Published in final edited form as:

Curr Opin Cardiol. 2010 May ; 25(3): 198–204. doi:10.1097/HCO.0b013e328337ba52.

The genetics of dilated cardiomyopathy

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Abstract

Purpose of review—More than forty different individual genes have been implicated in the inheritance of dilated cardiomyopathy. For a subset of these genes, mutations can lead to a spectrum of cardiomyopathy that extends to hypertrophic cardiomyopathy and left ventricular noncompaction. In nearly all cases, there is an increased risk of arrhythmias. With some genetic mutations, extracardiac manifestations are likely to be present. The precise genetic etiology can usually not be discerned from the cardiac and/or extracardiac manifestations and requires molecular genetic diagnosis for prognostic determination and cardiac care.

Recent findings—Newer technologies are influencing genetic testing, especially cardiomyopathy genetic testing, where an increased number of genes are now routinely being tested simultaneously. While this approach to testing multiple genes is increasing the diagnostic yield, the analysis of multiple genes in one test is also resulting in a large amount of genetic information of unclear significance.

Summary—Genetic testing is highly useful in the care of patients and families, since it guides diagnosis, influences care and aids in prognosis. However, the large amount of benign human genetic variation may complicate genetic results, and often requires a skilled team to accurately interpret the findings.

Keywords

genetic mutations; cardiomyopathy; heart failure; arrhythmia

Introduction: Incidence of inherited dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is characterized by left ventricular dilatation and impaired systolic function and is a leading cause of heart failure. DCM is considered idiopathic if no other discernable cause such as ischemia, valvular disease or hypertension is present. However, the multifactorial etiology, such as hypertension in addition to a genetic defect, may lead to more severe disease with earlier onset. Idiopathic DCM is considered familial when more than one first degree relative has been diagnosed with DCM or had a sudden cardiac death at a young age [1]. DCM is inherited in 20%-50% of cases [2-4] and abnormalities are frequently seen on echocardiogram in asymptomatic relatives [3]. Inheritance for idiopathic DCM is primarily autosomal dominant, although other modes of inheritance occur. DCM can also occur secondarily in conjunction with systemic disease or

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The authors have no conflicts of interest relevant to the topic of this manuscript.

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syndromes. Determining the precise gene responsible for familial DCM impacts medical management and allows for early identification of those at risk.

Technology advances and genetic testing for cardiomyopathy

Inherited DCM is caused by mutations in at least 40 different individual genes. Taking into account genes implicated through animal modeling studies, the number of genes that can cause DCM is greater than 100. Since there are few clinical clues to indicate the precise gene mutation that causes DCM, clinical genetic testing that includes more genes increases diagnostic yield. Traditional genetic testing has been carried out by PCR amplification of exons and their immediate intronic flanking these regions. This strategy optimizes the ability to detect small point mutations such as deletions, insertions or substitutions. Since most cardiomyopathy mutations are autosomal dominant, the detection of heterozygous genetic variation is essential. Traditional genetic testing utilizes dideoxy (also known as Sanger) sequencing where chain termination is induced by the insertion of dideoxy nucleotides. Dideoxy sequencing is limited by the length of sequence that can be determined with a single reaction, thus raising the cost associated with mutation detection. Alternative formats, including an array-based method have been used for cardiomyopathy testing. This format detects mutations by hybridizing patient DNA to a chip where each exon has been arrayed. This approach improves cost effectiveness since the array contains multiple exons of many genes. While the chip based approach was intended for diagnosis of hypertrophic cardiomyopathy, the genetic overlap between hypertrophic and dilated cardiomyopathy extended the strategy as to be useful for DCM.

Newer sequencing approaches, referred to as “next generation” utilize DNA synthesis, rather than chain termination, to determine DNA sequence. This chemistry captures DNA fragments usually onto solid state platform, which in turn permits reduced reagent need and the capacity to analyze exponentially in a highly parallel format [5]. Given its capacity, next generation sequencing is expected to provide genetic testing at dramatically lower costs. Testing of multiple (50-200 genes) is highly feasible with this technology and thus it is suitable for cardiomyopathy testing. At this writing, next generation sequencing is being introduced for cardiomyopathy testing. The capacity of next generation sequencing will shift mutation detection, and with this approach entire genes, including introns, can be sequenced. These technologies are not designed to readily detect copy number variation that arises from larger genomic insertions and deletions, and thus, they may under sample certain types of mutations biasing results to point mutants.

Genes linked to DCM

The spectrum of genes linked to DCM is broad (Figure 1). The large number of genes that can be mutated in DCM parallels the large number of genes implicated in mental retardation or cancer. In addition to the gene spectrum for DCM, each gene harbors a large number of “private” mutations (or alleles), where the mutation is unique to a family. Genetic variation includes those variants that are much more highly prevalent in a population and also includes rare genetic variants (present in less than 1-5% of a given population). The role of private variation is one explanation offered to explain the hidden heritability of complex genetic traits [6]. For DCM, rare genetic variants unequivocally play a major role in determining disease.

Despite the seemingly vast number of genes and mutations linked to DCM, many of the genes can be usefully grouped by function and/or the intracellular localization of the gene products. The cardiomyocyte is the primary cell implicated in cardiomyopathy, and the unique and highly organized cell structure helps provide rationale for deciphering the genetics of cardiomyopathy.

Nuclear envelope proteins

The nuclear envelope is composed of two lipid bilayers, the outer nuclear membrane, which is contiguous with the endoplasmic reticulum, and the inner nuclear membrane. One of the most common genes implicated in familial DCM is *LMNA*, encoding the intermediate filament proteins lamins A and C (Table 1). *LMNA* mutations account for 5-8% of familial DCM cases [7-9]. Lamin A and lamin C are both encoded by *LMNA*, differing only in their carboxy-terminus. Lamins A and C assemble into higher order structures to constitute the nuclear intermediate filament network. This network provides structure to the nucleus and provides a scaffold for other nuclear proteins. *LMNA* gene mutations may be associated with extracardiac features including skeletal muscle weakness and contractures in the form of Emery-Dreifuss muscular dystrophy (EDMD) or limb girdle muscular dystrophy type. *LMNA* mutations can also produce Hutchinson-Guilford progeria syndrome, lipodystrophy and Charcot-Marie-Tooth syndrome type 2B [10,11]. Cardiovascular disease with *LMNA* mutations can be limited to DCM with or without conduction system disease. However, conduction system disease *prior* to DCM can also occur with *LMNA* mutations [9,12-16]. The conduction system disease with *LMNA* mutations is severe and is associated with sudden cardiac death (SCD), at a frequency reported as high as 46% [15,17]. The estimated penetrance of cardiac-related phenotypes in patients with *LMNA* mutations is 7% under age 20, 66% between ages 20 to 39, 86% between ages 40 to 59 and 100% after age 60 [16]. In a study of disease course in *LMNA* patients, those with implantable cardioverter defibrillators (ICDs) were found to be effective as primary prevention [16,18]. In a more recent study, this data is corroborated by finding forty-four percent of those individuals over the age of 40 had SCD or ICD intervention, and one-fifth (21%) under the age of 40 with 7% being under the age of 20 [16]. This data, as well as the presence of conduction system disease prior to onset of DCM, support that ICD therapy should be considered in *LMNA* patients, especially those who need pacemakers. These findings emphasize the importance of a genetic diagnosis in patients with idiopathic familial DCM.

Emerin, nesprin and LAP2 α are each nuclear membrane associated proteins, and mutations in each of the genes encoding these proteins have been implicated in cardiomyopathy. Mutations in *EMD*, encoding emerin, result in X-linked Emery-Dreifuss muscular dystrophy. Typically X-linked EDMD patients have skeletal involvement including progressive muscle weakness and contractures. Lamin associated polypeptide 2 α (LAP2 α) mutations lead to cardiomyopathy in humans and mice [19,20]. Nesprin-1 and nesprin-2 are spectrin-repeat proteins that interact with and are binding partners of emerin and lamin A. Together these components form the LINC complex that links the nucleus to the cytoplasm [21]. Mutations in nesprin-1 (*SYNE1*) and nesprin-2 (*SYNE2*) have been identified in EDMD and cardiomyopathy patients and this finding is reinforced by the phenotype in mouse models with disruption of nesprin-1 [22-24]. Like *LMNA* mutations, nesprin-1 mutations can lead to a range of phenotypes [25].

The sarcomere in DCM

The sarcomere is the basic unit of muscle contraction and is composed of thick and thin filaments. The thick filament is composed of predominantly myosin and myosin binding proteins. The thin filament is composed primarily of cardiac actin, α -tropomyosin and troponins. Mutations in the sarcomere genes cause both hypertrophic cardiomyopathy (HCM) and DCM. Sarcomere mutations have been identified in 25% of idiopathic DCM cases [26] and account for 10% of familial DCM [27]. The most common sarcomere genes identified in familial DCM are β -myosin heavy chain (*MYH7*) (10%) [28] and Troponin T (*TNNT2*) (2.9%) [28-30]. Other sarcomere genes identified in familial DCM are α -tropomyosin (*TPM1*) [31] [32], troponin C (*TNNC1*) [29], troponin I (*TNNI3*) [33] cardiac actin (*ACTC*) [34]. Autosomal recessive familial dilated cardiomyopathy has also been

caused by mutations in cardiac troponin I (*TNNI3*) [35]. Compound heterozygotes have been reported in the autosomal dominant familial DCM sarcomere genes, and could be as high as 25% of DCM cases [26], thus indicating a need for comprehensive sarcomere mutation screening for DCM, as is recommended for HCM. Intra- and interfamilial phenotypic variability is common with sarcomere gene mutations, ranging from minimal LV dilatation to severe LV dilatation and heart failure requiring heart transplant.

Because of the significant overlap in HCM and DCM causing genes, debate ensues over whether cardiomyopathy is a continuum such that DCM occurs secondary to a progressed and end-stage HCM and thus the result of the HCM causing sarcomere mutation, or conversely that DCM is the primary cardiomyopathy without an HCM phase. Cases of DCM as the initial presenting cardiomyopathy have been reported with sarcomere mutations, and thus could be a distinct entity of sarcomere mutations [26]. Another cardiomyopathy that could be potentially classified as being along this continuum is left ventricular noncompaction cardiomyopathy (LVNC). LVNC, characterized by a spongy morphological appearance of the myocardium, can be present in the absence of other extracardiac developmental disorders, in adults and with associated DCM or isolated with a family history of DCM. Mutations in sarcomere genes account for as much as 17% of LVNC [36] and may be present in dilated cardiomyopathy with hypertrabeculation [37].

Cytoskeletal gene mutations in DCM

Dystrophin links the sarcolemmal membrane proteins to the cytoplasmic γ -actin stabilizes the plasma membrane in heart and skeletal muscle. Deletions occur commonly in dystrophin, and those that ablate dystrophin production cause classical severe skeletal muscle weakness and DCM in Duchenne muscular dystrophy. Mutations that leave some dystrophin expression yield the less severe Becker muscular dystrophy phenotype. An analysis of Becker Muscular Dystrophy gene mutations highlights regions of the dystrophin protein that may be prone to cardiomyopathy [38]. There is however a subset of patients, up to 6.5% of male patients with DCM, with deletions/point mutations in dystrophin that have DCM with minimal skeletal muscle involvement [39,40]. Molecularly, X-linked DCM can be explained by differential function of dystrophin between heart and muscle, or more commonly, deletion of sequences that affect heart but not skeletal muscle expression of dystrophin.

The sarcoglycans (α , β , γ and δ) are a group of transmembrane proteins that interact with dystrophin and like dystrophin, they are primarily found in heart and skeletal muscle. Mutations in any of the sarcoglycans produce an autosomal recessive limb-girdle muscular dystrophy phenotype of progressive early onset muscle weakness, with mutations in β , γ and δ sarcoglycan also causing significant DCM [41-44]. Mutations in the gene encoding δ -sarcoglycan lead to cardiomyopathy without clinically obvious skeletal muscle disease [45]. Fukutin-related protein (FKRP) is required for the dystrophin glycoprotein complex to remain intact. Mutations in the FKRP gene cause a phenotypic spectrum from limb-girdle muscular dystrophy with DCM [46,47] to DCM with minimal muscle weakness [48].

The Z-disc defines the lateral boundaries of the sarcomere. Z-discs provide an anchoring site for actin filaments and titin and are the primary conduits of force generated by contraction as they are aligned to adjacent myofibrils to coordinate contraction. Z-disc proteins are positioned as intra and intercellular signaling nodes [49]. Thus aberrant proteins associated with the Z-discs can result in disease. Desmin is an intermediate filament of skeletal and cardiac muscle and maintains the structural and functional integrity of myofibrils and functions as a cytoskeletal protein linking Z bands to the plasma membrane. Mutations in the desmin (*DES*) gene are associated with an autosomal dominant skeletal myopathy, cardiac conduction block and cardiomyopathy, however can also cause a cardiac only

phenotype [50-52]. Cypher/ZASP (*LDB3*) is a Z-disc component in skeletal and cardiac muscle, in which mutations play a causative role in isolated DCM, isolated left ventricular noncompaction and familial DCM with left ventricular noncompaction [53-56]. Muscle LIM protein (MLP) is another Z-disc protein and part of mechanical stretch sensing and contributes to less than 1% of familial DCM [30,57]. Titin (*TTN*) is a large sarcomere protein found in cardiac and skeletal muscles. Titin's amino-terminus is anchored to the Z-disc and the carboxy-terminus is bound to the myosin thick filament [58]. Idiopathic familial DCM causative mutations in the *TTN* gene have been identified [59,60], although the large size of this gene has precluded its systematic screening in DCM patients. Therefore, the true incidence of *TTN* mutations may be underrepresented.

Other DCM genes

Other genes encoding proteins that act as part of calcium regulation and ion channels have been identified as causative of DCM. Not surprisingly, many of these also cause conduction defects. Phospholamban (*PLN*) is a transmembrane phosphoprotein that inhibits the cardiac sarcoplasmic reticular adenosine triphosphatase pump. *PLN* gene mutations lead to disease through myocellular calcium dysregulation [61]. Interestingly, the R14 deletion of *PLN* has been associated with both mild and severe forms of cardiomyopathy with variable conduction system disease, underscoring the phenotypic variability that can be associated with DCM [4,62,63]. Cardiac sodium channel (*SCN5A*) gene mutations, traditionally identified as causative of Long QT syndrome type III [64] and Brugada syndrome [65], were identified in idiopathic DCM with atrial fibrillation and without corrected QT-interval prolongation or ST-segment elevation [66,67] and is thus another cause of DCM with conduction system disease.

Another distinct mechanism of DCM is mediated through perturbation of transcription cofactors and RNA binding. Ankyrin repeat domain 1 (*ANKRD1*) is the gene encoding CARP, a transcription cofactor that is present in the I-band region of the sarcomere as a member of the titin-N2A mechanosensory unit [68]. Mutations in *ANKRD1* have recently been identified as causative in sporadic and familial DCM at a rate of 1.9% [69]. *EYA4* encodes a transcriptional coactivator, which interacts with DNA binding transcription factors. Mutations in *EYA4* are predicted to alter cochlear and cardiac gene expression as the mutation causing phenotype is one of DCM and sensorineural hearing loss [70]. Ribonucleic acid binding protein (*RBM20*) mutations recently identified through genome-wide linkage analysis as causative for familial DCM with reported conduction defects [71]. *RBM20* encodes RNA binding motif protein 20, which has a RNA-recognition motif followed by an RS domain; features characteristic of RNA binding SR protein family that assemble in the spliceosome. *RBM20* mutations accounted for 3% of DCM cases, 5% of familial DCM and 13% of cases with a history of sudden death [71].

Summary and recommendations

Guidelines have been published for genetic testing in DCM [72]. Rapidly evolving technology will both reduce cost and increase the number of genes that can be screened, and thus guidelines will likely be modified. The major confounding feature that will be increasingly encountered in interpreting genetic testing is the “variant of unknown significance” or VUS, where a genetic change has been identified but it cannot be stated with reasonable certainty whether this represents a benign or disease causing variant. Strategies to reduce the VUS classification include generating larger databases of normal human variation, as can be anticipated from the 1000 genome sequencing effort [73], and working with related family members to determine whether the VUS segregates with disease within the individual family.

Presymptomatic genetic testing is typically recommended in at-risk family members with identified gene mutations since it is less costly than repeated imaging, an alternative surveillance method for at risk family members. However, once a gene mutation carrier is identified, cardiac imaging is a key adjunct in determining disease progression and risk. Echocardiography and increasingly cardiac magnetic resonance imaging (MRI) are being used for monitoring disease progression. Early features of cardiomyopathy can be detected using echocardiographic tissue Doppler or MRI to detect late gadolinium enhancement (LGE) as a reflection of myocardial scar [74-77]. There is growing evidence of LGE in HCM being a predictor of ventricular arrhythmias [78-84]. The combination of genetic and imaging information should provide an accurate means of following interventions aimed at preventing or slowing onset of disease. Managing genetic information in the context of individuals and families with or at risk of developing DCM benefits from a team of experts including genetic counselors and cardiologists including those specialized in heart failure and electrophysiology [72,85].

Acknowledgments

The authors are supported by Doris Duke Charitable Foundation and NIH R01 HL61322, HL92443.

Abbreviations

DCM	dilated cardiomyopathy
HCM	hypertrophic cardiomyopathy
ICD	implantable cardioverter defibrillator
LGE	late gadolinium enhancement
LVNC	left ventricular noncompaction
SCD	sudden cardiac death
VUS	variant of unknown significance

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Figure 1. Genes linked to DCM

Shown is an electron micrograph of a cardiomyocyte. The genes that encode proteins linked to specific intracellular locations and cell functions are depicted. The white size bar represents 2 μ m.