Published in final edited form as:

Circ Res. 2017 September 15; 121(7): 731–748. doi:10.1161/CIRCRESAHA.116.309396.

Dilated cardiomyopathy: genetic determinants and mechanisms

Elizabeth M McNally[1] and **Luisa Mestroni**[2]

[1]Center for Genetic Medicine, Northwestern University Feinberg School of Medicine, Chicago IL

[2]Cardiovascular Institute, University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Abstract

Nonischemic dilated cardiomyopathy often has a genetic etiology. Because of the large number of genes and alleles attributed to dilated cardiomyopathy, comprehensive genetic testing encompasses ever-increasing gene panels. Genetic diagnosis can help predict prognosis, especially with regard to arrhythmia risk for certain subtypes. Moreover, cascade genetic testing in family members can identify those who are at-risk or with early stage disease, offering the opportunity for early intervention. This review will address diagnosis and management of dilated cardiomyopathy, including the role of genetic evaluation. We will also overview distinct genetic pathways linked to dilated cardiomyopathy and their pathogenetic mechanisms. Historically, cardiac morphology has been used to classify cardiomyopathy subtypes. Determining genetic variants is emerging as an additional adjunct to help further refine subtypes of dilated cardiomyopathy, especially where arrhythmia risk is increased, and ultimately contribute to clinical management.

Keywords

congestive heart failure; dilated cardiomyopathy; mutations; lamin A/C; titin; genetic testing; therapy; diagnostic method; arrhythmia

Subject Terms

Cardiomyopathy; Genetics

Prevalence and etiology of dilated cardiomyopathy

Cardiomyopathies are defined as myocardial disorders in which the heart is structurally and functionally abnormal. Morphologically defined subtypes include hypertrophic (HCM), dilated (DCM), arrhythmogenic (AC) and left ventricular noncompaction (LVNC) cardiomyopathies[1, 2], and each of these subtypes can be genetically mediated (Figure 1). DCM is characterized by an enlarged and poorly contractile left ventricle (LV). DCM can be attributed to genetic and nongenetic causes including hypertension, valve disease, inflammatory/infectious causes and toxins[3]. Even these “nongenetic” forms of

Correspondence: Elizabeth M McNally, Center for Genetic Medicine, Northwestern University, Feinberg School of Medicine, elizabeth.mcnally@northwestern.edu; Luisa Mestroni, Cardiovascular Institute, University of Colorado Anschutz Medical Campus, 12700 E 19th Ave # F442, Aurora, Colorado 80045-2507 (USA), Luisa.Mestroni@ucdenver.edu.

Disclosures: EMM is a consultant to Invitae; LM is consultant to Array Biopharma.

cardiomyopathy, can be influenced by an individual's genetic profile and, furthermore, mixed etiologies may be present. In DCM, the degree of LV systolic dysfunction is variable, and LV systolic dysfunction is often progressive. DCM is a major risk factor for developing heart failure (HF) as the presence of reduced systolic function does not imply symptoms. Notably, DCM is often associated with an increased risk of severe arrhythmia indicating the pathological involvement of the cardiac conduction system.

Randomized clinical heart failure trials typically report 30–40% of subjects with a nonischemic DCM compared to ischemic DCM[3]. Clinical trials are evaluating interventions to reduce CHF symptoms, these studies may focus on the later stages of disease. Similarly, a recent survey of hospitalized patients in the United States in which the mean age was 75 years (n=156,013) found that ischemic cardiomyopathy was more common than nonischemic (59% compared to 41%)[4]. Of nonischemic DCM, hypertension accounted for 48% and idiopathic was the next most common at 31%. In this study, individuals with nonischemic DCM were more likely to be female, nonwhite, and younger that those with ischemic cardiomyopathy.

The true prevalence of DCM, and of genetically mediated DCM, is not fully known. An early estimate of DCM prevalence derived from a study carried out from 1975 to 1984 in Olmstead County, MN, USA[5]. This epidemiological study relied on echocardiography, angiography or autopsy evaluation of DCM cases and resulted in a prevalence of 36.5/100,000 individuals, or 1 in 2,700 with a male to female ratio of 3.4 in a European-American population[5]. The prevalence of DCM varies likely reflecting geographic and ethnic differences, as well as the methodologies used[6–10]. Studies from England (8.3/100,000)[11], Italy (7.0/100,000)[12], and Japan (14/100,000)[9], each report similar DCM prevalence. However, the prevalence of DCM is likely underestimated. The prior studies relied on older less sensitive imaging modalities[13]. More recently, Hershberger and colleagues used a different approach to estimate DCM prevalence, based on the known ratio of idiopathic DCM to HCM of approximately 2:1, prevalence estimates of heart failure and prevalence estimates of left ventricular dysfunction as a surrogate for DCM[14]. With this approach, a much higher prevalence of DCM is estimated, in the range of 1:250. Similarly, estimates of *familial* DCM prevalence varies: a meta-analysis of 23 studies found a prevalence estimate of 23% with a range of 2% to 65% indicating a significant heterogeneity in diagnostic criteria, and a frequency progressively increasing over time due to more systematic clinical screening[15]. In the clinical practice and in the current guidelines, the prevalence of familial DCM is assumed to be around 30 – 50%[1, 3, 13, 16–18]. In patients with familial DCM, approximately 40% has an identifiable genetic cause[17]. Also in sporadic DCM pathogenic genetic variants can be identified, although the frequency of genetic causes in this population is not well defined[17].

Clinical diagnosis of DCM

DCM has been defined by the presence of: a) fractional shortening (FS) less than 25% (> 2SD) and/or ejection fraction less than 45% (> 2SD); and b) left ventricular end diastolic diameter (LVEDD) greater than 117% (>2SD of the predicted value of 112% corrected for age and body surface area, BSA), excluding any known cause of myocardial disease[19]. In

the context of a familial DCM, these criteria are used to diagnose the proband in a family[19] and the strategy for evaluation is shown in Figure 2. *Familial* DCM is defined by the presence of: a) two or more affected relatives with DCM meeting the above criteria; or b) a relative of a DCM patient with unexplained sudden death before the age of 35 years[19]. Family members may be classified as *affected*, *unaffected*, or *unknown* when subtle cardiac abnormalities are present but not sufficient for a definitive diagnosis. Less common forms of primary cardiomyopathies are peripartum, tachycardia-induced, stress-provoked Takotsubo cardiomyopathy and myocarditis, according to the 2006 AHA definition and classification[2]. Interestingly, myocarditis and peripartum cardiomyopathy can occur in a familial setting and are believed to have a genetic component[20–22]. Secondary forms of cardiomyopathies, in which cardiomyopathy arises from systemic disorders such as amyloidosis, hemochromatosis, and due to toxicity from agents like doxorubicin are also under genetic influence or may arise due to primary genetic mutations[23, 24]. Neuromuscular disease is also commonly associated with cardiomyopathy, and cardiomyopathy typically arises from the primary responsible genetic mutation exerting pathological effects directly in the myocardium (see below). With the increase in using genetic testing, especially testing in family members, it is now possible to use cardiac imaging modalities to ascertain early features of disease in gene mutation positive individual who do not fully manifest disease. Since many of these studies examine gene positive individuals at one point in time, a full view of DCM is progression has not been delineated. Definitive studies on DCM in progression in genetically at-risk individuals must span many years. Imaging studies have identified chamber size dimensions, strain abnormalities and contrast enhancement each as features of early DCM[23].

Imaging - Echocardiography

To diagnose DCM, LV measurements can be determined using multiple imaging modalities. M-mode and 2-dimensional echocardiography are frequently used to determine LV internal dimensions in systole and diastole (LVIDd, LVIDs, respectively) (Figure 1). It was originally thought that LV dilation occurs in response to reduced function. However, in genetic DCM, where genetic markers make it feasible to monitor LV dimensions over many years, increased LV dimensions typically precede detectable reduction in function[25–27]. This state of LV enlargement is recognized as a prodome to DCM. Enlarged LV dimensions contrast with what is seen in hypertrophic cardiomyopathy (HCM), where the earliest findings in genetically mediated, sarcomere-positive HCM are reduced LV dimensions[28]. Strain and strain rate differences can be detected by echocardiography in first degree relatives of those with newly diagnosed nonischemic DCM, indicating that LV dimensions are not the earliest detectable differences in familial DCM[29, 30].

Imaging - Cardiac Magnetic Resonance (CMR)

LV chamber dimensions and function, including strain measurements, are also accurately determined by CMR imaging. Contrast agents, mainly gadolinium, are used to evaluate fibrosis and therefore provide additional information on myocardial tissue quality. In DCM, the degree of fibrosis, marked by delayed gadolinium enhancement, is a predictor of all-cause mortality and need for future hospitalization[31]. Specifically, delayed enhancement is

associated with increased risk for ventricular arrhythmias[32–34]. Delayed enhancement may also reflect features beyond fibrosis including edema and inflammatory infiltrate[35].

DCM can also be associated with LV noncompaction seen using either echocardiography or CMR. A ratio of greater than 2.3:1 for the noncompacted to compacted layer of LV myocardium is considered abnormal, but notably can be detected in normal hearts[36]. Recent studies have suggested that hypertrabeculation is seen in a high fraction (36%) of adult DCM, although this was not associated with adverse outcomes compared to DCM without these noncompaction features[37].

Endomyocardial Biopsy (EMB)

EMB has been used to confirm etiology in some forms of DCM, although with improved cardiac imaging, EMB is less frequently used. In some settings, for example, iron overload, amyloid, and other infiltrative processes myocardial biopsy may still be highly useful[38]. The complication rates with EMB range from 1–3%, and serious complications including perforation and tamponade occur at 0.5%[38]. EMB has been used to evaluate myocarditis and in the setting of unexplained HF[39, 40]. The nonuniform nature of infiltrative disease limits the sensitivity of myocardial biopsy, as the RV septum is targeted for sampling[41]. For the majority of genetic cardiomyopathies, genetic testing is favored over EMB. Of the genetic cardiomyopathies, ARVC may be evaluated by EMB, although more recent work suggests that alternative and more easily accessible cell types can be used to diagnose ARVC and avoid EMB[42, 43].

Non-invasive arrhythmia monitoring

DCM is associated with an increased risk for cardiac arrhythmias and sudden cardiac death (SCD)[44], and specific genetic DCM subtypes are especially prone to arrhythmias. CMR, especially the identification of delayed enhancement, can help risk stratify for sudden death[34]. Because of increased risk for SCD, there is need for arrhythmia surveillance in order to more appropriately deploy device management, including pacemakers and/or internal cardioverter defibrillators (ICDs). Symptomatic and even life-threatening bradycardia and tachycardia may occur in genetic DCM. Personal history of syncope or near syncope should be ascertained, and patient education to increase awareness of symptoms is needed. Holter monitoring, for its ease, remains a mainstay using 24–48 hour sampling. Other external event recorders are similarly transcutaneous and provide real-time, transmitted data as well as triggered monitoring. External loop recorders and now implantable loop recorders offer longer-term information. Those with familial DCM are likely to have more findings of ventricular ectopy and ventricular tachycardia (VT) on monitoring[45]. For primary prevention of SCD in DCM, risk stratification often relies on evaluating the specific genetic etiology (see below), family history, delayed enhancement and presence of VT on monitoring.

Clinical manifestations including neuromuscular findings

The range of clinical manifestations in DCM ranges from none to overt heart failure. With the increase in familial and genetic screening, it is now more common to identify the minimally to mildly affected stage of DCM in younger individuals. Using genetic markers, strain defects can be detected by echo or CMR. LGE may be present even when the heart appears still normal, suggesting that disease is ongoing. There is an emerging view that this represents an early stage of disease and one in which early institution of treatment should benefit. Although it is generally thought that arrhythmia risk scales with degree of LV dysfunction, for several subtypes of genetic cardiomyopathy, arrhythmias may be the earliest manifestation[46–49]. Specifically, in *LMNA* and *SCN5A*-mediated cardiomyopathies, arrhythmias including atrial fibrillation with slow ventricular response or ventricular arrhythmias may be the presenting finding. There is little in the clinical evaluation that makes it possible to distinguish one genetic subtype of DCM from another. This "phenocopying" is what has driven gene panel testing since with this approach multiple genes are screened at the same time. A DCM gene panel is shown in Figure 3, and a comprehensive list of DCM genes in Table 1.

Neuromuscular disease may accompany cardiomyopathy, and in some forms of neuromuscular disease, the presenting feature may be irregular heart rhythms. *LMNA* mutations can present with or without muscle disease, and the muscle disease ranges from limb girdle muscular dystrophy to Emery Dreifuss Muscular Dystrophy, which is typically associated with contractures of the elbows and Achilles tendons[50]. *LMNA* mutations are inherited in an autosomal manner, seen as multiple affected family members in each generation. Both X-linked and autosomal neuromuscular diseases can also associate with cardiomyopathy, and this includes Duchenne Muscular Dystrophy as well as the autosomal recessive forms of sarcoglycanopathies[51]. In these disorders, skeletal muscle disease usually appears in childhood with a typical dilated cardiomyopathy arising in the teenage years or early twenties. DCM in neuromuscular disease is highly amenable to treatment and responds well to guideline directed medical therapy. Both forms of myotonic muscular dystrophy, type 1 and type 2, can also be associated with DCM[52–55]. Atrial and ventricular arrhythmias are common in these tri- and tetra-nucleotide repeat expansion disorders, and should be aggressively managed. Myotonic dystrophy type 2 usually present in older individuals and in this case, genetic testing panels usually do not include these genes and thus the diagnosis can be easily missed especially if neuromuscular symptoms are not so pronounced.

DCM Genetics

The majority of genetic DCM is inherited in an autosomal dominant pattern with variable expressivity and penetrance (Figure 4), although specific forms of autosomal recessive, X-linked recessive and mitochondrial inheritance each occur[14, 19, 56]. *De novo* mutations also contribute to genetic cardiomyopathy and are defined when neither biological parent carries the offspring's mutation. *De novo* mutations have been described in many different genes, and the presence of a *de novo* variant can be used to define the pathogenic status of genetic variants since the frequency of *de novo* variation in each genome is exceedingly rare. Thus, a

novel mutation introducing a protein altering change in a cardiomyopathy gene is typically considered pathogenic.

Interpreting whether genetic variants are pathogenic is increasing complex, owing to the vast amount of rare variation in each human genome. The emerging consensus around interpretation of genetic variation and its effect on phenotype relies on a classification system ranging from pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign and benign[57]. The availability of large control cohorts provides invaluable information of the frequency of variants, and the largest available data set is currently ExAC (Exome Aggregation Consortium) (http://exac.broadinstitute.org), which collected exome sequencing data of over 60,000 individuals from a series of studies including the 1000 Genomes Project and the Exome Sequencing Project (http://evs.gs.washington.edu/EVS). The current trend is to consider putative pathogenic variants as those that are either unique to the DCM patient or family[58], or extremely rare, (MAF $<1 \times 10^{-4}$)[59]. The recently adopted, more stringent criteria for genetic testing have prompted the reclassification of variants and indicate the needs of a continuous reanalysis of data[58]. The use of whole exome/genome sequencing in clinical laboratories warrants strong criteria to discriminate common variants. At present, genetic testing typically relies on self-reported ethnicity testing, and it is important to match ethnicity between the proband and testing databases. However, at this point, this integration of common and rare variation is not routinely being used in cardiomyopathy genetic testing, potentially contributing to false positive interpretation[60].

DCM is genetically heterogeneous, and DCM genes encode proteins of broad cellular functions. Mutations in genes encoding cytoskeletal, sarcomeric, mitochondrial, desmosomal, nuclear membrane and RNA binding proteins have all been linked to DCM. Thus, the pathological mechanisms that lead to DCM are very diverse. The genes below are listed in order of frequency for their contribution to genetic DCM with focus on the most commonly implicated genes and their mechanism of action if known.

TTN

The discovery of the role of *TTN* truncating variants in DCM has been major advance[61]. The *TTN* gene encodes the giant protein titin, which is the largest known protein expressed in the heart. Titin functions as a spring, providing passive force and regulating sarcomere contraction and signaling[62]. Titin is a large ~35,000 aa protein that spans half the length of the sarcomere from Z-disc to M-band, and is referred to as a “third” filament with the thin and thick filaments that comprise the sarcomere. Proposed as a molecular rule for the sarcomere, titin has domains that can accommodate passive stiffness[63]. Titin’s I band region includes the PEVK (proline-glutamate-valine-lysine) repetitive region, which is thought to directly regulate passive tension. The I band region of the *TTN* gene is encoded by 220 of TTN’s 360 exons. The large size, repetitive nature, and extensive alternative splicing of *TTN* makes it challenging for genetic analysis. The PEVK region is just carboxyl to the N2A and N2B regions that interact with the FHL (four and half LIM protein), identified as a modifier for HCM[64]. Notably, *TTN* is differentially spliced throughout heart development and adaptively to distinct physiological states including HF[65]. The larger N2A form is associated with a more compliant ventricle (Figure 5). In contrast, the smaller N2B form lacks more of

the repetitive units and is associated with stiffer heart. Deep RNA sequencing of *TTN* from failed hearts suggests highly variable exon usage in this region consistent with even subtler defects in cardiac elasticity that may be variable across regions of the LV[66].

Using a *TTN* specific array designed to capture all *TTN* exons, it was shown that truncating variants of *TTN* contribute to 20–25% of nonischemic DCM[61]. Prior to this, only a few missense *TTN* variants had been described linked to DCM[67]. Induced pluripotent stem cells (iPSC) differentiated into cardiomyocytes in culture demonstrate a paucity of sarcomeres, suggesting that force may be impaired directly through sarcomere loss in *TTN* truncations[68]. In these studies and others it has been shown that *TTN* truncations are observed at a low frequency in the general population, ranging from 1–3%[61, 66, 69]. There is a tendency for *TTN* truncations in DCM to distribute to the A band, rather than the I band[66], and *TTN* truncations can also be associated with mild DCM[70]. A recent study showed that truncating variants in the general population are linked to eccentric cardiac remodeling, suggesting that *TTN* truncations may be “at-risk” alleles[71].

Peripartum cardiomyopathy is a heterogeneous syndrome of mixed etiology. Yet a subset of peripartum cardiomyopathy is attributable to *TTN* truncating variants[72, 73]. Peripartum cardiomyopathy can be associated with recovered LV function after pregnancy. Moreover, the observation that *TTN* truncating variants can be associated with recovery of function in DCM after LV assist device (LVAD) placement also suggests a dynamic state of *TTN* truncating variants[74]. Additional genes with mutations beyond *TTN* have also been described in peripartum cardiomyopathy[21]. Overall, the presence of *TTN* truncating variants in the general population argues for caution in interpreting these variants and again underscores the importance of familial segregation analysis. At this point, until more is known, the presence of a *TTN* truncation variant should trigger at least intermittent cardiac imaging and management aimed at reducing other stressors to the heart.

TTN has a high prevalence of missense variants, both rare and common[75]. *TTN* missense variants have been reported in ARVC and other forms of cardiomyopathy[67, 75–78]. Additionally, *TTN* missense variants have also been reported in skeletal myopathy, including the common tibial myopathy[79, 80]. The enormous number of *TTN* missense variants makes these variants exceedingly complex to interpret in the context of broad genetic testing on individuals with DCM.

Zebrafish have been used successfully to model myopathies due to *TTN* mutations, demonstrating both cardiac and skeletal muscle defects[81]. A mouse models with an in frame deletion in the PEVK region of *TTN* develops diastolic dysfunction, consistent with the complex role of titin for both systolic and diastolic dysfunction[82]. In both rats and mice with heterozygous *TTN* truncation mutations, additional stressors like transaortic constriction are used to promote the development of DCM[71, 83].

LMNA

LMNA missense and truncating mutations account for 5–8% of genetic DCM[84, 85]. Like *TTN*, *LMNA* mutations are inherited in an autosomal dominant manner. The single *LMNA* gene encodes lamins A and C, and differential splicing at the 3′ end results in two proteins

that are identical across their first 566 amino acids; mutations in *LMNA* lead to a constellation of diseases from premature aging, to myopathies and DCM[86]. Mutations that alter processing of lamin A lead to accumulation of prelamin A (sometimes called progerin) and these have been associated with the premature aging syndrome Hutchinson Gilford Progeria[87]. *LMNA* mutations linked to autosomal dominant DCM are both missense and frameshifting in nature, and these mutations may occur anywhere along the length of the coding region. DCM-associated mutations are not specifically associated with Prelamin A accumulation; thus, the basic mechanisms underlying the premature aging syndrome versus DCM appear to be distinct. The mechanisms responsible for autosomal dominant DCM *LMNA* mutations may be a mix of multiple defects including dominant-negative function as well as haploinsufficiency[88, 89]. Lamins A and C are implicated in many different cellular processes from regulating gene expression, mechanosensing, DNA replication, and nuclear to cytoplasmic transport.

Loss of *LMNA* leads to a defect in mechanosignaling[90, 91]. Mechanosignaling defects were observed in cell with a homozygous deletion in the mouse *Lmna* gene. Male mice heterozygously deleted for *Lmna* exhibit cardiomyopathy features in later life, suggesting that mice can be used to model laminopathy[92]. In *LMNA* associated adult-onset DCM, the mTOR pathway can be activated and, in animal models, inhibition mTOR by temsirolimus or rapamycin was able to rescue the DCM phenotype[93, 94]. Mitogen activated protein kinase (MAPK) signaling is increased in these models, leading to clinical trials testing compounds aimed at reducing this signaling[95]. Recently, early phase, encouraging results were reported from a Phase 2 registration trial on A797 (Array Biopharma), an oral, selective p38 mitogen-activated protein kinase inhibitor in 12 patients with *LMNA*–associated DCM[96].

LMNA mutations associate frequently with a signature of dysrhythmias that includes sinus node dysfunction, atrial fibrillation, AV node dysfunction, VT and ventricular fibrillation and SCD[46, 47]. Notably, cardiac conduction system disease may precede the development of LV dilation and dysfunction, and the presence of early conduction system disease may suggest and LMNA mutation. Aspects of the arrhythmia and LV dysfunction phenotypes are not fully replicated in the mouse models; namely atrial fibrillation and ventricular arrhythmias are not frequently seen and a homozygous mutation is often needed to generate DCM. Heterozygous truncating *LMNA* mutations have a higher arrhythmia risk than missense variants[47], and a prolonged PR interval indicates cardiac conduction system disease in laminopathy[97]. The susceptibility of the cardiac conduction system to *LMNA* mutations is not well understood.

PLN

The *PLN* gene encodes phospholamban, a 52 aa residue transmembrane protein that, when unphosphorylated, inhibits sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA). Several dominant mutations in *PLN* have been associated with DCM, including the R14del mutation that appears to be a founder mutation in the Netherlands and Germany. Thus, in some populations the percentage of DCM due to *PLN* mutations is quite high. The phenotype with *PLN* mutations is variable. Early onset DCM with lethal ventricular arrhythmias was described[98, 99]. Similarly, individuals from the Netherlands with the R14del founder

mutation have a severe phenotype[100]. However, other reports suggest a milder phenotype[101, 102]. Identifying the same primary mutation(s) with a range of phenotype dependent on genetic background supports that other factors, including genetic factors, may modify the outcome of DCM due to *PLN* mutations.

iPSCs with the R14del PLN mutation were generated and found to display features of cellular cardiomyopathy including aberrant Ca^{2+} handling after caffeine and a higher percentage of irregular Ca^{2+} transients, and these features were reversed after gene editing to correct the primary mutation[103]. These same cells were used to engineer three dimensional human heart tissues and in this setting, more clear cut cardiomyopathic features were seen including reduced developed force that was improved after genetic correction[104]. In iPSC-derived cardiomyocytes and in hearts from *PLN*-mutation carriers, aggregates of phospholamban were seen in a perinuclear and cytoplasmic pattern suggesting that aggregated phospholamban contributes to the pathology possibly through aberrant autophagy[105].

RBM20

RNA binding motif 20 is an RNA binding protein expressed highly in both atria and ventricle. Dominant mutations in the *RBM20* gene were first described in DCM, where they contribute to 1–5% of DCM[106, 107]. RBM20 is 1227 aa in length and contains a ribonucleic acid recognition motif (RRM) domain between residues 525 to 600 aa. A second conserved domain is found between 650 and 725, and the mutations originally described in nonischemic DCM fall within or near these domains. More recently, mutations in a third conserved region were identified in a glutamate rich region[108]. As an RNA binding protein, RBM20 is implicated in tissue specific splicing relevant to development and adaptation to disease states. In the heart, RBM20 regulates cardiac splicing including the splicing of *TTN*[109–111]. Thus, the downstream molecular consequences of RBM20 mutations may share similarities to those occurring from *TTN* truncating variants.

iPSC-derived cardiomyocytes with the RBM20 R636S mutation develop a gene expression and splicing profile consistent with cardiomyopathy affecting not only *TTN* but also the *CAMK2D* and *CACNA1C* genes[112]. Sarcomeres within these RBM20 mutant lines were thinner, similar to what was described for *TTN* mutant iPSC-cardiomyocytes[68]. Recently, RBM20 was implicated in the production of circular RNAs from the *TTN* locus, and mice deleted for *RBM20* failed to produce these *Ttn*-derived circular RNAs[113]. Although the function of circular RNAs is not known, the authors described that a subset of *Ttn*-derived circular RNAs were misregulated in DCM.

SCN5A

SCN5A encodes the major sodium channel expressed in the heart and heterozygous dominant mutations in *SCN5A* are also found in primary arrhythmia syndromes including the Long QT and Brugada syndromes. Missense mutations in *SCN5A* have also been described in familial DCM, and these mutations carry a higher risk for arrhythmias[48, 49]. There is considerable genetic heterogeneity in the *SCN5A* gene in the general population, making it challenging to interpret rare variation in the *SCN5A* gene[59]. Genotype-phenotype

association studies may guide genotype-based therapies. For example, the *SCN5A* R222Q falls within the S4 voltage sensor and is thought to enhance excitability. Treatment with lidocaine was observed to suppress the bigeminy associated with cardiomyopathy[114].

iPSCs have been used to model *SCN5A* mutations associated with primary human arrhythmia syndrome[115–117]. Transgenic directed inducible expression of the *Scn5A* F1759A in mice leads to atrial fibrillation and persistent sodium currents in atria and ventricles[118]. Along with atrial fibrillation, these mice have progressive reduced LVEF consistent with a model for DCM. Thus, the distinct roles of *SCN5A* in the myocardium and the conduction system lead to a combination of arrhythmia and myocyte dysfunction.

Cytoskeletal genes

Genes encoding cardiac cytoskeletal proteins have been implicated in DCM (Figure 6). For example, mutations in dystrophin link to X-linked DCM and cardiomyopathy in Duchenne Muscular Dystrophy[119–121]. Along with dystrophin mutations, mutations in the sarcoglycan genes produce cardiomyopathy, usually associated with muscular dystrophy[51, 122]. In these disorders, the gene products play a normal and essential role in managing sarcolemmal stability. Thus, in the absence of these genes, the sarcolemma becomes unstable leading to cardiomyocytes loss and heart dysfunction. A number of emerging therapies for restoring dystrophin expression are being tested or have been approved recently[123, 124]. Antisense oligonucleotides are being delivered to produce internally truncated dystrophin proteins, and stop codon suppression compounds promote read through of premature stop codons. The degree to which these drugs access the human heart is not well known and ongoing studies will be in a position to assess this in humans.

More recently *FLNC* mutations, in the gene encoding filamin C, have been described in DCM[125–127]. Filamin C interacts with the dystrophin complex, and deletion of *Flnc* from the mouse leads to skeletal myopathy[128, 129]. In humans, truncating mutations lead to cardiomyopathy that is associated with a high rate of ventricular arrhythmias and SCD suggesting that filamin C has a role in the cardiac conduction system in addition to the cardiomyocyte.

Mitochondrial mutations

Both nuclear encoded and mitochondrially encoded mitochondrial genes lead to cardiomyopathy[130–133]. Mutations in the mitochondrial genomes may be difficult to identify and interpret given the role of heteroplasmy and the fact that most genetic testing relies on peripheral blood DNA, which may or may not match what occurs in the heart. Nuclear encoded mitochondrial genes follow either autosomal dominant or recessive inheritance, while mitochondrially encoded genes shows maternal inheritance.

Additional genetic mutations in DCM

The proteins encoding the sarcomere, the unit of contraction, are also implicated in DCM. Recent data from clinical genetic testing indicates that *MYH7, TNNT2* and *TPM1* are the most frequent mutated sarcomere genes in DCM, ranging from approximately 2 to 4%, while *MYBPC3* mutations are rare[58]. Recently, truncations of the gene encoding obscurin

have been found in both LVNC and DCM phenotypes[134]. DCM may be best considered as a cardiomyopathy of mixed origin, familial in approximately 30–50% of patients, consistent with its being a genetic disease. Non-familial or idiopathic DCM may still have a genetic origin, albeit a complex one. Since all DCM mutations have variable expressivity, this may support a model of oligogenic contribution along with environmental or other pathogenic stimuli. As it currently, stands not all DCM genes have been discovered. Thus, the etiology in nonfamilial cases could be as yet undiscovered genes, low penetrance, *de novo* mutations, "missing heritability" due to multiple genes with weaker effect, copy number variations, enhancer region mutations, and intronic variants, or may be the result of the interaction between modifier genes and the environment[13, 135].

Digenic/oligogenic etiology

Occasionally, digenic variants have been reported; while it is possible that some of these variants may in fact be VUS or benign, in other cases the digenic condition have been found to segregate in informative kindred and associate with a more severe phenotype. This is the case of a large family cosegregating a *LMNA* mutation, where relatives with an additional *TTN* truncation showed worse outcome and distinct pathological changes[136]. With the growth of gene panels for cardiomyopathy genetic testing, it is not uncommon to identify more than one potential pathogenic variant. Segregation analysis may be helpful to clarify "primary" versus other variants. Compound mutations *MYBPC3* lead to early onset, sometime neonatal cardiomyopathy[137–139]. Thus, in families with multiple affected members with DCM, a broad gene panel on a younger, affected proband may provide a more comprehensive view of potential variation. Segregation testing for variants of interest can then help clarify those variants with greatest effect.

Genetic testing

Family screening

Genetic evaluation of DCM should begin with extensive and accurate evaluation of the patient's family history, involving at least three generations and including history of cardiomyopathy as well as history of sudden unexpected death at young age (<35)[3, 19, 140]. This information will guide genetic testing, provide good care to family members, and aid in the interpretation of the results and help identifying relatives at risk of disease.

Clinical cascade screening of relatives is recommended per AHA and ESC guidelines[3, 141]. First-degree relatives of affected family members should be clinically evaluated (Figure 2). First line of screening usually relies on ECG and echocardiography to evaluate ventricular size and function. Clinical history should evaluate signs and symptoms for arrhythmias and any history of neuromuscular disease. Other cost effective tools to consider in family member screening include ascertaining arrhythmia history and Holter monitoring[45]. A diagnosis of familial DCM is made where two or more family members are affected by DCM[19].

Clinical Genetic testing

According to the 2016 AHA Scientific Statement on DCM[3], genetic testing is recommended (with moderate level of consensus) in patients with familial (Level of Evidence A) and non-familial 'idiopathic' cardiomyopathy in conjunction with genetic counseling (Level of Evidence B), while there is strong level of consensus in recommending mutation-specific genetic testing for family members after the identification of a DCM-causative mutation in the proband (Level of Evidence B). Reflecting lack of full consensus in the field, the 2016 ESC Position Statement[141] is slightly different and recommends genetic testing in all familial DCM, or non-familial with clinical clues (such as atrio-ventricular block or CK elevation). Interestingly, the ESC Position Statement recommends that genetic testing should be oriented by clinical diagnostic clues and restricted to genes known to cause DCM, while considering large panels of genes only when the family structure is large enough to permit segregation analysis.

Multiple commercial and academic vendors provide genetic testing gene panels under certification of the Clinical Laboratory Improvement Amendment (CLIA). A typical DCM gene panel includes approximately 40–50 genes (Figure 3)[58, 142]. The probability of positive genetic testing in familial DCM is overall in the range of 40% with the current next-generation sequencing panels, and seems not different compared to sporadic cases[13, 58]. A pancardiomyopathy panel, as opposed to a DCM panel, is chosen when the phenotype is unclear and a more comprehensive screening is preferred. The level of evidence to support testing for some genes has been questioned, and this is largely based on a high level of genetic variation in those genes in the population at large[143]. Larger panels may yield greater difficulty in interpreting the results because of variant of unknown significance (VUS). Indeed, in a survey of 766 patients screened in a clinical laboratory, with the introduction of next generation sequencing technology and larger panels, while the rate of positive testing increased from 10% to 40%, the number of VUS increased 10 fold[13, 58, 144].

Genetic Counseling

Genetic counselors, especially those with experience in cardiovascular testing, provide both pre- and post-test counseling. With the increasing complexity of cardiomyopathy genetic testing, referral to specialized cardiovascular genetic clinics should be considered[140]. Pre-test genetic counseling should involve discussion of potential genetic results, (pathogenic mutations, variants of uncertain significance and benign genetic variants). This counseling should also discuss the impact on insurability, reproduction and lifestyle. Post-test counseling focuses on variant interpretation/possible reinterpretation, reproductive risks to offspring and family testing.

If a genetic mutation is identified, genetic cascade screening can be conducted with family members. Cascade genetic testing evaluates the specific family mutation, rather than a gene panel. Site specific testing is of low cost and rapid turnaround so that this can be a cost-effective strategy to eliminate the need to serially follow gene mutation-negative family members. For gene mutation-positive family members, current guidelines suggest an annual clinical follow up with ECG and echocardiography[3, 140, 141].

In the absence of an informative genetic testing, asymptomatic first degree relatives should be examined every 3 to 5 years[140]. This strategy may allow prompt therapeutic measures in carriers showing sign of myocardial dysfunction. Even in the absence of a positive genetic testing, longitudinal studies have shown the benefit of family screening and monitoring. In approximately 10% of cases, mild myocardial dysfunction may progress into overt DCM within 5 years[27, 145]. Furthermore, clinical family screening in DCM helps to identify affected relatives at earlier stages of disease, and this associates with improved survival as compared to sporadic DCM[146].

Management of DCM

Established medical therapies

Management of DCM is focused on 1) LV dimension and function, 2) arrhythmia surveillance and treatment, and 3) reducing congestive symptoms if present. Symptomatic DCM and heart failure with reduced LVEF (HFrEF) is managed following current AHA/ACC and ESC guidelines. Guideline directed therapy includes angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB), in association with beta-blockers, aldosterone antagonists, and in selected cases, vasodilators[147–149]. Medications should be titrated to the dose used in clinical trials unless limited by side effects[150]. DCM patients on optimal therapy with complete left bundle branch block (LBBB) may benefit from cardiac resynchronization[147, 148, 151, 152]. The improvement of survival with ICDs in patients with LVEF less than 35% is also well established[147, 148]. Patients with refractory heart failure may require advanced therapies including left ventricular assist devices or cardiac transplant[147, 148].

Two newer medications for those not responding to optimal medical therapy include the angiotensin receptor-neprylisin inhibitor (ARNI, valsartan/sacubitril) and the sinoatrial modulator, ivabradine[3, 148, 151]. Updated guidelines recommend switching from ACEi/ARB to ARNI in class II-III patients who are not responding to optimal medical therapy (ESC guidelines[148]) or even in those responding to optimal therapy, considering the evidence of superior benefit of ARNI over ACEi/ARBS in terms of mortality and morbidity (AHA/ACC/HFSA guidelines[153]). Ivabradine instead can be added to optimal medical therapy to reduce morbidity in patients with sinus rhythm and a heart rate over 70 bmp[3, 148]. The treatment of patients with a LVEF between 40% and 50%, defined in the ESC guidelines HF with midrange ejection fraction (HFmrEF) and in the ACC/AHA/HFSA guidelines HF with improved ejection fraction remain less clear[151].

Arrhythmia management

Arrhythmia management in genetic DCM patients follows the general recommendations for prevention of SCD and ICD implantation based on the reduced LVEF (<35%). However, there are notable exceptions. First, a subset of patients with DCM present early in the disease course with life-threatening ventricular arrhythmias (2%)[154] or with frequent ventricular arrhythmias (30%), which are unrelated to the severity of left ventricular dysfunction[45]. These patients mirror the arrhythmogenic presentation of ARVC and are described as arrhythmogenic DCM (AR-DCM)[45]. AR-DCM patients who present with

syncope, NSVT and frequent premature ventricular contractions, show a higher incidence of life-threatening arrhythmic events (SCD, sustained ventricular tachycardia, cardiac arrest) compared with the other DCM patients, while they show no difference in outcome of heart failure. The coexistence of a family history of SCD and the AR-DCM phenotype predicts a high risk of SCD events (Figure 7). These recent data suggest that ventricular arrhythmias should be systematically and carefully evaluated with monitoring, and that family history of ventricular arrhythmias predicts a poor prognosis and increased risk of SCD.

AR-DCM can be genetically determined, and a clear association between risk of SCD and gene has been established with the *LMNA* gene. Indeed, the 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[155], recommend an ICD in patients with DCM and a confirmed disease-causing *LMNA* mutation and clinical risk factors (NSVT during ambulatory electrocardiogram monitoring, LVEF 45%, male sex and truncating mutations (class IIa, level B). Likewise, the HRS/ACC/AHA Expert Consensus Statement on the use of ICD therapy inpatients highlighted the increased risk for SCD in *LMNA* carriers[156]. Risk factors for SCD identified in two large *LMNA* carrier cohorts in Europe[47] and in the U.S.[157] include NSVT during ambulatory electrocardiogram monitoring[47], LVEF < 45[47] to 50%[157], male sex and truncating mutations[47, 157]. Kumar et al. reported life-threatening ventricular arrhythmia rates of 3% to 7%/year, which is higher or comparable to other known groups of high-risk patients including those with LVEF < 25%, ARVC, HCM and high-risk ischemic cardiomyopathy.

DCM also carries an increased stroke risk, although less is known about the specific risk in genetic cardiomyopathy. As such, anticoagulation should be considered to reduce the risk of stroke in DCM with atrial fibrillation in particular in the presence of additional risk factor for cardioembolic events such as history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack, or ≥75 years of age[147].

Management of genotype-positive/ phenotype-negative patients

Genetic testing identifies genotype-positive/ phenotype-negative family members, and this information is useful for prevention strategies, lifestyle recommendations including participation in competitive sports, and possible arrhythmia management. The current guidelines recommend observation in asymptomatic at-risk relatives with yearly clinical assessment[140]. There is less consensus concerning the medical management, timing and the type of intervention in these patients. Current guidelines recommend control of risk factors in this stage, such as hypertension[147]. ESC and AHA suggest restriction from competitive sports in DCM genotype-positive/ phenotype-negative, although evidence is lacking to support these recommendations[158]. When initial signs of ventricular dysfunction present during follow-up, earlier institution of medical therapy can begin, although the exact timing of this is not known[140].

Cardiac Regeneration for DCM?

DCM is usually associated with cardiomyocytes loss, and the human heart has limited regenerative capacity. Strategies for regeneration and repair include the application of a cell suspension, growth factors, miRNAs and the implantation of an engineered tissue[159–161].

Various studies and clinical trials have tested cardiac progenitor cells (CPCs), bone marrow-derived stem cells, and pluripotent stem cells[162]. Frustratingly, these clinical interventions demonstrated safety but often failed to prove functional improvement. The mechanism underlying the potential effects of bone marrow derived stem cells (BMSCs) is unclear; the injected cells do not appear to remain in the cardiac tissue, but may release paracrine factors and recruit CPCs[159].

Stem cells are now being used to provide cellular models of DCM. The absence of human cardiomyocyte cell lines has been a problem for advancing research in human cardiomyopathy. iPSCs can be more readily generated from human patients with DCM, and these cells can be differentiated into cardiomyocytes for study. A major limitation of iPSC derived cardiomyocytes is their relative immaturity and variability from culture to culture, but nonetheless these cells can be used to study cellular properties reflective of DCM features. As yet, these stem cells are not yet sufficiently mature for treating cardiomyopathy[159], although they are yielding an important platform for understanding mechanisms and testing therapies[163].

Conclusions and future directions

Better understanding of the DCM phenome and recent improvements in sequencing technology to define DCM genome will eventually improve the diagnosis, prevention and therapy of this disease. Next generation sequencing technology provides a cost-effective and accurate diagnostic method to yield biomarkers that indicate disease risk, especially within families. With this progress, criteria for pathogenic mutations are evolving and becoming more and more stringent, and may require re-evaluation of the molecular diagnosis over time. Several questions still remain in DCM management that prompt future investigations, such as the interpretation of genetic testing, the correct treatment of pre-clinical asymptomatic DCM gene carriers, and the development of gene- and mechanism-specific therapies.

Acknowledgments

NIH HL128075 to EMB; NIH UL1 TR001082, R01 HL69071, R01 116906 and in part by a Trans-Atlantic Network of Excellence grant from the Leducq Foundation (14-CVD 03) to LM.

Nonstandard Abbreviations

AC	arrhythmogenic cardiomyopathy
ACEi	angiotensin converting enzyme inhibitor
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor-neprylisin inhibitor
BMSC	bone marrow derived stem cell
CLIA	Clinical Laboratory Improvement Amendment
CMR	cardiac magnetic resonance

CPC	cardiac progenitor cell
DCM	dilated cardiomyopathy
EMB	endomyocardial biopsy
ExAC	exome aggregation consortium
FHL	four and half LIM
FS	fractional shortening
HCM	hypertrophic cardiomyopathy
HFrEF	heart failure with reduced ejection fraction
HFmrEF	heart failure with midrange ejection fraction
ICD	implantable cardioverter-defibrillator
iPSC	induced pluripotent stem cell
LVAD	left ventricular assist device
LVEDD	left ventricular end diastolic dimension
LVIDd	left ventricular internal dimension in diastole
LVIDs	left ventricular internal dimension in systole
LVNC	left ventricular noncompaction
LV	left ventricle
MAF	minor allele frequency
NSVT	nonsustained ventricular tachycardia
PEVK	proline-glutamate-valine-lysine
RRM	ribonucleic acid recognition motif
SCD	sudden cardiac death
VUS	variant of uncertain significance
VT	ventricular tachycardia

References

1. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, Dubourg O, Kuhl U, Maisch B, McKenna WJ, Monserrat L, Pankuweit S, Rapezzi C, Seferovic P, Tavazzi L, Keren A. Classification of the cardiomyopathies: A position statement from the european society of cardiology working group on myocardial and pericardial diseases. European heart journal. 2008; 29:270–276. [PubMed: 17916581]
2. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB. Contemporary definitions and classification of the cardiomyopathies: An american heart

association scientific statement from the council on clinical cardiology, heart failure and transplantation committee; quality of care and outcomes research and functional genomics and translational biology interdisciplinary working groups; and council on epidemiology and prevention. Circulation. 2006; 113:1807–1816. [PubMed: 16567565]

3. Bozkurt B, Colvin M, Cook J, Cooper LT, Deswal A, Fonarow GC, Francis GS, Lenihan D, Lewis EF, McNamara DM, Pahl E, Ramachandran VS, Ramasubbu K, Rasmusson K, Towbin JA, Yancy C, American Heart Association Committee on Heart F, Transplantation of the Council on Clinical C, Council on Cardiovascular Disease in the Y, Council on C, Stroke N, Council on E, Prevention, Council on Quality of C, Outcomes R. Current diagnostic and treatment strategies for specific dilated cardiomyopathies: A scientific statement from the american heart association. Circulation. 2016
4. Shore S, Grau-Sepulveda MV, Bhatt DL, Heidenreich PA, Eapen ZJ, Hernandez AF, Yancy CW, Fonarow GC. Characteristics, treatments, and outcomes of hospitalized heart failure patients stratified by etiologies of cardiomyopathy. JACC Heart Fail. 2015; 3:906–916. [PubMed: 26454848]
5. Codd MB, Sugrue DD, Gersh BJ, Melton LJ 3rd. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in olmsted county, minnesota, 1975–1984. Circulation. 1989; 80:564–572. [PubMed: 2766509]
6. Torp A. Incidence of congestive cardiomyopathy. Postgrad Med J. 1978; 54:435–439. [PubMed: 704513]
7. Gillum RF. Idiopathic cardiomyopathy in the united states, 1970–1982. Am Heart J. 1986; 111:752–755. [PubMed: 3513505]
8. Manolio TA, Baughman KL, Rodeheffer R, Pearson TA, Bristow JD, Michels VV, Abelmann WH, Harlan WR. Prevalence and etiology of idiopathic dilated cardiomyopathy (summary of a national heart, lung, and blood institute workshop. Am J Cardiol. 1992; 69:1458–1466. [PubMed: 1590237]
9. Miura K, Nakagawa H, Morikawa Y, Sasayama S, Matsumori A, Hasegawa K, Ohno Y, Tamakoshi A, Kawamura T, Inaba Y. Epidemiology of idiopathic cardiomyopathy in japan: Results from a nationwide survey. Heart. 2002; 87:126–130. [PubMed: 11796547]
10. Amoah AG, Kallen C. Aetiology of heart failure as seen from a national cardiac referral centre in africa. Cardiology. 2000; 93:11–18. [PubMed: 10894901]
11. Williams DG, Olsen EG. Prevalence of overt dilated cardiomyopathy in two regions of england. Br Heart J. 1985; 54:153–155. [PubMed: 4015924]
12. Rakar S, Sinagra G, Di Lenarda A, Poletti A, Bussani R, Silvestri F, Camerini F. Epidemiology of dilated cardiomyopathy. A prospective post-mortem study of 5252 necropsies. The heart muscle disease study group. European heart journal. 1997; 18:117–123. [PubMed: 9049523]
13. Sweet M, Taylor MR, Mestroni L. Diagnosis, prevalence, and screening of familial dilated cardiomyopathy. Expert Opin Orphan Drugs. 2015; 3:869–876. [PubMed: 27547593]
14. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: The complexity of a diverse genetic architecture. Nat Rev Cardiol. 2013; 10:531–547. [PubMed: 23900355]
15. Petretta M, Pirozzi F, Sasso L, Paglia A, Bonaduce D. Review and metaanalysis of the frequency of familial dilated cardiomyopathy. Am J Cardiol. 2011; 108:1171–1176. [PubMed: 21798502]
16. Grunig E, Tasman JA, Kucherer H, Franz W, Kubler W, Katus HA. Frequency and phenotypes of familial dilated cardiomyopathy. Journal of the American College of Cardiology. 1998; 31:186–194. [PubMed: 9426039]
17. Ganesh SK, Arnett DK, Assimes TL, Basson CT, Chakravarti A, Ellinor PT, Engler MB, Goldmuntz E, Herrington DM, Hershberger RE, Hong Y, Johnson JA, Kittner SJ, McDermott DA, Meschia JF, Mestroni L, O'Donnell CJ, Psaty BM, Vasan RS, Ruel M, Shen WK, Terzic A, Waldman SA, American Heart Association Council on Functional G, Translational B, American Heart Association Council on E, Prevention, American Heart Association Council on Basic Cardiovascular S, American Heart Association Council on Cardiovascular Disease in the Y, American Heart Association Council on C, Stroke N, American Heart Association Stroke C. Genetics and genomics for the prevention and treatment of cardiovascular disease: Update: A scientific statement from the american heart association. Circulation. 2013; 128:2813–2851. [PubMed: 24297835]

18. Mestroni L, Rocco C, Gregori D, Sinagra G, Di Lenarda A, Miocic S, Vatta M, Pinamonti B, Muntoni F, Caforio AL, McKenna WJ, Falaschi A, Giacca M, Camerini. Familial dilated cardiomyopathy: Evidence for genetic and phenotypic heterogeneity. Heart muscle disease study group. Journal of the American College of Cardiology. 1999; 34:181–190. [PubMed: 10400009]
19. Mestroni L, Maisch B, McKenna WJ, Schwartz K, Charron P, Rocco C, Tesson F, Richter A, Wilke A, Komajda M. Guidelines for the study of familial dilated cardiomyopathies. Collaborative research group of the european human and capital mobility project on familial dilated cardiomyopathy. European heart journal. 1999; 20:93–102. [PubMed: 10099905]
20. Lopez-Ayala JM, Pastor-Quirante F, Gonzalez-Carrillo J, Lopez-Cuenca D, Sanchez-Munoz JJ, Oliva-Sandoval MJ, Gimeno JR. Genetics of myocarditis in arrhythmogenic right ventricular dysplasia. Heart Rhythm. 2015; 12:766–773. [PubMed: 25616123]
21. Morales A, Painter T, Li R, Siegfried JD, Li D, Norton N, Hershberger RE. Rare variant mutations in pregnancy-associated or peripartum cardiomyopathy. Circulation. 2010; 121:2176–2182. [PubMed: 20458009]
22. van Spaendonck-Zwarts KY, van Tintelen JP, van Veldhuisen DJ, van der Werf R, Jongbloed JD, Paulus WJ, Dooijes D, van den Berg MP. Peripartum cardiomyopathy as a part of familial dilated cardiomyopathy. Circulation. 2010; 121:2169–2175. [PubMed: 20458010]
23. Japp AG, Gulati A, Cook SA, Cowie MR, Prasad SK. The diagnosis and evaluation of dilated cardiomyopathy. Journal of the American College of Cardiology. 2016; 67:2996–3010. [PubMed: 27339497]
24. Burridge PW, Li YF, Matsa E, Wu H, Ong SG, Sharma A, Holmstrom A, Chang AC, Coronado MJ, Ebert AD, Knowles JW, Telli ML, Witteles RM, Blau HM, Bernstein D, Altman RB, Wu JC. Human induced pluripotent stem cell-derived cardiomyocytes recapitulate the predilection of breast cancer patients to doxorubicin-induced cardiotoxicity. Nat Med. 2016; 22:547–556. [PubMed: 27089514]
25. Fatkin D. Guidelines for the diagnosis and management of familial dilated cardiomyopathy. Heart Lung Circ. 2011; 20:691–693. [PubMed: 21885340]
26. Crispell KA, Hanson EL, Coates K, Toy W, Hershberger RE. Periodic rescreening is indicated for family members at risk of developing familial dilated cardiomyopathy. Journal of the American College of Cardiology. 2002; 39:1503–1507. [PubMed: 11985914]
27. Mahon NG, Murphy RT, MacRae CA, Caforio AL, Elliott PM, McKenna WJ. Echocardiographic evaluation in asymptomatic relatives of patients with dilated cardiomyopathy reveals preclinical disease. Ann Intern Med. 2005; 143:108–115. [PubMed: 16027452]
28. Captur G, Lopes LR, Mohun TJ, Patel V, Li C, Bassett P, Finocchiaro G, Ferreira VM, Esteban MT, Muthurangu V, Sherrid MV, Day SM, Canter CE, McKenna WJ, Seidman CE, Bluemke DA, Elliott PM, Ho CY, Moon JC. Prediction of sarcomere mutations in subclinical hypertrophic cardiomyopathy. Circ Cardiovasc Imaging. 2014; 7:863–871. [PubMed: 25228707]
29. Sefa Okten M, Tuluce K, Yakar Tuluce S, Kilic S, Soner Kemal H, Sayin A, Vuran O, Yagmur B, Mutlu I, Simsek E, Soydas Cinar C, Gurgun C. Screening first-degree relatives of patients with idiopathic dilated cardiomyopathy. Herz. 2016
30. Cordero-Reyes AM, Youker K, Estep JD, Torre-Amione G, Nagueh SF. Molecular and cellular correlates of cardiac function in end-stage dcm: A study using speckle tracking echocardiography. JACC Cardiovasc Imaging. 2014; 7:441–452. [PubMed: 24726255]
31. Assomull RG, Prasad SK, Lyne J, Smith G, Burman ED, Khan M, Sheppard MN, Poole-Wilson PA, Pennell DJ. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. Journal of the American College of Cardiology. 2006; 48:1977–1985. [PubMed: 17112987]
32. Gao P, Yee R, Gula L, Krahn AD, Skanes A, Leong-Sit P, Klein GJ, Stirrat J, Fine N, Pallaveshi L, Wisenberg G, Thompson TR, Prato F, Drangova M, White JA. Prediction of arrhythmic events in ischemic and dilated cardiomyopathy patients referred for implantable cardiac defibrillator: Evaluation of multiple scar quantification measures for late gadolinium enhancement magnetic resonance imaging. Circ Cardiovasc Imaging. 2012; 5:448–456. [PubMed: 22572740]
33. Perazzolo Marra M, De Lazzari M, Zorzi A, Migliore F, Zilio F, Calore C, Vettor G, Tona F, Tarantini G, Cacciavillani L, Corbetti F, Giorgi B, Miotto D, Thiene G, Basso C, Iliceto S, Corrado D. Impact of the presence and amount of myocardial fibrosis by cardiac magnetic resonance on

arrhythmic outcome and sudden cardiac death in nonischemic dilated cardiomyopathy. Heart Rhythm. 2014; 11:856–863. [PubMed: 24440822]

34. Gulati A, Jabbour A, Ismail TF, Guha K, Khwaja J, Raza S, Morarji K, Brown TD, Ismail NA, Dweck MR, Di Pietro E, Roughton M, Wage R, Daryani Y, O'Hanlon R, Sheppard MN, Alpendurada F, Lyon AR, Cook SA, Cowie MR, Assomull RG, Pennell DJ, Prasad SK. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. Jama. 2013; 309:896–908. [PubMed: 23462786]
35. Ordovas KG, Higgins CB. Delayed contrast enhancement on mr images of myocardium: Past, present, future. Radiology. 2011; 261:358–374. [PubMed: 22012903]
36. Dawson DK, McLernon DJ, Raj VJ, Maceira AM, Prasad S, Frenneaux MP, Pennell DJ, Kilner PJ. Cardiovascular magnetic resonance determinants of left ventricular noncompaction. Am J Cardiol. 2014; 114:456–462. [PubMed: 24934759]
37. Amzulescu MS, Rousseau MF, Ahn SA, Boileau L, de Meester de Ravenstein C, Vancraeynest D, Pasquet A, Vanoverschelde JL, Pouleur AC, Gerber BL. Prognostic impact of hypertrabeculation and noncompaction phenotype in dilated cardiomyopathy: A cmr study. JACC Cardiovasc Imaging. 2015; 8:934–946. [PubMed: 26189121]
38. Gil KE, Pawlak A, Gil RJ, Frontczak-Baniewicz M, Bil J. The role of invasive diagnostics and its impact on the treatment of dilated cardiomyopathy: A systematic review. Adv Med Sci. 2016; 61:331–343. [PubMed: 27589574]
39. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Helio T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: A position statement of the european society of cardiology working group on myocardial and pericardial diseases. European heart journal. 2013; 34:2636–2648. 2648a–2648d. [PubMed: 23824828]
40. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, Levine GN, Narula J, Starling RC, Towbin J, Virmani R. The role of endomyocardial biopsy in the management of cardiovascular disease: A scientific statement from the american heart association, the american college of cardiology, and the european society of cardiology. Circulation. 2007; 116:2216–2233. [PubMed: 17959655]
41. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, Levine GN, Narula J, Starling RC, Towbin J, Virmani R. The role of endomyocardial biopsy in the management of cardiovascular disease: A scientific statement from the american heart association, the american college of cardiology, and the european society of cardiology endorsed by the heart failure society of america and the heart failure association of the european society of cardiology. European heart journal. 2007; 28:3076–3093. [PubMed: 17959624]
42. Asimaki A, Tandri H, Huang H, Halushka MK, Gautam S, Basso C, Thiene G, Tsatsopoulou A, Protonotarios N, McKenna WJ, Calkins H, Saffitz JE. A new diagnostic test for arrhythmogenic right ventricular cardiomyopathy. N Engl J Med. 2009; 360:1075–1084. [PubMed: 19279339]
43. Asimaki A, Protonotarios A, James CA, Chelko SP, Tichnell C, Murray B, Tsatsopoulou A, Anastasakis A, te Riele A, Kleber AG, Judge DP, Calkins H, Saffitz JE. Characterizing the molecular pathology of arrhythmogenic cardiomyopathy in patient buccal mucosa cells. Circ Arrhythm Electrophysiol. 2016; 9:e003688. [PubMed: 26850880]
44. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000; 342:1077–1084. [PubMed: 10760308]
45. Spezzacatene A, Sinagra G, Merlo M, Barbati G, Graw SL, Brun F, Slavov D, Di Lenarda A, Salcedo EE, Towbin JA, Saffitz JE, Marcus FI, Zareba W, Taylor MR, Mestroni L, Familial Cardiomyopathy R. Arrhythmogenic phenotype in dilated cardiomyopathy: Natural history and predictors of life-threatening arrhythmias. J Am Heart Assoc. 2015; 4:e002149. [PubMed: 26475296]
46. van Berlo JH, de Voogt WG, van der Kooi AJ, van Tintelen JP, Bonne G, Yaou RB, Duboc D, Rossenbacker T, Heidbuchel H, de Visser M, Crijns HJ, Pinto YM. Meta-analysis of clinical characteristics of 299 carriers of lmna gene mutations: Do lamin a/c mutations portend a high risk of sudden death? J Mol Med (Berl). 2005; 83:79–83. [PubMed: 15551023]

47. van Rijsingen IA, Arbustini E, Elliott PM, Mogensen J, Hermans-van Ast JF, van der Kooi AJ, van Tintelen JP, van den Berg MP, Pilotto A, Pasotti M, Jenkins S, Rowland C, Aslam U, Wilde AA, Perrot A, Pankuweit S, Zwinderman AH, Charron P, Pinto YM. Risk factors for malignant ventricular arrhythmias in lamin a/c mutation carriers a european cohort study. Journal of the American College of Cardiology. 2012; 59:493–500. [PubMed: 22281253]
48. McNair WP, Sinagra G, Taylor MR, Di Lenarda A, Ferguson DA, Salcedo EE, Slavov D, Zhu X, Caldwell JH, Mestroni L. Scn5a mutations associate with arrhythmic dilated cardiomyopathy and commonly localize to the voltage-sensing mechanism. Journal of the American College of Cardiology. 2011; 57:2160–2168. [PubMed: 21596231]
49. Mann SA, Castro ML, Ohanian M, Guo G, Zodgekar P, Sheu A, Stockhammer K, Thompson T, Playford D, Subbiah R, Kuchar D, Aggarwal A, Vandenberg JI, Fatkin D. R222q scn5a mutation is associated with reversible ventricular ectopy and dilated cardiomyopathy. Journal of the American College of Cardiology. 2012; 60:1566–1573. [PubMed: 22999724]
50. Brown CA, Lanning RW, McKinney KQ, Salvino AR, Cherniske E, Crowe CA, Darras BT, Gominak S, Greenberg CR, Grosmann C, Heydemann P, Mendell JR, Pober BR, Sasaki T, Shapiro F, Simpson DA, Suchowersky O, Spence JE. Novel and recurrent mutations in lamin a/c in patients with emery-dreifuss muscular dystrophy. Am J Med Genet. 2001; 102:359–367. [PubMed: 11503164]
51. McNally EM. New approaches in the therapy of cardiomyopathy in muscular dystrophy. Annu Rev Med. 2007; 58:75–88. [PubMed: 17217326]
52. Tanawuttiwat T, Wagner KR, Tomaselli G, Nazarian S. Left ventricular dysfunction and conduction disturbances in patients with myotonic muscular dystrophy type i and ii. JAMA Cardiol. 2016
53. Sommerville RB, Vincenti MG, Winborn K, Casey A, Stitziel NO, Connolly AM, Mann DL. Diagnosis and management of adult hereditary cardio-neuromuscular disorders: A model for the multidisciplinary care of complex genetic disorders. Trends Cardiovasc Med. 2017; 27:51–58. [PubMed: 27452966]
54. McNally EM, Sparano D. Mechanisms and management of the heart in myotonic dystrophy. Heart. 2011; 97:1094–1100. [PubMed: 21642660]
55. Wahbi K, Babuty D, Probst V, Wissocque L, Labombarda F, Porcher R, Becane HM, Lazarus A, Behin A, Laforet P, Stojkovic T, Clementy N, Dussauge AP, Gourraud JB, Pereon Y, Lacour A, Chapon F, Milliez P, Klug D, Eymard B, Duboc D. Incidence and predictors of sudden death, major conduction defects and sustained ventricular tachyarrhythmias in 1388 patients with myotonic dystrophy type 1. European heart journal. 2016
56. McNally EM, Golbus JR, Puckelwartz MJ. Genetic mutations and mechanisms in dilated cardiomyopathy. J Clin Invest. 2013; 123:19–26. [PubMed: 23281406]
57. McNally EM, Barefield DY, Puckelwartz MJ. The genetic landscape of cardiomyopathy and its role in heart failure. Cell Metab. 2015; 21:174–182. [PubMed: 25651172]
58. Pugh TJ, Kelly MA, Gowrisankar S, Hynes E, Seidman MA, Baxter SM, Bowser M, Harrison B, Aaron D, Mahanta LM, Lakdawala NK, McDermott G, White ET, Rehm HL, Lebo M, Funke BH. The landscape of genetic variation in dilated cardiomyopathy as surveyed by clinical DNA sequencing. Genet Med. 2014; 16:601–608. [PubMed: 24503780]
59. Walsh R, Thomson KL, Ware JS, Funke BH, Woodley J, McGuire KJ, Mazzarotto F, Blair E, Seller A, Taylor JC, Minikel EV, Exome Aggregation C. MacArthur DG, Farrall M, Cook SA, Watkins H. Reassessment of mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60, 706 reference samples. Genet Med. 2016
60. Li Q, Gruner C, Chan RH, Care M, Siminovitch K, Williams L, Woo A, Rakowski H. Genotype-positive status in patients with hypertrophic cardiomyopathy is associated with higher rates of heart failure events. Circ Cardiovasc Genet. 2014; 7:416–422. [PubMed: 24909666]
61. Herman DS, Lam L, Taylor MR, Wang L, Teekakirikul P, Christodoulou D, Conner L, DePalma SR, McDonough B, Sparks E, Teodorescu DL, Cirino AL, Banner NR, Pennell DJ, Graw S, Merlo M, Di Lenarda A, Sinagra G, Bos JM, Ackerman MJ, Mitchell RN, Murry CE, Lakdawala NK, Ho CY, Barton PJ, Cook SA, Mestroni L, Seidman JG, Seidman CE. Truncations of titin causing dilated cardiomyopathy. N Engl J Med. 2012; 366:619–628. [PubMed: 22335739]
62. LeWinter MM, Granzier HL. Cardiac titin and heart disease. J Cardiovasc Pharmacol. 2014; 63:207–212. [PubMed: 24072177]

63. Anderson BR, Granzier HL. Titin-based tension in the cardiac sarcomere: Molecular origin and physiological adaptations. Prog Biophys Mol Biol. 2012; 110:204–217. [PubMed: 22910434]
64. Christodoulou DC, Wakimoto H, Onoue K, Eminaga S, Gorham JM, DePalma SR, Herman DS, Teekakirikul P, Conner DA, McKean DM, Domenighetti AA, Aboukhalil A, Chang S, Srivastava G, McDonough B, De Jager PL, Chen J, Bulyk ML, Muehlschlegel JD, Seidman CE, Seidman JG. 5'rna-seq identifies fhl1 as a genetic modifier in cardiomyopathy. J Clin Invest. 2014; 124:1364–1370. [PubMed: 24509080]
65. Nagueh SF, Shah G, Wu Y, Torre-Amione G, King NM, Lahmers S, Witt CC, Becker K, Labeit S, Granzier HL. Altered titin expression, myocardial stiffness, and left ventricular function in patients with dilated cardiomyopathy. Circulation. 2004; 110:155–162. [PubMed: 15238456]
66. Roberts AM, Ware JS, Herman DS, Schafer S, Baksi J, Bick AG, Buchan RJ, Walsh R, John S, Wilkinson S, Mazzarotto F, Felkin LE, Gong S, MacArthur JA, Cunningham F, Flannick J, Gabriel SB, Altshuler DM, Macdonald PS, Heinig M, Keogh AM, Hayward CS, Banner NR, Pennell DJ, O'Regan DP, San TR, de Marvao A, Dawes TJ, Gulati A, Birks EJ, Yacoub MH, Radke M, Gotthardt M, Wilson JG, O'Donnell CJ, Prasad SK, Barton PJ, Fatkin D, Hubner N, Seidman JG, Seidman CE, Cook SA. Integrated allelic, transcriptional, and phenomic dissection of the cardiac effects of titin truncations in health and disease. Sci Transl Med. 2015; 7:270ra276.
67. Gerull B, Gramlich M, Atherton J, McNabb M, Trombitas K, Sasse-Klaassen S, Seidman JG, Seidman C, Granzier H, Labeit S, Frenneaux M, Thierfelder L. Mutations of ttn, encoding the giant muscle filament titin, cause familial dilated cardiomyopathy. Nat Genet. 2002; 30:201–204. [PubMed: 11788824]
68. Hinson JT, Chopra A, Nafissi N, Polacheck WJ, Benson CC, Swist S, Gorham J, Yang L, Schafer S, Sheng CC, Haghighi A, Homsy J, Hubner N, Church G, Cook SA, Linke WA, Chen CS, Seidman JG, Seidman CE. Heart disease. Titin mutations in ips cells define sarcomere insufficiency as a cause of dilated cardiomyopathy. Science. 2015; 349:982–986. [PubMed: 26315439]
69. Golbus JR, Puckelwartz MJ, Fahrenbach JP, Dellefave-Castillo LM, Wolfgeher D, McNally EM. Population-based variation in cardiomyopathy genes. Circ Cardiovasc Genet. 2012; 5:391–399. [PubMed: 22763267]
70. Jansweijer JA, Nieuwhof K, Russo F, Hoorntje ET, Jongbloed JD, Lekanne Deprez RH, Postma AV, Bronk M, van Rijsingen IA, de Haij S, Biagini E, van Haelst PL, van Wijngaarden J, van den Berg MP, Wilde AA, Mannens MM, de Boer RA, van Spaendonck-Zwarts KY, van Tintelen JP, Pinto YM. Truncating titin mutations are associated with a mild and treatable form of dilated cardiomyopathy. Eur J Heart Fail. 2016
71. Schafer S, de Marvao A, Adami E, Fiedler LR, Ng B, Khin E, Rackham OJ, van Heesch S, Pua CJ, Kui M, Walsh R, Tayal U, Prasad SK, Dawes TJ, Ko NS, Sim D, Chan LL, Chin CW, Mazzarotto F, Barton PJ, Kreuchwig F, de Kleijn DP, Totman T, Biffi C, Tee N, Rueckert D, Schneider V, Faber A, Regitz-Zagrosek V, Seidman JG, Seidman CE, Linke WA, Kovalik JP, O'Regan D, Ware JS, Hubner N, Cook SA. Titin-truncating variants affect heart function in disease cohorts and the general population. Nat Genet. 2016
72. van Spaendonck-Zwarts KY, Posafalvi A, van den Berg MP, Hilfiker-Kleiner D, Bollen IA, Sliwa K, Alders M, Almomani R, van Langen IM, van der Meer P, Sinke RJ, van der Velden J, Van Veldhuisen DJ, van Tintelen JP, Jongbloed JD. Titin gene mutations are common in families with both peripartum cardiomyopathy and dilated cardiomyopathy. European heart journal. 2014; 35:2165–2173. [PubMed: 24558114]
73. Ware JS, Li J, Mazaika E, Yasso CM, DeSouza T, Cappola TP, Tsai EJ, Hilfiker-Kleiner D, Kamiya CA, Mazzarotto F, Cook SA, Halder I, Prasad SK, Pisarcik J, Hanley-Yanez K, Alharethi R, Damp J, Hsich E, Elkayam U, Sheppard R, Kealey A, Alexis J, Ramani G, Safirstein J, Boehmer J, Pauly DF, Wittstein IS, Thohan V, Zucker MJ, Liu P, Gorcsan J 3rd, McNamara DM, Seidman CE, Seidman JG, Arany Z. Shared genetic predisposition in peripartum and dilated cardiomyopathies. N Engl J Med. 2016; 374:233–241. [PubMed: 26735901]
74. Felkin LE, Walsh R, Ware JS, Yacoub MH, Birks EJ, Barton PJ, Cook SA. Recovery of cardiac function in cardiomyopathy caused by titin truncation. JAMA Cardiol. 2016; 1:234–235. [PubMed: 27437901]

75. Norton N, Li D, Rampersaud E, Morales A, Martin ER, Zuchner S, Guo S, Gonzalez M, Hedges DJ, Robertson PD, Krumm N, Nickerson DA, Hershberger RE. Exome sequencing and genome-wide linkage analysis in 17 families illustrate the complex contribution of ttn truncating variants to dilated cardiomyopathy. Circ Cardiovasc Genet. 2013; 6:144–153. [PubMed: 23418287]

76. Gigli M, Begay RL, Morea G, Graw SL, Sinagra G, Taylor MR, Granzier H, Mestroni L. A review of the giant protein titin in clinical molecular diagnostics of cardiomyopathies. Front Cardiovasc Med. 2016; 3:21. [PubMed: 27493940]

77. Akinrinade O, Ollila L, Vattulainen S, Tallila J, Gentile M, Salmenpera P, Koillinen H, Kaartinen M, Nieminen MS, Myllykangas S, Alastalo TP, Koskenvuo JW, Helio T. Genetics and genotype-phenotype correlations in finnish patients with dilated cardiomyopathy. European heart journal. 2015; 36:2327–2337. [PubMed: 26084686]

78. Begay RL, Graw S, Sinagra G, Merlo M, Slavov D, Gowan K, Jones KL, Barbati G, Spezzacatene A, Brun F, Di Lenarda A, Smith JE, Granzier HL, Mestroni L, Taylor M. Role of titin missense variants in dilated cardiomyopathy. J Am Heart Assoc. 2015; 4

79. Ceyhan-Birsoy O, Agrawal PB, Hidalgo C, Schmitz-Abe K, DeChene ET, Swanson LC, Soemedi R, Vasli N, Iannaccone ST, Shieh PB, Shur N, Dennison JM, Lawlor MW, Laporte J, Markianos K, Fairbrother WG, Granzier H, Beggs AH. Recessive truncating titin gene, ttn, mutations presenting as centronuclear myopathy. Neurology. 2013; 81:1205–1214. [PubMed: 23975875]

80. Hackman P, Vihola A, Haravuori H, Marchand S, Sarparanta J, De Seze J, Labeit S, Witt C, Peltonen L, Richard I, Udd B. Tibial muscular dystrophy is a titinopathy caused by mutations in ttn, the gene encoding the giant skeletal-muscle protein titin. Am J Hum Genet. 2002; 71:492–500. [PubMed: 12145747]

81. Zou J, Tran D, Baalbaki M, Tang LF, Poon A, Pelonero A, Titus EW, Yuan C, Shi C, Patchava S, Halper E, Garg J, Movsesyan I, Yin C, Wu R, Wilsbacher LD, Liu J, Hager RL, Coughlin SR, Jinek M, Pullinger CR, Kane JP, Hart DO, Kwok PY, Deo RC. An internal promoter underlies the difference in disease severity between n- and c-terminal truncation mutations of titin in zebrafish. Elife. 2015; 4:e09406. [PubMed: 26473617]

82. Granzier HL, Radke MH, Peng J, Westermann D, Nelson OL, Rost K, King NM, Yu Q, Tschope C, McNabb M, Larson DF, Labeit S, Gotthardt M. Truncation of titin's elastic pevk region leads to cardiomyopathy with diastolic dysfunction. Circ Res. 2009; 105:557–564. [PubMed: 19679835]

83. Zhou Q, Kesteven S, Wu J, Aidery P, Gawaz M, Gramlich M, Feneley MP, Harvey RP. Pressure overload by transverse aortic constriction induces maladaptive hypertrophy in a titin-truncated mouse model. Biomed Res Int. 2015; 2015:163564. [PubMed: 26504781]

84. van Tintelen JP, Hofstra RM, Katerberg H, Rossenbacker T, Wiesfeld AC, du Marchie Sarvaas GJ, Wilde AA, van Langen IM, Nannenberg EA, van der Kooi AJ, Kraak M, van Gelder IC, van Veldhuisen DJ, Vos Y, van den Berg MP. High yield of lmna mutations in patients with dilated cardiomyopathy and/or conduction disease referred to cardiogenetics outpatient clinics. Am Heart J. 2007; 154:1130–1139. [PubMed: 18035086]

85. Parks SB, Kushner JD, Nauman D, Burgess D, Ludwigsen S, Peterson A, Li D, Jakobs P, Litt M, Porter CB, Rahko PS, Hershberger RE. Lamin a/c mutation analysis in a cohort of 324 unrelated patients with idiopathic or familial dilated cardiomyopathy. Am Heart J. 2008; 156:161–169. [PubMed: 18585512]

86. Lu JT, Muchir A, Nagy PL, Worman HJ. Lmna cardiomyopathy: Cell biology and genetics meet clinical medicine. Dis Model Mech. 2011; 4:562–568. [PubMed: 21810905]

87. Young SG, Meta M, Yang SH, Fong LG. Prelamin a farnesylation and progeroid syndromes. J Biol Chem. 2006; 281:39741–39745. [PubMed: 17090536]

88. Narula N, Favalli V, Tarantino P, Grasso M, Pilotto A, Bellazzi R, Serio A, Gambarin FI, Charron P, Meder B, Pinto Y, Elliott PM, Mogensen J, Bolognesi M, Bollati M, Arbustini E. Quantitative expression of the mutated lamin a/c gene in patients with cardiolaminopathy. Journal of the American College of Cardiology. 2012; 60:1916–1920. [PubMed: 23062543]

89. Dittmer TA, Sahni N, Kubben N, Hill DE, Vidal M, Burgess RC, Roukos V, Misteli T. Systematic identification of pathological lamin a interactors. Mol Biol Cell. 2014; 25:1493–1510. [PubMed: 24623722]

90. Nikolova V, Leimena C, McMahon AC, Tan JC, Chandar S, Jogia D, Kesteven SH, Michalicek J, Otway R, Verheyen F, Rainer S, Stewart CL, Martin D, Feneley MP, Fatkin D. Defects in nuclear

structure and function promote dilated cardiomyopathy in lamin a/c-deficient mice. J Clin Invest. 2004; 113:357–369. [PubMed: 14755333]

91. Lammerding J, Schulze PC, Takahashi T, Kozlov S, Sullivan T, Kamm RD, Stewart CL, Lee RT. Lamin a/c deficiency causes defective nuclear mechanics and mechanotransduction. J Clin Invest. 2004; 113:370–378. [PubMed: 14755334]
92. Chandar S, Yeo LS, Leimena C, Tan JC, Xiao XH, Nikolova-Krstevski V, Yasuoka Y, Gardiner-Garden M, Wu J, Kesteven S, Karlsdotter L, Natarajan S, Carlton A, Rainer S, Feneley MP, Fatkin D. Effects of mechanical stress and carvedilol in lamin a/c-deficient dilated cardiomyopathy. Circ Res. 2010; 106:573–582. [PubMed: 20019332]
93. Ramos FJ, Chen SC, Garelick MG, Dai DF, Liao CY, Schreiber KH, MacKay VL, An EH, Strong R, Ladiges WC, Rabinovitch PS, Kaeberlein M, Kennedy BK. Rapamycin reverses elevated mtorc1 signaling in lamin a/c-deficient mice, rescues cardiac and skeletal muscle function, and extends survival. Sci Transl Med. 2012; 4:144ra103.
94. Choi JC, Muchir A, Wu W, Iwata S, Homma S, Morrow JP, Worman HJ. Temsirolimus activates autophagy and ameliorates cardiomyopathy caused by lamin a/c gene mutation. Sci Transl Med. 2012; 4:144ra102.
95. Wu W, Muchir A, Shan J, Bonne G, Worman HJ. Mitogen-activated protein kinase inhibitors improve heart function and prevent fibrosis in cardiomyopathy caused by mutation in lamin a/c gene. Circulation. 2011; 123:53–61. [PubMed: 21173351]
96. MacRae C, Taylor MRG, Mestroni L, Moses JR, Ashley EA, Wheeler MT, Lakdawala NK, Hershberger RE, Ptaszynski M, Sandor V, Saunders ME, Oliver C, Lee PA, Judge DP. Phase 2 study of a797, an oral, selective p38 mitogen-activated protein kinase inhibitor, in patients with lamin a/c-related dilated cardiomyopathy. European heart journal. 2016; 37:1011. [PubMed: 27489891]
97. Hasselberg NE, Edvardsen T, Petri H, Berge KE, Leren TP, Bundgaard H, Haugaa KH. Risk prediction of ventricular arrhythmias and myocardial function in lamin a/c mutation positive subjects. Europace. 2014; 16:563–571. [PubMed: 24058181]
98. Haghighi K, Kolokathis F, Gramolini AO, Waggoner JR, Pater L, Lynch RA, Fan GC, Tsiapras D, Parekh RR, Dorn GW 2nd, MacLennan DH, Kremastinos DT, Kranias EG. A mutation in the human phospholamban gene, deleting arginine 14, results in lethal, hereditary cardiomyopathy. Proc Natl Acad Sci U S A. 2006; 103:1388–1393. [PubMed: 16432188]
99. Liu GS, Morales A, Vafiadaki E, Lam CK, Cai WF, Haghighi K, Adly G, Hershberger RE, Kranias EG. A novel human r25c-phospholamban mutation is associated with super-inhibition of calcium cycling and ventricular arrhythmia. Cardiovasc Res. 2015; 107:164–174. [PubMed: 25852082]
100. van der Zwaag PA, van Rijsingen IA, Asimaki A, Jongbloed JD, van Veldhuisen DJ, Wiesfeld AC, Cox MG, van Lochem LT, de Boer RA, Hofstra RM, Christiaans I, van Spaendonck-Zwarts KY, Lekanne dit Deprez RH, Judge DP, Calkins H, Suurmeijer AJ, Hauer RN, Saffitz JE, Wilde AA, van den Berg MP, van Tintelen JP. Phospholamban r14del mutation in patients diagnosed with dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy: Evidence supporting the concept of arrhythmogenic cardiomyopathy. Eur J Heart Fail. 2012; 14:1199–1207. [PubMed: 22820313]
101. DeWitt MM, MacLeod HM, Soliven B, McNally EM. Phospholamban r14 deletion results in late-onset, mild, hereditary dilated cardiomyopathy. Journal of the American College of Cardiology. 2006; 48:1396–1398. [PubMed: 17010801]
102. Truszkowska GT, Bilinska ZT, Kosinska J, Sleszycka J, Rydzanicz M, Sobieszczanska-Malek M, Franaszczyk M, Bilinska M, Stawinski P, Michalak E, Malek LA, Chmielewski P, Foss-Nieradko B, Machnicki MM, Stoklosa T, Poninska J, Szumowski L, Grzybowski J, Piwonski J, Drygas W, Zielinski T, Ploski R. A study in polish patients with cardiomyopathy emphasizes pathogenicity of phospholamban (pln) mutations at amino acid position 9 and low penetrance of heterozygous null pln mutations. BMC Med Genet. 2015; 16:21. [PubMed: 25928149]
103. Karakikes I, Stillitano F, Nonnenmacher M, Tzimas C, Sanoudou D, Termglinchan V, Kong CW, Rushing S, Hansen J, Ceholski D, Kolokathis F, Kremastinos D, Katoulis A, Ren L, Cohen N, Gho JM, Tsiapras D, Vink A, Wu JC, Asselbergs FW, Li RA, Hulot JS, Kranias EG, Hajjar RJ. Correction of human phospholamban r14del mutation associated with cardiomyopathy using targeted nucleases and combination therapy. Nat Commun. 2015; 6:6955. [PubMed: 25923014]

104. Stillitano F, Turnbull IC, Karakikes I, Nonnenmacher M, Backeris P, Hulot JS, Kranias EG, Hajjar RJ, Costa KD. Genomic correction of familial cardiomyopathy in human engineered cardiac tissues. European heart journal. 2016; 37:3282–3284. [PubMed: 27450564]

105. Te Rijdt WP, van Tintelen JP, Vink A, van der Wal AC, de Boer RA, van den Berg MP, Suurmeijer AJ. Phospholamban p.Arg14del cardiomyopathy is characterized by phospholamban aggregates, aggresomes, and autophagic degradation. Histopathology. 2016; 69:542–550. [PubMed: 26970417]

106. Brauch KM, Karst ML, Herron KJ, de Andrade M, Pellikka PA, Rodeheffer RJ, Michels VV, Olson TM. Mutations in ribonucleic acid binding protein gene cause familial dilated cardiomyopathy. Journal of the American College of Cardiology. 2009; 54:930–941. [PubMed: 19712804]

107. Li D, Morales A, Gonzalez-Quintana J, Norton N, Siegfried JD, Hofmeyer M, Hershberger RE. Identification of novel mutations in rbm20 in patients with dilated cardiomyopathy. Clin Transl Sci. 2010; 3:90–97. [PubMed: 20590677]

108. Beqqali A, Bollen IA, Rasmussen TB, van den Hoogenhof MM, van Deutekom HW, Schafer S, Haas J, Meder B, Sorensen KE, van Oort RJ, Mogensen J, Hubner N, Creemers EE, van der Velden J, Pinto YM. A mutation in the glutamate-rich region of rna-binding motif protein 20 causes dilated cardiomyopathy through missplicing of titin and impaired frank-starling mechanism. Cardiovasc Res. 2016; 112:452–463. [PubMed: 27496873]

109. Guo W, Schafer S, Greaser ML, Radke MH, Liss M, Govindarajan T, Maatz H, Schulz H, Li S, Parrish AM, Dauksaite V, Vakeel P, Klaassen S, Gerull B, Thierfelder L, Regitz-Zagrosek V, Hacker TA, Saupe KW, Dec GW, Ellinor PT, MacRae CA, Spallek B, Fischer R, Perrot A, Ozcelik C, Saar K, Hubner N, Gotthardt M. Rbm20, a gene for hereditary cardiomyopathy, regulates titin splicing. Nat Med. 2012; 18:766–773. [PubMed: 22466703]

110. Li S, Guo W, Dewey CN, Greaser ML. Rbm20 regulates titin alternative splicing as a splicing repressor. Nucleic Acids Res. 2013; 41:2659–2672. [PubMed: 23307558]

111. Maatz H, Jens M, Liss M, Schafer S, Heinig M, Kirchner M, Adami E, Rintisch C, Dauksaite V, Radke MH, Selbach M, Barton PJ, Cook SA, Rajewsky N, Gotthardt M, Landthaler M, Hubner N. Rna-binding protein rbm20 represses splicing to orchestrate cardiac pre-mrna processing. J Clin Invest. 2014; 124:3419–3430. [PubMed: 24960161]

112. Wyles SP, Li X, Hrstka SC, Reyes S, Oommen S, Beraldi R, Edwards J, Terzic A, Olson TM, Nelson TJ. Modeling structural and functional deficiencies of rbm20 familial dilated cardiomyopathy using human induced pluripotent stem cells. Hum Mol Genet. 2016; 25:254–265. [PubMed: 26604136]

113. Khan MA, Reckman YJ, Aufiero S, van den Hoogenhof MM, van der Made I, Beqqali A, Koolbergen DR, Rasmussen TB, van der Velden J, Creemers EE, Pinto YM. Rbm20 regulates circular rna production from the titin gene. Circ Res. 2016; 119:996–1003. [PubMed: 27531932]

114. Nair K, Pekhletski R, Harris L, Care M, Morel C, Farid T, Backx PH, Szabo E, Nanthakumar K. Escape capture bigeminy: Phenotypic marker of cardiac sodium channel voltage sensor mutation r222q. Heart Rhythm. 2012; 9:1681–1688.e1681. [PubMed: 22710484]

115. Davis RP, Casini S, van den Berg CW, Hoekstra M, Remme CA, Dambrot C, Salvatori D, Oostwaard DW, Wilde AA, Bezzina CR, Verkerk AO, Freund C, Mummery CL. Cardiomyocytes derived from pluripotent stem cells recapitulate electrophysiological characteristics of an overlap syndrome of cardiac sodium channel disease. Circulation. 2012; 125:3079–3091. [PubMed: 22647976]

116. Liang P, Sallam K, Wu H, Li Y, Itzhaki I, Garg P, Zhang Y, Vermglinchan V, Lan F, Gu M, Gong T, Zhuge Y, He C, Ebert AD, Sanchez-Freire V, Churko J, Hu S, Sharma A, Lam CK, Scheinman MM, Bers DM, Wu JC. Patient-specific and genome-edited induced pluripotent stem cell-derived cardiomyocytes elucidate single-cell phenotype of brugada syndrome. Journal of the American College of Cardiology. 2016; 68:2086–2096. [PubMed: 27810048]

117. Malan D, Friedrichs S, Fleischmann BK, Sasse P. Cardiomyocytes obtained from induced pluripotent stem cells with long-qt syndrome 3 recapitulate typical disease-specific features in vitro. Circ Res. 2011; 109:841–847. [PubMed: 21799153]

118. Wan E, Abrams J, Weinberg RL, Katchman AN, Bayne J, Zakharov SI, Yang L, Morrow JP, Garan H, Marx SO. Aberrant sodium influx causes cardiomyopathy and atrial fibrillation in mice. J Clin Invest. 2016; 126:112–122. [PubMed: 26595809]
119. Feng J, Yan J, Buzin CH, Towbin JA, Sommer SS. Mutations in the dystrophin gene are associated with sporadic dilated cardiomyopathy. Mol Genet Metab. 2002; 77:119–126. [PubMed: 12359139]
120. Jefferies JL, Eidem BW, Belmont JW, Craigen WJ, Ware SM, Fernbach SD, Neish SR, Smith EO, Towbin JA. Genetic predictors and remodeling of dilated cardiomyopathy in muscular dystrophy. Circulation. 2005; 112:2799–2804. [PubMed: 16246949]
121. Ortiz-Lopez R, Li H, Su J, Goytia V, Towbin JA. Evidence for a dystrophin missense mutation as a cause of x-linked dilated cardiomyopathy. Circulation. 1997; 95:2434–2440. [PubMed: 9170407]
122. Tsubata S, Bowles KR, Vatta M, Zintz C, Titus J, Muhonen L, Bowles NE, Towbin JA. Mutations in the human delta-sarcoglycan gene in familial and sporadic dilated cardiomyopathy. J Clin Invest. 2000; 106:655–662. [PubMed: 10974018]
123. Haas M, Vlcek V, Balabanov P, Salmonson T, Bakchine S, Markey G, Weise M, Schlosser-Weber G, Brohmann H, Yerro CP, Mendizabal MR, Stoyanova-Beninska V, Hillege HL. European medicines agency review of ataluren for the treatment of ambulant patients aged 5 years and older with duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene. Neuromuscul Disord. 2015; 25:5–13. [PubMed: 25497400]
124. Niks EH, Aartsma-Rus A. Exon skipping: A first in class strategy for duchenne muscular dystrophy. Expert Opin Biol Ther. 2016:1–12.
125. Begay RL, Tharp CA, Martin A, Graw SL, Sinagra G, Miani D, Sweet ME, Slavov DB, Stafford N, Zeller MJ, Alnefaie R, Rowland TJ, Brun F, Jones KL, Gowan KLM, Garrity DM, Taylor MRG. Flnc gene splice mutations cause dilated cardiomyopathy. JACC Basic to Translational Science. 2016; 1:344–359. [PubMed: 28008423]
126. Ortiz-Genga MF, Cuenca S, Dal Ferro M, Zorio E, Salgado-Aranda R, Climent V, Padron-Barthe L, Duro-Aguado I, Jimenez-Jaimez J, Hidalgo-Olivares VM, Garcia-Campo E, Lanzillo C, Suarez-Mier MP, Yonath H, Marcos-Alonso S, Ochoa JP, Santome JL, Garcia-Giustiniani D, Rodriguez-Garrido JL, Dominguez F, Merlo M, Palomino J, Pena ML, Trujillo JP, Martin-Vila A, Stolfo D, Molina P, Lara-Pezzi E, Calvo-Iglesias FE, Nof E, Calo L, Barriales-Villa R, Gimeno-Blanes JR, Arad M, Garcia-Pavia P, Monserrat L. Truncating flnc mutations are associated with high-risk dilated and arrhythmogenic cardiomyopathies. Journal of the American College of Cardiology. 2016; 68:2440–2451. [PubMed: 27908349]
127. Golbus JR, Puckelwartz MJ, Dellefave-Castillo L, Fahrenbach JP, Nelakuditi V, Pesce LL, Pytel P, McNally EM. Targeted analysis of whole genome sequence data to diagnose genetic cardiomyopathy. Circ Cardiovasc Genet. 2014; 7:751–759. [PubMed: 25179549]
128. Thompson TG, Chan YM, Hack AA, Brosius M, Rajala M, Lidov HG, McNally EM, Watkins S, Kunkel LM. Filamin 2 (fln2): A muscle-specific sarcoglycan interacting protein. J Cell Biol. 2000; 148:115–126. [PubMed: 10629222]
129. Dalkilic I, Schienda J, Thompson TG, Kunkel LM. Loss of filaminc (flnc) results in severe defects in myogenesis and myotube structure. Mol Cell Biol. 2006; 26:6522–6534. [PubMed: 16914736]
130. Arbustini E, Diegoli M, Fasani R, Grasso M, Morbini P, Banchieri N, Bellini O, Dal Bello B, Pilotto A, Magrini G, Campana C, Fortina P, Gavazzi A, Narula J, Vigano M. Mitochondrial DNA mutations and mitochondrial abnormalities in dilated cardiomyopathy. Am J Pathol. 1998; 153:1501–1510. [PubMed: 9811342]
131. Ashrafian H, Docherty L, Leo V, Towlson C, Neilan M, Steeples V, Lygate CA, Hough T, Townsend S, Williams D, Wells S, Norris D, Glyn-Jones S, Land J, Barbaric I, Lalanne Z, Denny P, Szumska D, Bhattacharya S, Griffin JL, Hargreaves I, Fernandez-Fuentes N, Cheeseman M, Watkins H, Dear TN. A mutation in the mitochondrial fission gene dnm1l leads to cardiomyopathy. PLoS Genet. 2010; 6:e1001000. [PubMed: 20585624]
132. Grasso M, Diegoli M, Brega A, Campana C, Tavazzi L, Arbustini E. The mitochondrial DNA mutation t12297c affects a highly conserved nucleotide of trna(leu(cun)) and is associated with dilated cardiomyopathy. Eur J Hum Genet. 2001; 9:311–315. [PubMed: 11313776]

133. Sibbing D, Pfeufer A, Perisic T, Mannes AM, Fritz-Wolf K, Unwin S, Sinner MF, Gieger C, Gloeckner CJ, Wichmann HE, Kremmer E, Schafer Z, Walch A, Hinterseer M, Nabauer M, Kaab S, Kastrati A, Schomig A, Meitinger T, Bornkamm GW, Conrad M, von Beckerath N. Mutations in the mitochondrial thioredoxin reductase gene txnrd2 cause dilated cardiomyopathy. European heart journal. 2011; 32:1121–1133. [PubMed: 21247928]

134. Rowland TJ, Graw SL, Sweet ME, Gigli M, Taylor MR, Mestroni L. Obscurin variants in patients with left ventricular noncompaction. Journal of the American College of Cardiology. 2016; 68:2237–2238. [PubMed: 27855815]

135. Marian AJ. The case of “missing causal genes” and the practice of medicine: A sherlock holmes approach of deductive reasoning. Circ Res. 2016; 119:21–24. [PubMed: 27340268]

136. Roncarati R, Viviani Anselmi C, Krawitz P, Lattanzi G, von Kodolitsch Y, Perrot A, di Pasquale E, Papa L, Portararo P, Columbaro M, Forni A, Faggian G, Condorelli G, Robinson PN. Doubly heterozygous lmna and ttn mutations revealed by exome sequencing in a severe form of dilated cardiomyopathy. Eur J Hum Genet. 2013; 21:1105–1111. [PubMed: 23463027]

137. Wessels MW, Herkert JC, Frohn-Mulder IM, Dalinghaus M, van den Wijngaard A, de Krijger RR, Michels M, de Coo IF, Hoedemaekers YM, Dooijes D. Compound heterozygous or homozygous truncating mybpc3 mutations cause lethal cardiomyopathy with features of noncompaction and septal defects. Eur J Hum Genet. 2015; 23:922–928. [PubMed: 25335496]

138. Zahka K, Kalidas K, Simpson MA, Cross H, Keller BB, Galambos C, Gurtz K, Patton MA, Crosby AH. Homozygous mutation of mybpc3 associated with severe infantile hypertrophic cardiomyopathy at high frequency among the amish. Heart. 2008; 94:1326–1330. [PubMed: 18467358]

139. Dellefave LM, Pytel P, Mewborn S, Mora B, Guris DL, Fedson S, Waggoner D, Moskowitz I, McNally EM. Sarcomere mutations in cardiomyopathy with left ventricular hypertrabeculation. Circ Cardiovasc Genet. 2009; 2:442–449. [PubMed: 20031619]

140. Hershberger RE, Lindenfeld J, Mestroni L, Seidman CE, Taylor MR, Towbin JA, Heart Failure Society of A. Genetic evaluation of cardiomyopathy–a heart failure society of america practice guideline. J Card Fail. 2009; 15:83–97. [PubMed: 19254666]

141. Pinto YM, Elliott PM, Arbustini E, Adler Y, Anastasakis A, Bohm M, Duboc D, Gimeno J, de Groote P, Imazio M, Heymans S, Klingel K, Komajda M, Limongelli G, Linhart A, Mogensen J, Moon J, Pieper PG, Seferovic PM, Schueler S, Zamorano JL, Caforio AL, Charron P. Proposal for a revised definition of dilated cardiomyopathy, hypokinetic non-dilated cardiomyopathy, and its implications for clinical practice: A position statement of the esc working group on myocardial and pericardial diseases. European heart journal. 2016; 37:1850–1858. [PubMed: 26792875]

142. van Spaendonck-Zwarts KY, van Rijsingen IA, van den Berg MP, Lekanne Deprez RH, Post JG, van Mil AM, Asselbergs FW, Christiaans I, van Langen IM, Wilde AA, de Boer RA, Jongbloed JD, Pinto YM, van Tintelen JP. Genetic analysis in 418 index patients with idiopathic dilated cardiomyopathy: Overview of 10 years’ experience. Eur J Heart Fail. 2013; 15:628–636. [PubMed: 23349452]

143. Garcia J, Tahiliani J, Johnson NM, Aguilar S, Beltran D, Daly A, Decker E, Haverfield E, Herrera B, Murillo L, Nykamp K, Topper S. Clinical genetic testing for the cardiomyopathies and arrhythmias: A systematic framework for establishing clinical validity and addressing genotypic and phenotypic heterogeneity. Front Cardiovasc Med. 2016; 3:20. [PubMed: 27446933]

144. Harakalova M, Kummeling G, Sammani A, Linschoten M, Baas AF, van der Smagt J, Doevendans PA, van Tintelen JP, Dooijes D, Mokry M, Asselbergs FW. A systematic analysis of genetic dilated cardiomyopathy reveals numerous ubiquitously expressed and muscle-specific genes. Eur J Heart Fail. 2015; 17:484–493. [PubMed: 25728127]

145. Fatkin D, Yeoh T, Hayward CS, Benson V, Sheu A, Richmond Z, Feneley MP, Keogh AM, Macdonald PS. Evaluation of left ventricular enlargement as a marker of early disease in familial dilated cardiomyopathy. Circ Cardiovasc Genet. 2011; 4:342–348. [PubMed: 21636824]

146. Moretti M, Merlo M, Barbati G, Di Lenarda A, Brun F, Pinamonti B, Gregori D, Mestroni L, Sinagra G. Prognostic impact of familial screening in dilated cardiomyopathy. Eur J Heart Fail. 2010; 12:922–927. [PubMed: 20525703]

147. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL, American College of Cardiology F, American Heart Association Task Force on Practice G. 2013 accf/aha guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. Journal of the American College of Cardiology. 2013; 62:e147–239. [PubMed: 23747642]

148. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M. 2016 esc guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the european society of cardiology (esc)developed with the special contribution of the heart failure association (hfa) of the esc. European heart journal. 2016; 37:2129–2200. [PubMed: 27206819]

149. Zannad F, Gattis Stough W, Rossignol P, Bauersachs J, McMurray JJ, Swedberg K, Struthers AD, Voors AA, Ruilope LM, Bakris GL, O'Connor CM, Gheorghiade M, Mentz RJ, Cohen-Solal A, Maggioni AP, Beygui F, Filippatos GS, Massy ZA, Pathak A, Pina IL, Sabbah HN, Sica DA, Tavazzi L, Pitt B. Mineralocorticoid receptor antagonists for heart failure with reduced ejection fraction: Integrating evidence into clinical practice. European heart journal. 2012; 33:2782–2795. [PubMed: 22942339]

150. Mestroni L, Brun F, Spezzacatene A, Sinagra G, Taylor MR. Genetic causes of dilated cardiomyopathy. Prog Pediatr Cardiol. 2014; 37:13–18. [PubMed: 25584016]

151. Jessup M, Marwick TH, Ponikowski P, Voors AA, Yancy CW. 2016 esc and acc/aha/hfsa heart failure guideline update - what is new and why is it important? Nat Rev Cardiol. 2016; 13:623–628. [PubMed: 27625120]

152. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Gorcsan J 3rd, Gras D, Krum H, Sogaard P, Holzmeister J, Echo CRTSG. Cardiac-resynchronization therapy in heart failure with a narrow qrs complex. N Engl J Med. 2013; 369:1395–1405. [PubMed: 23998714]

153. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2016 acc/aha/hfsa focused update on new pharmacological therapy for heart failure: An update of the 2013 accf/aha guideline for the management of heart failure: A report of the american college of cardiology/american heart association task force on clinical practice guidelines and the heart failure society of america. Journal of the American College of Cardiology. 2016; 68:1476–1488. [PubMed: 27216111]

154. Losurdo P, Stolfo D, Merlo M, Barbati G, Gobbo M, Gigli M, Ramani R, Pinamonti B, Zecchin M, Finocchiaro G, Mestroni L, Sinagra G. Early arrhythmic events in idiopathic dilated cardiomyopathy. JACC Clin EP. 2016; 2:535–543.

155. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekval TM, Spaulding C, Van Veldhuisen DJ. 2015 esc guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the european society of cardiology (esc). Endorsed by: Association for european paediatric and congenital cardiology (aepc). European heart journal. 2015; 36:2793–2867. [PubMed: 26320108]

156. Kusumoto FM, Calkins H, Boehmer J, Buxton AE, Chung MK, Gold MR, Hohnloser SH, Indik J, Lee R, Mehra MR, Menon V, Page RL, Shen WK, Slotwiner DJ, Stevenson LW, Varosy PD, Welikovitch L. Hrs/acc/aha expert consensus statement on the use of implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials. Circulation. 2014; 130:94–125. [PubMed: 24815500]

157. Kumar S, Baldinger SH, Gandjbakhch E, Maury P, Sellal JM, Androulakis AF, Waintraub X, Charron P, Rollin A, Richard P, Stevenson WG, Macintyre CJ, Ho CY, Thompson T, Vohra JK, Kalman JM, Zeppenfeld K, Sacher F, Tedrow UB, Lakdawala NK. Long-term arrhythmic and

nonarrhythmic outcomes of lamin a/c mutation carriers. Journal of the American College of Cardiology. 2016; 68:2299–2307. [PubMed: 27884249]

158. Saberi S, Day SM. Exercise prescription for the athlete with cardiomyopathy. Cardiol Clin. 2016; 34:591–601. [PubMed: 27692227]
159. Rosen MR, Myerburg RJ, Francis DP, Cole GD, Marban E. Translating stem cell research to cardiac disease therapies: Pitfalls and prospects for improvement. Journal of the American College of Cardiology. 2014; 64:922–937. [PubMed: 25169179]
160. Eulalio A, Mano M, Dal Ferro M, Zentilin L, Sinagra G, Zacchigna S, Giacca M. Functional screening identifies mirnas inducing cardiac regeneration. Nature. 2012; 492:376–381. [PubMed: 23222520]
161. Mann DL, Lee RJ, Coats AJ, Neagoe G, Dragomir D, Pusineri E, Piredda M, Bettari L, Kirwan BA, Dowling R, Volterrani M, Solomon SD, Sabbah HN, Hinson A, Anker SD. One-year follow-up results from augment-hf: A multicentre randomized controlled clinical trial of the efficacy of left ventricular augmentation with algisyl in the treatment of heart failure. Eur J Heart Fail. 2016; 18:314–325. [PubMed: 26555602]
162. Feric NT, Radisic M. Strategies and challenges to myocardial replacement therapy. Stem Cells Transl Med. 2016; 5:410–416. [PubMed: 26933042]
163. Sun N, Yazawa M, Liu J, Han L, Sanchez-Freire V, Abilez OJ, Navarrete EG, Hu S, Wang L, Lee A, Pavlovic A, Lin S, Chen R, Hajjar RJ, Snyder MP, Dolmetsch RE, Butte MJ, Ashley EA, Longaker MT, Robbins RC, Wu JC. Patient-specific induced pluripotent stem cells as a model for familial dilated cardiomyopathy. Sci Transl Med. 2012; 4:130ra147.
164. Burke MA, Cook SA, Seidman JG, Seidman CE. Clinical and mechanistic insights into the genetics of cardiomyopathy. Journal of the American College of Cardiology. 2016; 68:2871–2886. [PubMed: 28007147]
165. Marian AJ, van Rooij E, Roberts R. Genetics and genomics of single-gene cardiovascular diseases: Common hereditary cardiomyopathies as prototypes of single-gene disorders. Journal of the American College of Cardiology. 2016; 68:2831–2849. [PubMed: 28007145]

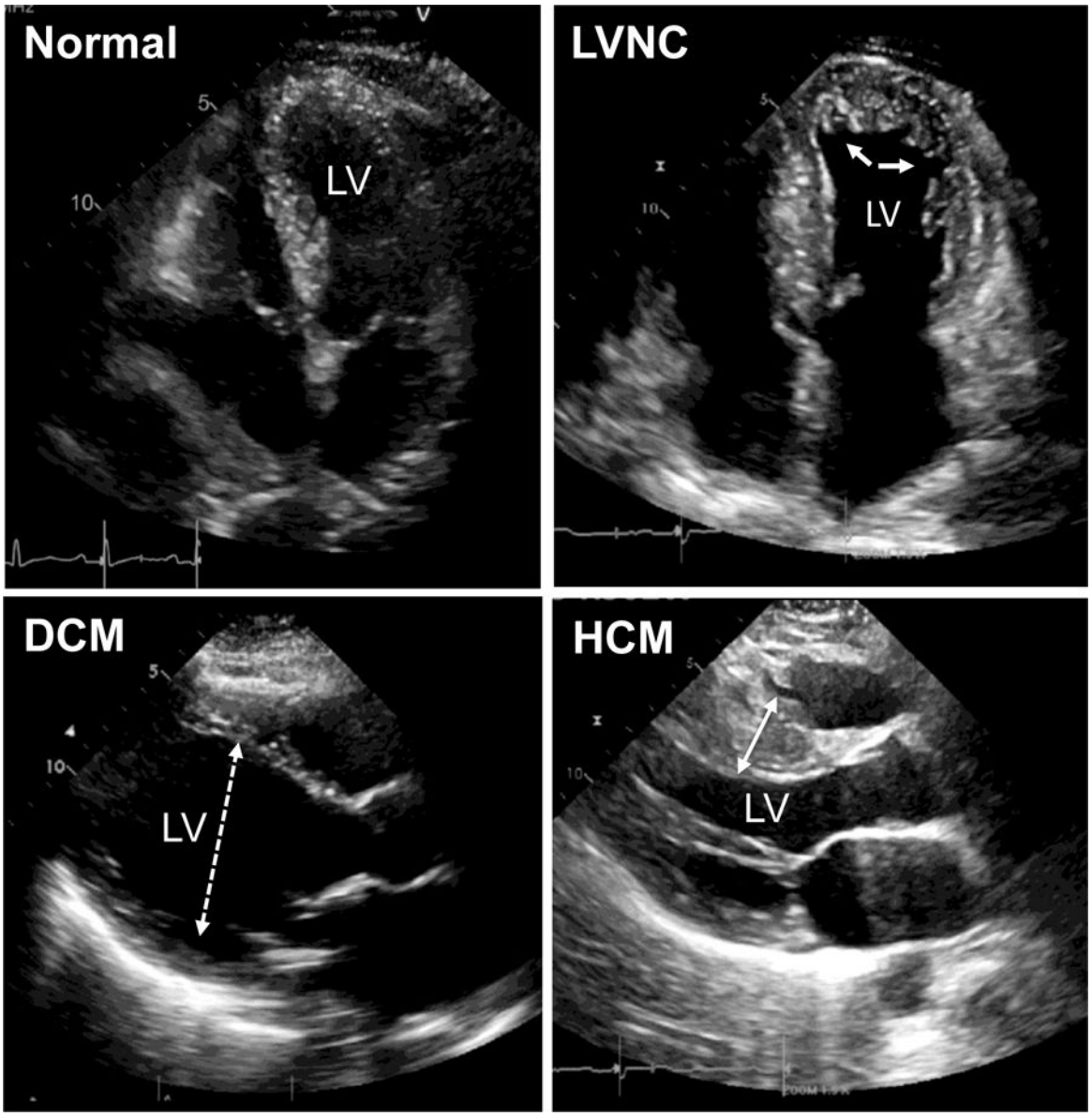

Figure 1. Echocardiography demonstrates forms of cardiomyopathy

Left ventricular noncompaction cardiomyopathy (LVNC) is shown in the upper right (arrows indicate deep trabeculations in the left ventricle (LV). Dilated cardiomyopathy (DCM) is defined by enlarged LV diameters (dashed double sided arrow). Hypertrophic cardiomyopathy (HCM) is defined with a thickened LV, including the septum (marked with double sided arrow).

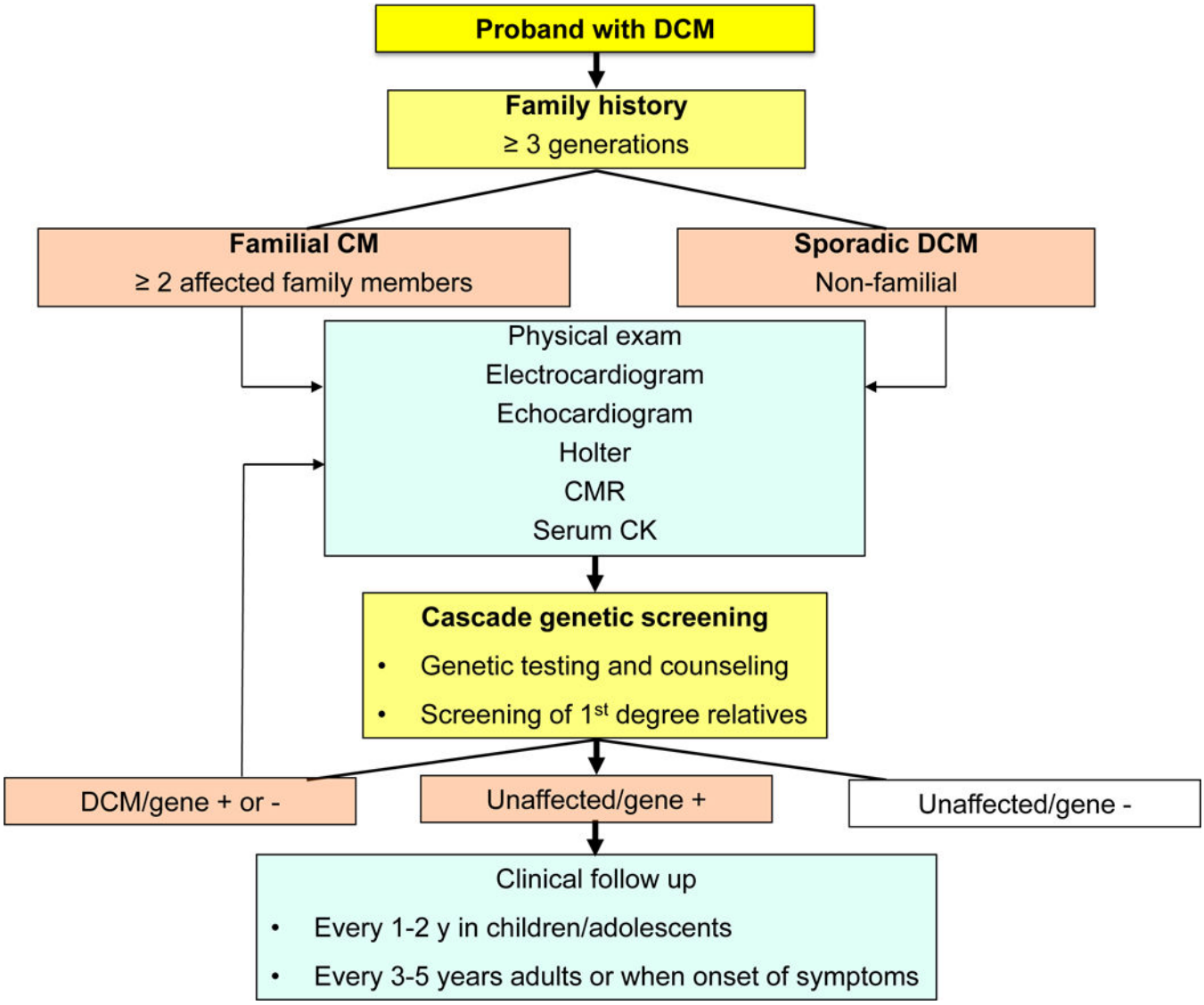

Figure 2. Algorithm for the management of a patient with nonischemic DCM

CMR: cardiac magnetic resonance, CK: creatine kinase. DCM patients should undergo an accurate family history examination. A comprehensive exam should include serum CK to evaluate skeletal muscle involvement. Genetic testing and genetic counseling should be offered to DCM patients, regardless of family history; 1st degree relatives should be examined (physical exam, ECG, echocardiogram). A positive genetic testing in the proband offers the possibility of a confirmatory genetic testing in relatives, which may guide follow up and need of further testing. Adapted from[14, 19, 140, 164]

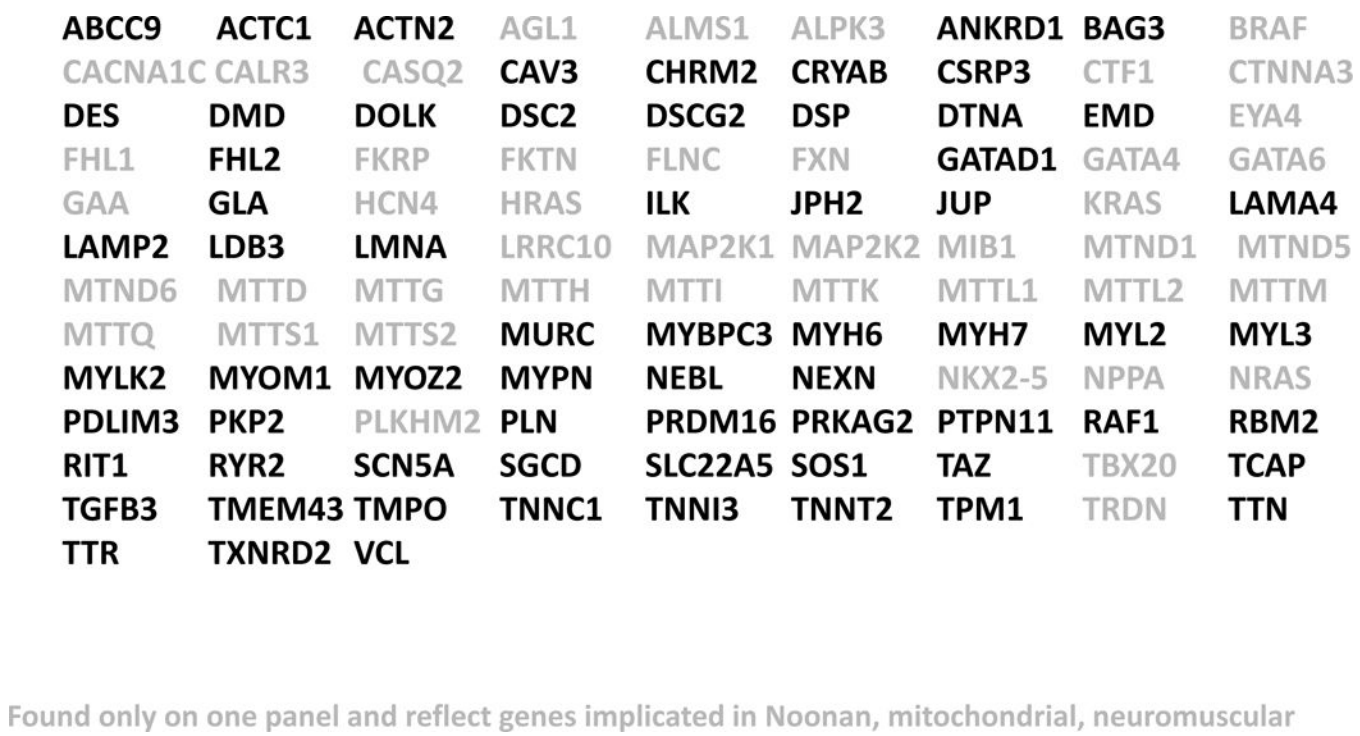

Figure 3. DCM gene panels are used for genetic testing

Shown is a list of 111 genes offered from multiple commercial testing laboratories for the evaluation of DCM. Those shown in black are commonly found on DCM panels from multiple sources, while those shown in gray are found on only some panels reflecting their role in syndromic cardiomyopathy such as Noonan syndrome, neuromuscular disease and/or mitochondrial myopathies.

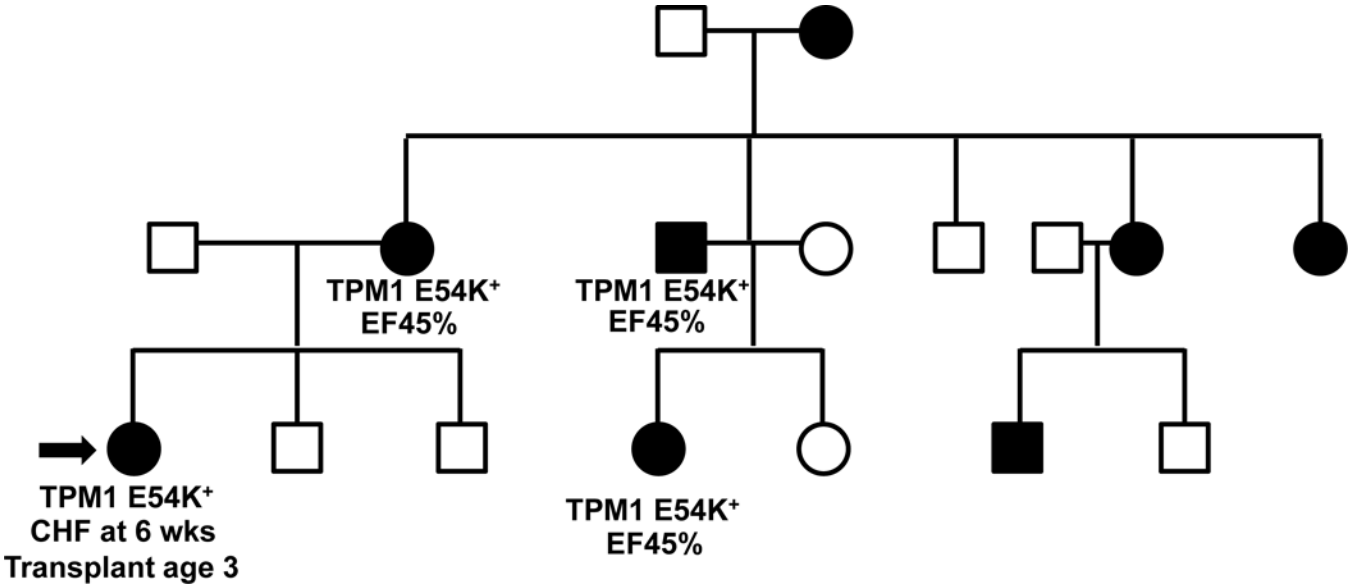

Figure 4.

A typical DCM pedigree is shown highlighting variable expressivity. Most DCM is inherited in an autosomal dominant pattern. Affected individuals with DCM are shown in black. A gene panel revealed the previously reported pathogenic TPM1 E54K variant. The proband (arrow) presented in early life requiring heart transplant during early childhood. Other members of the family are in their 3rd to 6th decade with LVEF 45%, demonstrating variable expressivity of the primary mutation. Environmental and additional genetic factors may contribute to variable expressivity.

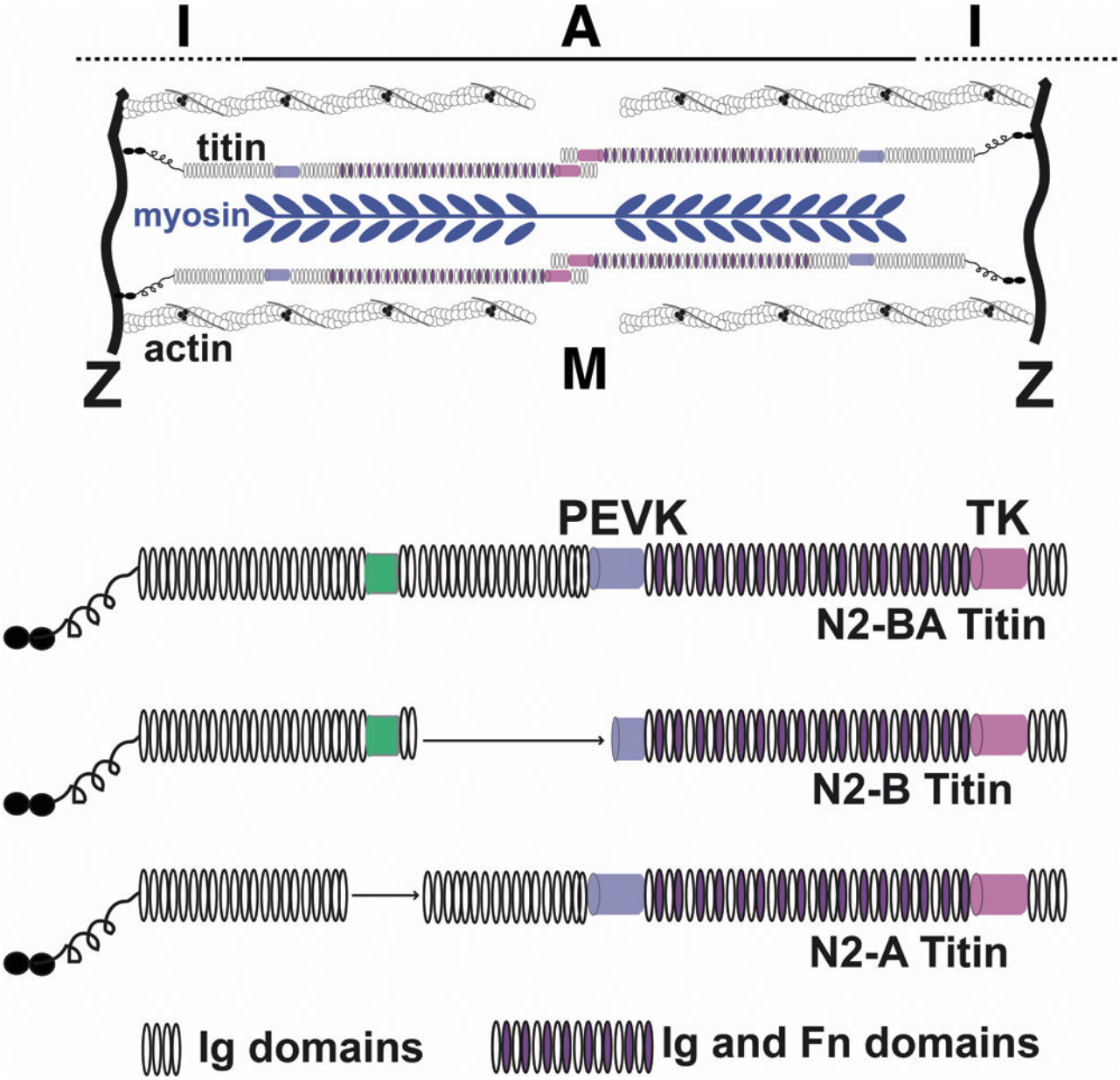

Figure 5.

Shown in the top is a schematic of the sarcomere with the position of the thick myosin-containing filaments and the thin actin-containing filaments. Titin is considered a third filament of the sarcomere since its spans from Z disk to M band. The lower schematics show the major splice forms of titin (N2-BA, N2-B, N2-A). The green box represents a unique sequence domain. The PEVK region is named for the repetitive amino acid sequences (proline, glutamine, valine, lysine).

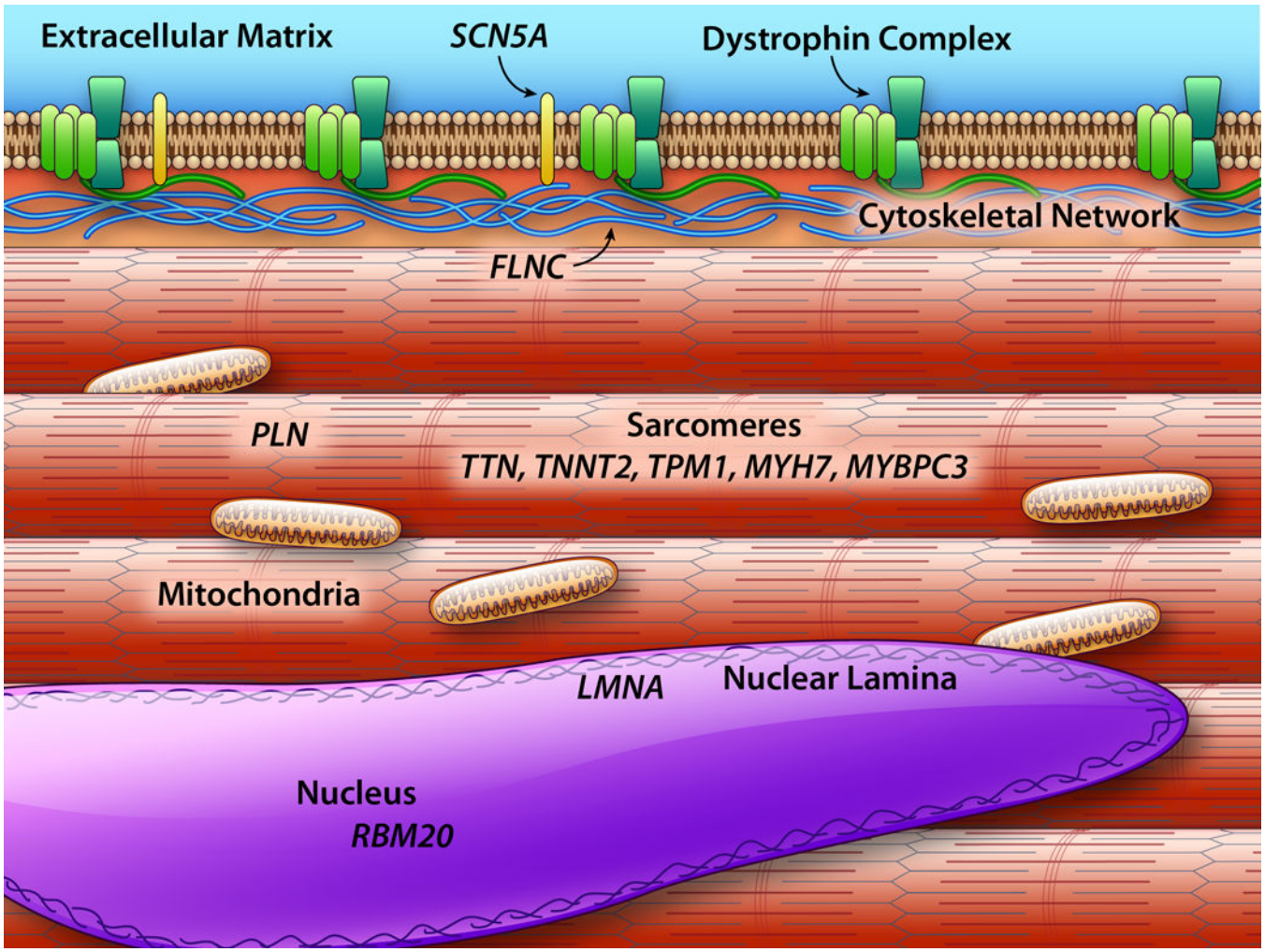

Figure 6.

Shown are major components within the cardiomyocyte with emphasis on compartments that contribute to genetically mediated DCM. The extracellular matrix is shown in gray. The dystrophin complex that includes the sarcoglycans (green) is mutated in forms of DCM with neuromuscular disease. The sarcomeres (pink) include components that are mutated in both HCM and DCM. Z band (dark red) is a mechanosensing hub that serves to transmit force from the sarcomeres. Mutations in both mitochondrially encoded (purple) and nuclear encoded mitochondria proteins lead to cardiomyopathy. The nuclear lamina include lamins A and C, and the gene *LMNA* is commonly mutated in DCM.

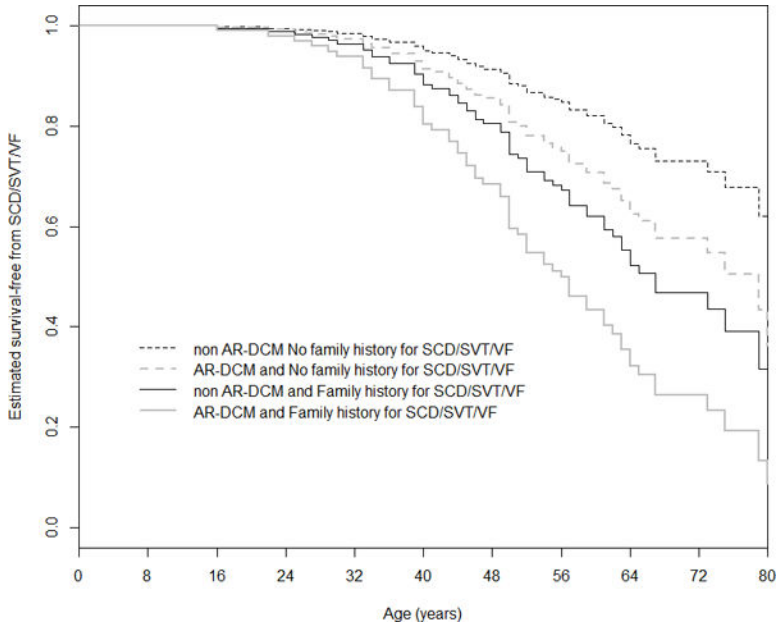

Figure 7. Sudden cardiac death and life-threatening ventricular arrhythmias in DCM

Cox-estimated event-free survival stratified by 2 risk factors, family history of SCD or ventricular arrhythmias (SVT or VF) and AR-DCM diagnosis, in a cohort of 285 DCM patients. The AR-DCM phenotype (p=0.02) and family history of SCD or ventricular arrhythmias (SCD/SVT/VF) (p=0.038) showed an additive prognostic effect on mortality for arrhythmic events. AR-DCM: Arrhythmogenic Dilated Cardiomyopathy; SCD/SVT/VF: sudden cardiac death, sustained ventricular tachycardia and ventricular fibrillation. From Spezzacatene et al.,[45] with permission.

Table 1

Frequency and phenotype correlates of definitive and putative DCM genes

Gene	Protein	Frequency and overlapping phenotypes
Sarcomere	**Force generation/transmission**	
MYH6	Alpha-myosin heavy chain	HCM, CHD, Sick Sinus Syndrome
MYH7*	Beta-myosin heavy chain	3–4% of DCM; HCM, LVNC
TPM1	Alpha-tropomyosin	1–2% of DCM; HCM, LVNC
ACTC1	Alpha cardiac actin	HCM, LVNC
TNNT2*	Cardiac troponin T	3% of DCM; HCM, LVNC
TNNC1	Cardiac troponin C	HCM, LVNC
TNNI3	Cardiac troponin I	HCM
MYBPC3	Myosin-binding protein C	HCM, LVNC
TTN*	Titin	12–25% of DCM; HCM, tibial muscle dystrophy
TNNI3K	Troponin I interacting kinase	Conduction defect, atrial fibrillation
MYL2	myosin light chain2, regulatory	HCM
MYL3	myosin light chain 3	HCM
MYLK2	Myosin Light Chain Kinase 2	HCM; in panels, not reported as DCM gene
MYOM1	myomesin 1	Myofibrillar myopathy; in panels, not reported as DCM gene
MYOZ2	myozenin 2	HCM
Z-disk	**Mechanosensing/mechanosignaling**	
ACTN2	Alpha-actinin 2	LVNC
BAG3	BCL2 Associated Athanogene 3	Myofibrillar myopathy
CRYAB	Alpha-B-crystallin	Protein aggregation myopathy
TCAP	Titin-cap/telethonin	LGMD2G
MYPN	Myopalladin	HCM, RCM
CSRP3	Muscle LIM protein	HCM
NEXN	Nexilin	HCM
FHL1	Four-and-a-half LIM protein1	EDMD, HCM
FHL2	Four-and-a-half LIM protein 2	HCM
ANKRD1	Cardiac ankyrin repeat protein	Congenital heart disease
MURC	Muscle Related Coiled-Coil Protein	
LDB3	Cypher/ZASP	LVNC
NEBL	nebulette	LVNC, HCM
Dystrophin complex	**Sarcolemma, structural integrity**	
DMD	Dystrophin	Duchenne/Becker muscular dystrophy
DTNA	Alpha-dystrobrevin	LVNC
SGCA	Alpha-sarcoglycan	LGMD2D
SGCB	Beta-sarcoglycan	LGMD2E
SGCD	Delta-sarcoglycan	LGMD2F

Gene	Protein	Frequency and overlapping phenotypes
SGCG	Gamma-sarcoglycan	LGMD2C
CAV3	Caveolin	HCM, LGMD1C, distal myopathy
ILK	Integrin-linked kinase	
FKTN	Fukutin	dystroglycanopathy, congenital muscular dystrophy
FKRP	Fukutin-related protein	dystroglycanopathy, LGMD
Cytoskeleton	**Mechanotransduction/mechanosignaling/structural integrity**	
DES	Desmin	<1% of DCM; Desminopathies, myofibrillar myopathy
VCL	Metavinculin	1% of DCM
FLNC	Filamin C	1% of DCM, AR-DCM; Myofibrillar myopathy, HCM, RCM
SYNM	Desmulin	
PDLIM3	PDZ LIM domain protein 3	
PLEC1	Plectin-1	LGMD2Q, epidermolysis bullosa
Desmosomes	**Cell–cell adhesion/mechanotransmission/mechanosignaling**	
DSC2	Desmocollin 2	ARVC, mild palmoplantar keratoderma
DSG2	Desmoglein 2	ARVC
DSP*	Desmoplakin	2% of DCM; ARVC
PKP2	Plakophilin 2	ARVC
CTNNA3	Catenin Alpha 3	ARVC; in panels, not reported as DCM gene
Sarcoplasmic reticulum and cytoplasm	**Ca homeostasis, contractility modulation, signaling**	
PLN	Phospholamban	ARVC, HCM
RYR2	Ryanodine receptor 2, Ca channel	ARVC, CPVT
CALR3	Calreticulin-3	ARVC, HCM; in panels, not reported as DCM gene
JPH2	Junctophilin 2	HCM
DOLK	Dolichol KINASE	Congenital disorder of glycosylation
MAP2K1	Mitogen-Activated Protein Kinase Kinase 1	Noonan Syndrome; in panels, not reported as DCM gene
MAP2K2	Mitogen-Activated Protein Kinase Kinase 2	HCM, Noonan Syndrome; in panels, not reported as DCM gene
NRAS	Neuroblastoma RAS Viral Oncogene Homolog	HCM, Noonan Syndrome
PRKAG2	Protein Kinase AMP-Activated Non-Catalytic Subunit Gamma 2	HCM, WPW
PTPN11	Protein Tyrosine Phosphatase, Non-Receptor Type 11	HCM, Noonan and Leopard Syndromes
RAF1	Proto-Oncogene	HCM, Noonan and Leopard Syndromes
RIT1	Ras Like Protein	Noonan Syndrome; in panels, not reported as DCM gene
SOS1	SOS Ras/Rac Guanine Nucleotide Exchange Factor 1	HCM, Noonan Syndrome; in panels, not reported as DCM gene
TRDN	Triadin	CVPT; in panels, not reported as DCM gene
Nuclear envelope	**Nuclear structural integrity, mechanotransduction, mechanosignaling**	

Gene	Protein	Frequency and overlapping phenotypes
LMNA*	Lamin A/C	4–8% of DCM; multiple phenotypes, LGMD1B, EDMD, progeria
EMD	Emerin	EDMD
LAP2/TMPO	Lamin-associated polypeptide 2	
SYNE1/2	Nesprin 1/2	EDMD, ataxia
Nucleus	**Transcription cofactors, gene expression**	
EYA4	Eyes absent 4	Deafness
FOXD4	Forkhead box D4	
HOPX	Homeobox only protein	
NFKB1	NF-kappa B1	
PRDM16	PR domain containing 16	LVNC
TBX20	T-box 20	Atrial septal defect
ZBTB17	Zinc finger and BTB domain containing protein 17	
RBM20*	RNA-binding protein 20	2% of DCM; RNA-binding protein of spliceosome of TTN and other proteins
GATA4	GATA binding protein 4	Atrial, ventricular septal defects, Fallot
GATA5	GATA binding protein 6	Atrial, ventricular septal defects, Fallot
GATAD1	GATA zinc finger domain-protein 1	
NKX2–5	Cardiac specific homeobox 1	Atrial, ventricular septal defects, Fallot, hypoplastic left heart
ALSM1	Centrosome And Basal Body Associated Protein	Alstrom Syndrome (phenocopy)
ALPK3	Alpha kinase 3	Pediatric cardiomyopathy
LRRC10	Leucine Rich Repeat Containing 10	
NPPA	Natriuretic paptide A	Atrial fibrillation
PLEKHM2	Pleckstrin Homology Domain	LVNC
TGFB3	Transforming Growth Factor Beta 3	ARVC; in panels, not reported as DCM gene
TMEM43	Transmembrane Protein 43	ARVC, EDMD; in panels, not reported as DCM gene
Ion channels		
SCN5A*	Type V Voltage-gated cardiac Na channel	2–3% of DCM; LQT, Brugada, atrial fibrillation, conduction defects
ABCC9	Sulfonylurea receptor 2A, component of ATP-sensitive potassium channel	Atrial fibrillation, osteochondrodysplasia
KCNQ1	Potassium channel	Atrial fibrillation, LQT1, Short QT1, Jervell and Lange-Nielsen syndrome
CACNA1C	Calcium Voltage-Gated Channel Subunit Alpha1 C	Brugada Syndrome, Timothy Sindrome
HCN4	Hyperpolarization Activated Cyclic Nucleotide Gated Potassium Channel 4	Brugada, Sick Sinus Syndrome
Mitochondria	**Supply and/or regulation of energy metabolism**	
CPT2	Carnitine palmitoyltransferase 2	carnitine deficiency, myopathy, lethal neonatal
FRDA/FXN	Frataxin	Fredreich ataxia
DNAJC19	HSP40 homolog, C19	3-methylglutaconic aciduria, type V
SDHA	Succinate dehydrogenase	Leigh syndrome

Gene	Protein	Frequency and overlapping phenotypes
SOD2	Superoxide dismutase	
TAZ/G4.5	Tafazzin	LVNC, Barth syndrome, endocardial fibroelastosis 2
CTF1	Cardiotrophin 1 cytokine	
mtDNA	Mitochondrially Encoded TRNA genes	Typically syndromic, mitochondial myopathy; in panels, not always reported as DCM genes
TXNRD2	Thioredoxin Reductase 2	
Extracellular matrix	**Cell adhesion and mechanosignaling**	
LAMA2	Laminin 2, merosin	Congenital muscular dystrophy
LAMA4	Laminin 4	
Lysosome		
LAMP2	Lysosome-associated membrane protein 2	Danon Disease
AGL	Amylo-Alpha-1, 6-Glucosidase, 4-Alpha-Glucanotransferase	Glycogen storage disease
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase	Cardiofaciocutaneous, Leopard, Noonan Syndromes
GAA	Glucosidase Alpha, Acid	Glycogen storage disease
GLA	Alpha galactosidase	Fabry Disease
Other		
PSEN1	Presenillin 1, Gamma secretase intramembrane protease complex	Alzheimer disease
PSEN2	Presenillin 2, Gamma secretase intramembrane protease complex	Alzheimer disease
CHRM2	Cholinergic Receptor Muscarinic 2	
HFE	Hemochromatosis	Phenocopy
HRAS	HRas Proto-Oncogene, GTPase	HCM, Costello Syndrome; in panels, not reported as DCM gene
KRAS	KRAS Proto-Oncogene, GTPase	HCM, Costello Syndrome; in panels, not reported as DCM gene
MIB1	Mitogen-Activated Protein Kinase Kinase 2	LVNC; in panels, not reported as DCM gene
SLC22A5	Cation/Carnitine Transporter	Skeletal myopathy
TTR	Transthyretin	Amyloidosis (phenocopy)

Legend: frequent (asterisk), definitive (bold) and putative DCM genes,[14, 23, 58, 164, 165] OMIM (www.omim.org, accessed 01/19/2017); GeneCards (www.genecards.org, accessed 01/19/2017). AR-DCM: arrhythmogenic DCM; ARVC: arrhythmogenic right ventricular cardiomyopathy; CPVT: cathecolaminergic polymorphic ventricular tachycardia; DCM: dilated cardiomyopathy, EDMD: Emery-Dreyfuss muscular dystrophy, HCM: hypertrophic cardiomyopathy, LGMD: limb-girdle muscular dystrophy, LVNC: left ventricular noncompaction, RCM: restrictive cardiomyopathy.