clinical impact of genetic testing in DCM patients still represent important fields to be implemented.

Summary A pathogenic gene mutation can be identified in almost 40% of DCM patients. The recent discoveries and future research in the field of genotype-phenotype correlation may lead to a more personalized management of the mutation carriers towards the application of precision medicine in DCM.

Keywords Dilated cardiomyopathy · Next generation sequencing · Genotype-phenotype correlation · Lamin A/C · Filamin C · Precision medicine

Abbreviations

ARVC	Right ventricular arrhythmogenic cardiomyopathy
DCM	Dilated cardiomyopathy
DES	Desmin
DMD	Dystrophin
DSP	Desmoplakin
FLNC	Filamin C
HCM	Hypertrophic cardiomyopathy
ICD	Implantable cardioverter defibrillator
LDB3	LIM domain binding 3
LMNA	Lamin A/C

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LVEF	Left ventricular ejection fraction
LVRR	Left ventricular reverse remodeling
MYH7	Beta myosin heavy chain
MYBPC3	Myosin binding protein C3
MYPN	Myopalladin
NEBL	Nebulette
NEXN	Nexilin F-actin binding protein
NGS	Next generation sequencing
OBSL1	Obscurin like 1
RBM20	RNA-binding motif protein-20
RCM	Restrictive cardiomyopathy
SCD	Sudden cardiac death
SCN5A	Sodium channel protein type 5 subunit alpha
TNNT2	Cardiac troponin T2
TPM1	Tropomyosin
TTN	Titin
VUS	Variant of uncertain significance

Introduction

Dilated cardiomyopathy (DCM) is a complex disease with a detectable pathogenic gene mutation in almost 40% of the cases [1]. On the other hand, a complex interaction between environmental triggers (such as tachyarrhythmias, alcohol, chemotherapy, inflammation) and specific genetic backgrounds can lead to the dilated phenotype. The high heterogeneity of genes and mutations involved in the pathogenesis of DCM represents the current state of knowledge and, at the same time, a great challenge for future research. Even if the role of genetic testing in relatives has been established, the correct interpretation of pathogenicity of mutations, an extended comprehension of the genotype-phenotype correlation and the real impact of a genetic testing in DCM patients still represent important gaps of knowledge. Contemporary, a guide to the management of mutation carriers is advocated. This review explores all these aspects, with particular attention to their impact on the clinical approach to DCM patients.

Next Generation Sequencing: the Basis for a Growing Knowledge

Next generation sequencing (NGS) has significantly changed the approach to Mendelian diseases in cardiovascular medicine, through simultaneous sequencing of billions of DNA molecules, thus outweighing the time-consuming Sanger sequencing [2]. Nevertheless, Sanger technique is still used to confirm mutations, because of incomplete coverage of exons and reduced accuracy of NGS in characterizing certain genomic regions, such as long repeated sequences [3].

The novel rapid sequencing technology increased the spectrum of known pathogenic genes in DCM [4••], together with the creation of large datasets collecting exome-sequencing data from large-scale sequencing projects, such as the Exome Aggregation Consortium (ExAC - http://exac.broadinstitute.org), the Human Gene Mutation Database (HGMD - https://portal.biobase-international.com/hgmd/pro/), or ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), which serve as a comparative tool for newly identified variants. In early 2017, genetic data from 123,136 individuals sequenced by whole-exome sequencing and 15,496 individuals sequenced by whole-genome sequencing was made available by the Genome Aggregation Database investigators (gnomAD - http://gnomad.broadinstitute.org), which is the largest and most comprehensive source of genetic information of individuals of different ethnic backgrounds to date.

A wide range of gene panels are now available for analysis in clinical laboratories [5]. The selection of the genes to be included in these panels is debated as the genetic landscape of DCM is the most heterogeneous among cardiomyopathies. The decision may be guided by the experience of every single center. However, standard "core" panels with a large coverage (> 95%) should be shared between centers with high expertise.

Noteworthy, the growing knowledge provided by NGS is challenging to manage in clinical practice. Parallel to the spread of NGS, a growing number of rare variants have been identified [6], leading to a continuously evolving spectrum of pathogenic variants and genes [7, 8] involved in the DCM pathogenesis. Defining the pathogenicity of a certain variant is a complex process that finally leads to label the variant as pathogenic, likely pathogenic, of uncertain significance, likely benign and benign through different processes: (I) segregation analysis within families, (II) investigation of prior reports of disease association with the indexed variant, (III) assessment of its rarity in a control population, and (IV) analysis of biochemical characteristics and in silico predictive algorithms [9]. Moreover, a tool called InterVar has been recently developed to help human reviewers interpret the clinical significance of variants. InterVar can take a pre-annotated or VCF file as input and generate automated interpretation on 18 criteria [10].

Gene Diversity in DCM Background

Currently, more than 50 genes have been related to the pathogenesis of DCM [11], and overall, a causative variant has been identified in approximately 40% of familial DCM [12]. Nevertheless, also sporadic forms show a genetic background [13–15], and their familial distribution can often be missed by mean of family history alone, due to incomplete penetrance, and variable expression and age of onset of the disease [16].

The various genes implicated in DCM encode for proteins acting at different levels in the cardiomyocyte (Fig. 1). Titin

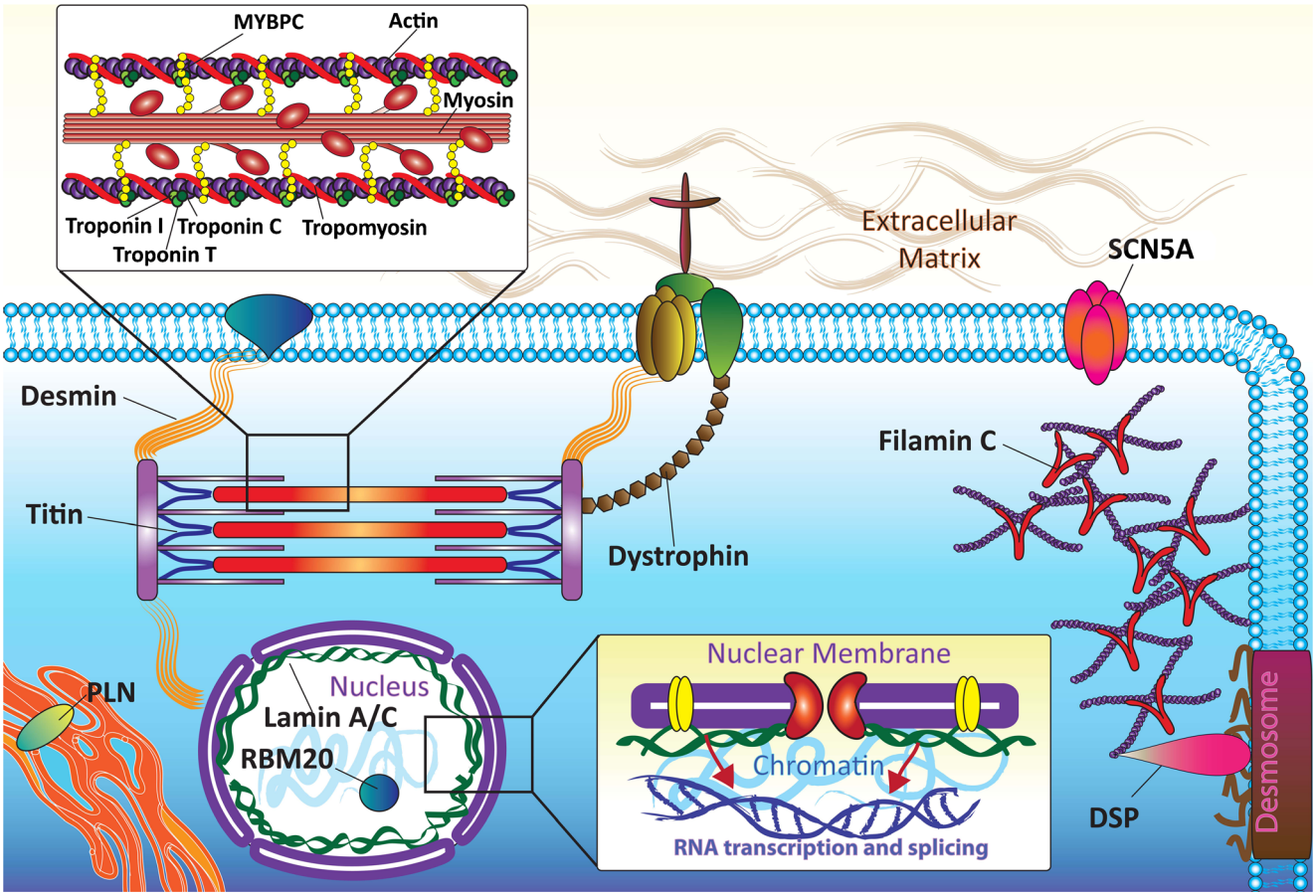

Fig. 1 Drawing of cardiomyocyte indicating multiple sites of abnormal gene products associated with DCM. (RBM20 = RNA-binding motif protein-20; DSP = desmoplakin; PLN = phospholamban; MYBPC3 = myosin binding protein C)

(*TTN*) is known as the largest sarcomeric protein that resides within the heart muscle. *TTN* is the most common gene involved in causing DCM. *TTN* truncating variants account for 19–25% of familial and 11–18% of sporadic forms [17]. However, not all *TTN* truncating variants are pathogenic, but they are also found in 2–3% of healthy population [18]. Besides *TTN*, *Beta Myosin heavy chain* (*MYH7), Cardiac Troponin T (TNNT2),* and *Tropomyosin (TPM1)* are sarcomeric genes most frequently mutated in DCM, with a prevalence of 5–10% [19]. *Myosin Binding Protein C 3 (MYBPC3)* mutations are also found in DCM, but they are more typical for hypertrophic cardiomyopathy (HCM) [20]. Cytoskeletal proteins account for about 11% of DCM cases [21•]. Among these, Filamin C (*FLNC*) is the most representative (4% of DCM and 3% of arrhythmogenic DCM) [22, 23•]. Desmin (*DES*) accounts for 1–2% of DCM mutations [24] and dystrophin (*DMD*) [25] is responsible for X-linked DCM.

A gene with many implications in the clinical management is the nuclear envelope protein Lamin A/C (*LMNA*), which is found in up to 8% of DCM patients [26]. Other genes have been related to DCM, particularly those coding for desmosomal proteins [27], sarcoplasmic reticulum phospholamban (*PLN*), the sodium channel SCN5A, RNA-binding motif protein-20 (*RBM20*) and many others [12].

DCM—a Multifaceted Disease

Three important features characterizing DCM have to be taken into account: (I) the extremely heterogeneous genetic background of the disease, which can lead to (II) overlapping phenotypes and (III) the weaker association with a causative monogenic variant, when compared to other cardiomyopathies, such as hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC).

The heterogeneous genetic background set the basis for the variable phenotypic expression that characterizes DCM. Overlap syndromes have been shown when the dilated phenotype combines with the phenotypic expression of other cardiomyopathies [22]. Moreover, many genes involved in DCM are common in other diseases, mainly ARVC, HCM, restrictive cardiomyopathy (RCM) and channelopathies [16]. For example, the same mutation in the gene coding for Troponin T 2 (TNNT2) has shown variable phenotypic expression

ranging from DCM to HCM and RCM within the same family [28]. The presence of overlapping phenotypes can influence the clinical management and should always be considered.

As already mentioned, incomplete penetrance and variable expression characterize DCM. Besides the genetic diversity, other factors may influence this feature. About 13% of patients show at least 2 mutations [4••] and in many cases the presence of compound mutations has been related to worse prognosis [29, 30]. It is possible that compound mutations cause sporadic or familial forms in which a causative variant cannot be identified. For example, it cannot be excluded that two or more variants of uncertain significance (VUS) in the same proband are disease-causing.

While discussing on DCM heterogeneity, it has to be considered how a concrete modulation of phenotypic expression could be promoted by interfering environmental factors. The presence of a low-grade chronic inflammation is a frequent finding in biopsies or post-mortem samples from genetic cardiomyopathies. Accordingly, a role of inflammation in favoring the expression of an overt phenotype in genetically predisposed subjects has been postulated [31].

Similarly, a genetic predisposition has been shown in toxic, peripartum [32], and tachycardia-induced cardiomyopathy [33]. In particular, variants in genes involved in alcohol metabolism or in pathways modulating anthracycline cardiotoxicity are well known to increase genetic susceptibility to toxic induced cardiac dysfunction [34, 35]. The very recent evidence of a similar prevalence of DCM—causing genes in two population of alcohol-induced cardiomyopathy and of DCM [36], highlights the need for a deeper understanding of genes–environmental interaction in the setting of toxic cardiomyopathy.

The role of the sustained exercise as a modulator of disease penetrance in the presence of a predisposing genetic background is also intriguing. Neurohormonal, mechanical and oxidative stressors that characterize competitive sports may in fact act as triggers for fatal arrhythmias and also for disease progression. This has been well demonstrated in ARVC [37], especially in the setting of desmosomal gene defects that can determine also dilated phenotype [38].

Finally, it is worth to consider environmental interaction not only for its role in promoting and modulating the phenotypic expression of disease, but also for its possible role in determining the prognosis [39]. Future focused research is advocated in order to address those important issues frequently faced in practically managing DCM patients.

Genetic Testing in Probands

When to perform genetic testing in DCM is still a matter of debate. According to guidelines [40], genetic testing should not routinely drive the diagnosis, but could be helpful in the diagnosis of selected borderline or doubtful cases, such as to distinguish left ventricular non-compaction or a left dominant arrhythmogenic cardiomyopathy from DCM. Instead, genetic testing is recommended when its result can lead to a decision, particularly in presence of red flags in personal or family history. For example, a family history of pacemaker implantation or sudden cardiac death (SCD), and the evidence of atrioventricular o intraventricular conduction delay may indicate a *LMNA* mutation [41•], which can eventually lead to early ICD implantation [42]. Nevertheless, the main implication of genetic testing in the proband remains the subsequent cascade genetic screening in relatives.

In the clinical practice, genetic test should be performed in DCM cases without a clear etiology, after having accurately excluded common causes of dilated phenotype (ischemic heart disease, hypertension, myocarditis, toxic, tachycardia) [41•].

Due to the suboptimal sensitivity of a known familial history in the identification of familial (or genetic) DCM, sporadic forms should be also considered for genetic testing especially in presence of particular phenotypic manifestations. Namely, a familial screening of an apparently sporadic DCM case, can lead to the identification of affected relatives, and to the reclassification of DCM clustering. Table 1 provides some recommendations and Fig. 2 shows a feasible algorithm for genetic testing in clinical practice.

Genetics in DCM: Implications for Relatives

A cascade familial genetic screening should follow the identification of a specific mutation in the proband [40, 43, 44]. The major goal of genetic testing is indeed the identification of at-risk relatives who share the same genetic predisposition of the proband. As autosomal dominant is the most frequent pattern of inheritance, a 50% probability of gene mutation transmission is expected [1].

Familial genetic screening can be helpful in obtaining an early diagnosis, in order to start therapeutic interventions stopping the progression of the disease and preventing complications. This is important, especially following the evidence of improved long-term clinical outcome in relatives, mostly attributable to the anticipation of diagnosis and treatment [45]. Furthermore, familial screening may add information on inheritance modality, penetrance of disease, and phenotype traits, which is helpful for the subsequent disease management. This aspect is relevant, mostly due to the variable expressivity of mutations either in the same gene or in different genes, within and between families [4••].

According to guidelines, genetic testing is recommended for first-degree relatives, starting from age of 10–12 years, when a specific mutation is identified in the proband [40], although earlier testing could be considered in laminopathies

Table 1 Recommendations for genetic testing in DCM

Probands	When?		Recommendation
	- Red flags:	- Conduction disease (various degree AV-block, intraventricular conduction delays) - Major ventricular arrhythmias - Family history of SCD - Skeletal muscle involvement (muscle weakness, elevated CK) - EKG abnormalities (posterolateral pseudonecrosis) - Echocardiographic abnormalities (posterolateral akinesia)	Recommended
	- Familial DCM		Recommended
	- Sporadic DCM after excluding secondary causes (i.e. ischemic heart disease, hypertension, myocarditis, toxic, tachycardia)		Can be useful
Relatives	When?		Recommendation
	- First-degree relatives, if a specific gene mutation is identified in the proband		Recommended (from age of 10–12 years)
	- Family history of SCD in a first-degree relative		Can be useful

AV, atrioventricular; DCM, dilated cardiomyopathy; SCD, sudden cardiac death

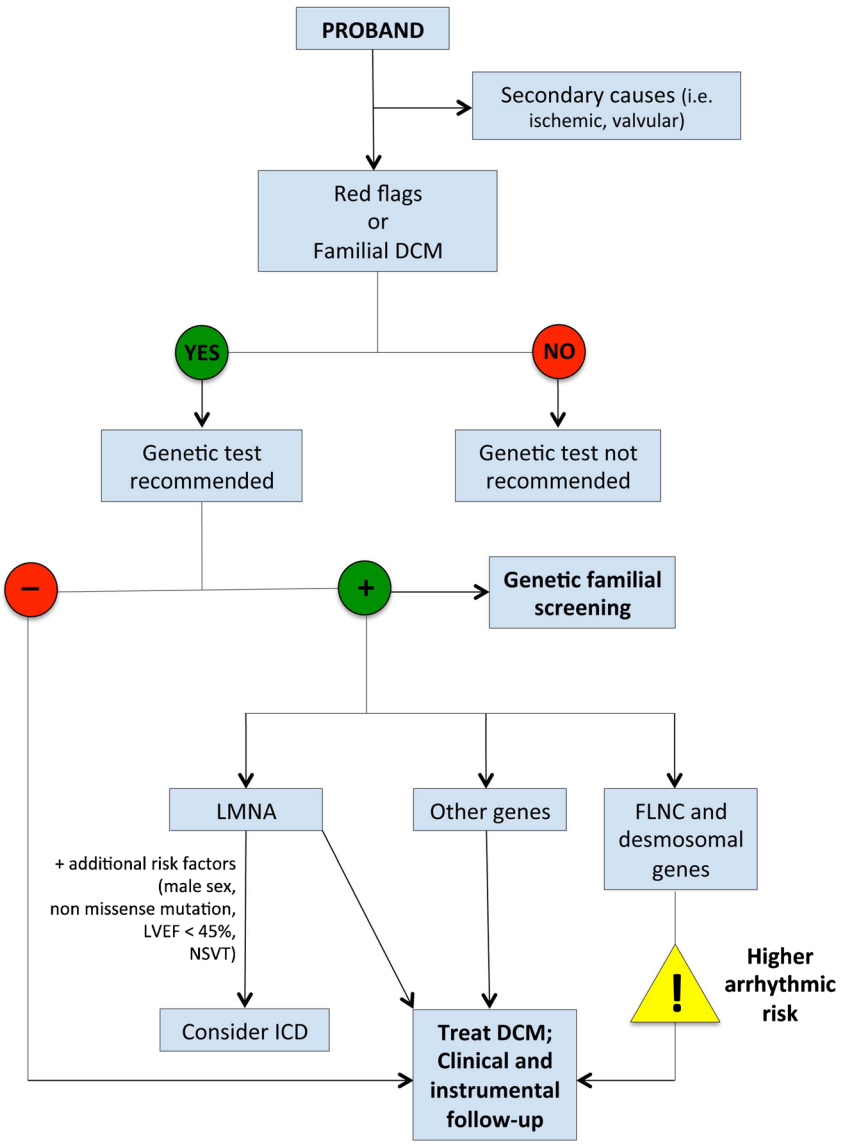

Fig. 2 Flow chart of genetic screening in DCM probands and relatives (dilated cardiomyopathy = DCM; ICD = implantable cardioverter defibrillator; LMNA = lamin A/C; LVEF = left ventricular ejection fraction; NSVT = non-sustained ventricular tachycardia)

[46] (Table 1). Sanger sequencing may be used to identify the indexed mutation, instead of performing a complete NGS panel.

Asymptomatic carriers of the indexed mutation deserve frequent clinical surveillance, by mean of medical history, physical examination, electrocardiogram, echocardiogram and, when appropriate, Holter-ECG and exercise testing. Re-evaluation should be performed every year between the age of 10 and 20 years and then every 1–3 years until the fifth or sixth decade of life, to detect also late-onset disease [40].

The detection of a preclinical phenotype, such as left ventricular enlargement in the absence of systolic dysfunction [47], should warn the clinician about the higher probability of developing an overt phenotype in presence of positive genotype.

However, currently there are no guidelines recommendations about starting therapy in genotype positive-phenotype negative relatives. Medical therapy with an angiotensin-converting-enzyme inhibitor (ACEi), in fact, should be started after the development of left ventricular dysfunction, either asymptomatic or symptomatic [42]. An exception is represented by *LMNA* mutations, which justify an invasive therapeutic approach despite the absence of clinical manifest disease in selected cases (see below, in dedicated paragraph). Moreover, mutation carriers should be informed about the transmission of mutation and the possibility that a pregnancy could unmask an overt phenotype.

Despite obvious benefit of genetic screening in relatives, the clinician has to deal with many limitations: (I) the incomplete penetrance and the variable age of onset of the disease make it impossible to predict whether and when a relative will develop the overt phenotype, although some mutations, such those affecting *LMNA*, have been associated to higher penetrance and severe phenotype [26, 48•]; (II) similarly, there is uncertainty about the severity of the disease, because of variable expressivity and poor information on genotype-phenotype correlation; (III) the difficult interpretation of the result of genetic testing, due to increasing frequency of VUS; (IV) although repeated screening in non-carrier relatives is not recommended, it is not possible to certainly exclude a pathogenic evolution, because of scarce knowledge on the role of environmental factors and predisposing gene variants that can coexist.

Future research should be focused on identifying early predictors of disease. In this sense, reduced global longitudinal strain represents the most promising tool in detecting subtle abnormalities in myocardial contraction [49]. The role of early initiation of therapy in preclinical phenotype for delaying or preventing disease development should also be established, but clinical trials are needed for this scope.

Genotype-Phenotype Correlation: Clinical Implications of Genetics

The expansion of clinical genetic testing by NGS-extended panels has increasingly allowed to identify genetic causes of DCM. However, in this transitional phase, the large spectrum of genes detected in DCM has led to a certain state of confusion [1]. Indeed, if the goal of the genetic characterization in DCM patients is to understand the relation between specific genotypes and disease expression, this is not always possible [50]. Although currently, genotype transposition to clinical management has important above-mentioned limitations, it would be useful for early diagnosis, prognostic stratification and targeted therapy in probands. Only few exceptions for genotype-phenotype correlation have been detected and classified in possible malignant forms of DCM. In the next paragraphs and in Table 2, an analysis on DCM genotype-phenotype correlation is reported.

Lamin A/C (LMNA)

LMNA is the gene with the strongest known association with a specific phenotype, and for this reason it is the only one mentioned in the current guidelines. Lamins are type V intermediate filament proteins and they are components of the cell nuclear envelope, interacting with membrane-associated proteins [26]. Lamins play an important structural role in different kind of cells, and they are involved in controlling the gene expression through the regulation of RNA transcription and splicing [26, 66]. Laminopathies are human diseases associated with *LMNA* mutations. In this category are included: lipodystrophy syndromes (i.e., Hutchinson–Gilford progeria syndrome), neuromuscular disorders (i.e., autosomal Emery-Dreifuss, Charcot-Marie-Tooth neuropathy, limb-girdle muscular dystrophies) and cardiac abnormalities [67]. Human disorders caused by *LMNA* mutations are considered as a continuum, with numerous overlapping of clinical manifestation [67]. Particularly, mutations of *LMNA* are associated with a cardiac phenotype characterized by DCM with early onset (between 30 and 40 years) of conduction disturbances, atrial fibrillation (AF), major ventricular arrhythmias and SCD, even without systolic left ventricular (LV) dysfunction [48, 50, 68]. The penetrance of the phenotypic expression is generally complete at the age of 70 [69]. The risk of ventricular arrhythmias and SCD in DCM patients with *LMNA* mutation has been significantly related to non-missense variants (insertion, deletion, truncations or mutations affecting splicing) versus missense variants [51]. In conclusion, *LMNA*-related DCM is a highly penetrant and age-dependent malignant disease, with high rates of major cardiac events (with a mortality rate of 12% at 4 years and up to 30% at 12 years) and frequent requirement of heart transplantation even by age 45 [70].

Table 2 Genotype-phenotype correlations: actual and evolving knowledge on genotype-phenotype correlation in the field of DCM

	Gene	Variant type in respect to effect on protein structure	Phenotype	Guidelines recommendations	References
Actual knowledge	*LMNA*	Truncating Non-missense	- AV-blocks, intraventricular conduction delays, supraventricular and ventricular arrhythmias, SCD; - Young age of onset and high penetrance; - Frequent requirement of heart transplantation.	Class IIa level of evidence B for ICD implantation in presence of risk factors (NSVT during ambulatory electrocardiogram monitoring, LVEF < 45% at first evaluation, male sex and non-missense mutations).	[42, 51]
Evolving knowledge	*TTN*	Truncating	- LVRR rate ≥ 50%; - Ventricular arrhythmias; - Cardiac fibrosis; - Reduced hypertrophy.	N/A	[17, 52, 53•, 54]
	FLNC	Truncating	- Ventricular arrhythmias and SCD; - LV inferolateral subepicardial /transmural fibrosis; - Overlapping phenotype with left dominant arrhythmogenic cardiomyopathy; - Right ventricular involvement; - Lower rate of LVRR.	N/A	[23, 55]
	DSP	Truncating	- Ventricular arrhythmias; - Right ventricular involvement; - LV fibrosis.	N/A	[56]
	DES	Missense Truncating	- Conduction system disease (various degree AV-block); - Ventricular arrhythmias and SCD; - Probably LV fibrosis;	N/A	[57, 58]
Conflicting evidence	*PLN*	Arg9Cys (Missense) Arg14del (Truncating)	- Early progressive HF and heart transplantation; - Ventricular arrhythmias.	N/A	[59–62]
	SCN5A	Arg222Gln (Missense)	- Ventricular and supraventricular arrhythmias (particularly AF); - AV-block.	N/A	[63]
	RBM20	Truncating Missense	- Supraventricular arrhythmias (particularly AF); - High penetrance; - Progressive HF.	N/A	[64, 65]

AF, atrial fibrillation; AV, atrioventricular; DCM, dilated cardiomyopathy; DES, desmin; DSP, desmoplakin; FLNC, filamin; HF, heart failure; ICD, implantable cardioverter defibrillator; LMNA, lamin; LV, left ventricle; LVEF, left ventricular ejection fraction; LVRR, left ventricular reverse remodeling; PLN, phospholamban; SCD, sudden cardiac death; RBM20, RNA-binding motif protein-20; TTN, titin

For these reasons, relevant clinical decision and recommendation are implicated when a *LMNA* mutation is detected in a DCM patient. First of all, restriction from competitive sports at any age is recommended [70]. Furthermore, *LMNA* is the only gene that has gained an indication for primary prevention ICD in the current guidelines. The ICD recommendation is valued in the presence of certain additional risk factors: non-sustained ventricular tachycardia during ambulatory electrocardiogram monitoring, left ventricular ejection fraction (LVEF) < 45% at first evaluation, male sex and non-missense mutation [51]. Eventually, in patients receiving an ICD, it has to be considered an atrial lead placement, although without criteria for dual-chamber pacemaker implantation [71].

Filamin C (FLNC)

Filamin C is a cytoskeletal (intermediate filament) protein that has been implicated in a series of skeletal myofibrillar myopathies involving the myocardial muscle, but also in isolated forms of DCM [72, 73], HCM [74] and RCM [75]. FLNC is one of the largest Z-disc proteins that crosslinks actin filaments in a three-dimensional actin web and anchors them to proteins and ion channels of the membranes, acting as the main contributor for sarcomeric and Z-disk stability [76, 77]. Additionally FLNC seems also involved in the connection between actin and intercalated discs [75]. *FLNC* truncating mutations have been associated with an alteration of cell-to-cell adhesion, also confirmed in the buccal mucosa of carriers, and with an increased deposition of fibrotic tissue between

cardiomyocytes, detectable as subepicardial-transmural fibrosis in inferolateral LV wall [23•]. *FLNC* truncating mutations are associated with a high predisposition to malignant ventricular arrhythmias and SCD [23•]. In a small cohort of *FLNC* mutation carriers, it has been reported an incidence of 15–20% of malignant ventricular arrhythmias/SCD and a rate mortality of 6% in a median follow-up of 5 years [23•]. In a smaller proportion of carriers (< 5%) also a biventricular dysfunction and dilatation has been recorded [23•]. The severe arrhythmogenic DCM phenotype caused by FLNC truncating mutations has been compared to the left dominant arrhythmogenic cardiomyopathy, with a high risk for potentially lethal ventricular arrhythmias and the consequential necessity of considering the implantation of an ICD [22].

Desmoplakin (DSP) and Other Desmosomal Genes

Desmoplakin is an intracellular component of desmosomes, interacting on one side with desmin and filamin and with plakophilin and plakoglobin on the other side. Mutations of *DSP* and the others desmosomal genes have been initially related to ARVC, but new evidences have demonstrated also a correlation with DCM [27]. Frameshift and nonsense mutations in *DSP*, impairing the intercellular junctions, could induce a predominant involvement of left ventricle with fibrosis and dysfunction in a high arrhythmic phenotype, with or without right ventricular involvement [56]. Further observational studies inherent to the prognosis and the clinical manifestation of *DSP* and desmosomal genes mutation carriers are needed. Desmosomal gene mutations, together with *LMNA* and *FLNC* variants have been the main cause of the so-called arrhythmogenic cardiomyopathy, an emerging disease entity, with overlapping genotypic and phenotypic aspects between DCM and ARVC, mainly characterized by life-threatening arrhythmic patterns [78].

Titin (TTN)

TTN is a giant sarcomeric muscle protein, localized between Z disc and M band in cardiomyocytes, establishing the passive elasticity of the tissue and mechano-sensing signaling [79]. The determinant role of *TTN* truncating mutations in the pathogenesis of DCM has been largely recognized [17]. Indeed, titin missense variants nowadays are considered mostly as benign, with very few exceptions [55, 80].

Incomplete penetrance and variable disease manifestations are the main characteristics of DCM induced by *TTN* truncating variants, with mild phenotypes most represented [17, 52]. However, it has been described that such mutations can develop an arrhythmogenic phenotype of DCM [53•, 54]. In recent studies, it has been noted an increased propensity to life-threatening ventricular arrhythmias of *TTN* truncating carriers in the presence of additional environmental factors [53•, 54]. Alterations in mitochondrial function, increased interstitial fibrosis and reduced ventricular hypertrophy have been found in the heart tissues of these patients, which could explain the higher risk of major arrhythmias [53•]. However, an impact on prognosis, in terms of death or heart transplantation, has not yet been demonstrated [53•, 54]. Future and additional data are needed in this field.

Desmin (DES)

Another important intermediate filament of the cardiomyocytes cytoskeleton is the desmin. As well as filamin, in the cytoplasm desmin interacts with desmosomes and Z-bands, but also with mitochondria and nuclei, playing a relevant role in the cell structure integrity [81].

DES mutations cause a heterogeneous spectrum of muscles diseases by involving skeletal muscles, myocardial tissue or both [82]. Desmin myopathy, a distinct subgroup in the family of myofibrillar myopathies, is a rare disease characterized by muscle weakness, initially distal, which usually begins in middle age [24]. The cardiac involvement of DES mutations can manifest with different phenotype, such as DCM (almost 1–2% of all DCM cases [24]), RCM, HCM, ARVC or their combinations, with high frequent involvement of the conduction system, leading to atrioventricular blocks [57, 58] and probably with diffuse level of LV fibrosis (unpublished).

Phospholamban (PLN)

Phospholamban is a transmembran protein involved in the cytoplasmic calcium homeostasis by the inhibition of the sarcoplasmic reticulum calcium transporting ATPase (SERCA2a) [1]. Multiple *PLN* dominant mutations have been described with variable phenotypes of DCM [59, 61]. A high percentage of *PLN* mutation carriers in some population have been recorded (15% cases of DCM in the Netherlands) [62]. Particularly two mutations are associated with DCM: Arg9Cys with a severe phenotype and an early progressive HF and heart transplantation [59, 60]; Arg14del with an early onset arrhythmic DCM characterized by malignant ventricular arrhythmias [62, 83–86]. Interestingly, Arg14del has been also described in some desmosome mutation-negative ARVC cases [62], perhaps depending on the genetic background [85, 86].

Sodium Channel Protein Type 5 Subunit Alpha (SCN5A)

SCN5A is the principal cardiomyocytes membrane sodium channel. Dominant *SCN5A* mutations have already been described in long QT and Brugada syndrome, two arrhythmic diseases [87]. Also familial forms of DCM characterized by higher risk of atrial and ventricular arrhythmias and

atrioventricular blocks have been associated with missense mutation in *SCN5A* [63]. The underlying mechanisms of *SCN5A* mutations pathogenicity in DCM carriers seem to be a primary dysfunction in electrical excitability in cardiomyocytes that induces a secondary ventricular dysfunction and dilatation [6, 20].

RNA-Binding Motif Protein-20 (RBM20)

RBM20 is considered as a gene with similar characteristics of *LMNA*, highly penetrant and pro-arrhythmogenic [12]. Dominant mutations in the *RBM20* gene have been described in approximately 1–5% of familial DCM [64, 88]. RBM20 is a nuclear RNA-binding protein, mainly expressed in the myocardial muscle of both atria and ventricles, with the important function of regulating the splicing of genes involved in cardiac development, such as *TTN*, *MYH7* and *TNNT2* [65, 89]. Latest literature data suggest a possible worse outcome with a fast progression of heart failure and high risk for arrhythmias (in particular AF) in *RBM20* mutation carriers [4••, 64, 65]. In the next future, an early identification of these gene mutations could represent an important step for pre-symptomatic interventions, as *LMNA*.

Left Ventricular Reverse Remodeling (LVRR) and the Need of Multiparametric Prognostic Risk Scores

In addition to the high arrhythmic risk, the outcome of DCM patients can be influenced by the progressive dilatation and dysfunction of the left ventricle leading to heart failure and heart transplantation [90, 91]. However, DCM has been recognized as a dynamic disease, with a reverse remodeling (LVRR) in about 40% of the cases. LVRR can be spontaneous or induced by phararmacological and non-pharmacological therapies and can significantly improve the prognosis of DCM patients [92]. Since the underlying mechanisms are largely unknown, initial studies are investigating the possible interaction between genetic background and response to therapy, in term of LVRR. In particular, mutations in cytoskeleton Z-disk genes (*DES*, *FLNC* and dystrophin [*DMD*], obscurin like 1 [*OBSL1*], nexilin F-actin binding protein [*NEXN*], myopalladin [*MYPN*], nebulette [*NEBL*], LIM domain binding 3 [*LDB3*]) have been associated to a lower rate of LVRR in a cohort of 152 DCM patients [21]. The strong impact of cytoskeleton Z-disk genes mutations on LVRR has been additionally confirmed by comparison with previously reported clinical predictors of LVRR [21].

The prognostic stratification of DCM patient is challenging, especially in the first phases of the disease. Despite the significantly improved DCM prognosis in the last decades [93], some patients are still rapidly doomed to ominous outcome. In this perspective, the development of multiparametric scores to improve the accuracy of early arrhythmic and LVRR prediction appears pivotal for the implementation of DCM management. A detailed clinical evaluation associated to a complete bio-humoral (including biomarkers) and instrumental evaluation by ECG, Holter-ECG, echocardiography (including echo 3-D and speckle tracking) and cardiac magnetic resonance (including quantification of late gadolinium enhancement and new techniques as T1 mapping or feature tracking analysis), cardiopulmonary exercise testing, should be comprehensively analyzed. The genotype-phenotype correlations and the pathways linking genetic background to environmental factors should be largely elucidated in the next future in order to include the early genetic characterization in multiparametric prognostic scores. Those scores should be rapidly applicable to each DCM patient, in order to obtain a more personalized therapy and an addressed periodic risk re-assessment [92].

Future Perspectives: Towards the Precision Medicine

Contractile function, force transmission, maintaining of cell and membrane structures, homeostasis of cytoplasmic ions and transcriptional regulation are all possible altered by specific gene mutation that could provide the dilated phenotype. Trying to understand the mechanisms by which each single gene mutation can induce the predisposition to heart failure or life-threatening arrhythmias is challenging. However, it is a key-point in order to further improve survival rates of DCM patients. In the last years a new possible approach to this complexity is arising. The application of the precision medicine to the management of DCM patients is intriguing. In each patient, different genes, although with different functions and roles in the cell balance, could lead to a common phenotype of DCM by interfering with a "final common pathway" [94, 95]. Indeed, the characterization of the components of a pathway could support novel pathway-specific therapies, which could interrupt the disease progression. For instance, relevant advances have been made in the pharmaceutical field of the laminopathies. ARRY-797 is a new molecule targeting *LMNA*, which showed promising results in a phase II clinical trial. This molecule is an inhibitor of the p38-MAPK pathway, which is upregulated in LMNA deficiency and induced by a strong cellular stress signals produced by the loss of function of LMNA proteins (*NCT02057341*). Furthermore, incremental knowledge on these signaling pathways could explain how environmental factors can affect disease phenotype and prognosis induced by specific gene mutations.

Conclusions

In the recent years, due the implemented knowledge of the genetic bases of DCM, the approach to clinical management of the disease is significantly changing. The fill of some remaining gaps of knowledge (namely the pathogenic role of certain mutations, the genotype-phenotype interaction, the identification of common pathways, and the interplay of specific gene mutations with environmental factors) represents important challenges in order to implement the early risk stratification and the therapeutic strategies. The final direction is towards the application of the precision medicine to DCM.

Compliance with Ethical Standards

Conflict of Interest Alessia Paldino, Giulia De Angelis, Marco Merlo, Marta Gigli, Matteo Dal Ferro, Giovanni Maria Severini, Luisa Mestroni and Gianfranco Sinagra declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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