Clinical and genetic issues in dilated cardiomyopathy: A review for genetics professionals

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Abstract: Dilated cardiomyopathy (DCM), usually diagnosed as idiopathic dilated cardiomyopathy (IDC), has been shown to have a familial basis in 20–35% of cases. Genetic studies in familial dilated cardiomyopathy (FDC) have shown dramatic locus heterogeneity with mutations identified in >30 mostly autosomal genes showing primarily dominant transmission. Most mutations are private missense, nonsense or short insertion/deletions. Marked allelic heterogeneity is the rule. Although to date most DCM genetics fits into a Mendelian rare variant disease paradigm, this paradigm may be incomplete with only 30–35% of FDC genetic cause identified. Despite this incomplete knowledge, we predict that DCM genetics will become increasingly relevant for genetics and cardiovascular professionals. This is because DCM causes heart failure, a national epidemic, with considerable morbidity and mortality. The fact that early, even pre-symptomatic intervention can prevent or ameliorate DCM, coupled with more cost-effective genetic testing, will drive further progress in the field. Ongoing questions include: whether sporadic (IDC) disease has a genetic basis, and if so, how it differs from familial disease; which gene-specific or genetic pathways are most relevant; and whether other genetic mechanisms (e.g., DNA structural variants, epigenetics, mitochondrial mutations and others) are operative in DCM. We suggest that such new knowledge will lead to novel approaches to the prevention and treatment of DCM. ***Genet Med* 2010: 12(11):655–667.**

Key Words: *genetics, dilated cardiomyopathy, genetic testing, genetic counseling*

Dilated cardiomyopathy (DCM) has recently emerged as having a genetic basis, much as did hypertrophic cardiomyopathy (HCM) in the 1990s. The discovery of genetic cause for some of DCM, otherwise thought to be idiopathic, and the rapid development of more cost-effective molecular genetic testing for rare variants bring an opportunity for collaboration between genetics professionals and cardiovascular specialists in DCM evaluation and diagnosis.

Knowledge of DCM is increasingly essential for genetics professionals in both general genetics practices staffed by clinical geneticists and genetic counselors and in cardiovascular genetic medicine clinics staffed by cardiovascular and genetic professionals.[1] This is because we predict that genetic DCM will rapidly emerge from an uncommon diagnosis rarely seen in either genetics or cardiology clinics, to a mainstream genetics diagnosis, now associated with >30 genes. This prediction is based on four key facts. First, DCM of all causes underlies at least half of the heart failure epidemic in the United States, where the heart failure syndrome is defined as an inadequate cardiac output to provide circulatory and nutrient support to the body. Heart failure, from American Heart Association statistics in 2010, affected approximately 5.8 million US citizens,[2] of which a significant portion will be diagnosed with DCM of unknown cause (otherwise characterized as idiopathic DCM [IDC]). Second, a genetic cause has been demonstrated for an estimated 30–35% of IDC (in familial or apparently sporadic cases), making testing feasible. Third, the recent dramatic progress with more cost-effective genetic testing makes predictive diagnosis possible and enhances presymptomatic diagnosis. Finally, and perhaps most importantly, presymptomatic interventions of DCM have proven value to prevent morbidity and mortality.

We also note that the classic Mendelian rare variant paradigm may be incomplete to characterize genetic DCM.[3] Although considerable progress has been made in discovering the genetic cause of a fraction of DCM, providing an initial foothold for clinical practice, we also predict that with the availability of exome and whole genome sequencing, our understanding of DCM genetics will transition into a more complex rare variant paradigm.[3] Hence, we will need genetics professionals to contribute to the DCM research effort and to help manage the clinical aspects of this important entity.

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DCM: EPIDEMIOLOGY, NOMENCLATURE, AND CLINICAL CHARACTERISTICS

Definition and diagnosis of DCM

DCM is characterized by left ventricular enlargement (LVE) and systolic dysfunction with an ejection fraction (EF) < 50%,[4] or, more stringently, <45% (Table 1).[5] Approximately 35–40% of DCM cases are assigned a diagnosis of IDC after detectable causes have been excluded. The most common DCM cause in the United States, ischemic heart disease due to coronary artery disease (CAD), needs to be excluded in men older than 40 years and women older than 45 years (or at younger ages if risk factors are present, e.g., cigarette smoking, diabetes, hypertension, or a strong family history of early coronary disease). Less common causes of DCM that need to be excluded include structural heart disease (congenital or valvular), thyroid disease, iron overload, and exposure to cardiotoxins such as anthracyclines, chest radiation, and other much less common conditions, including those accompanying inflammatory arthritides, myocarditis (e.g., giant cell myocarditis), protozoal infections (e.g., Chagas disease), and many others (Table 2). HCM may occasionally show characteristics of DCM (reduced systolic function and some dilatation) late in its course (Table 1). Extensive literature, not reviewed in this study, is available for HCM.[9–12]

DCM nomenclature: IDC

DCM can be used either as a generic term to include all causes of LVE and systolic dysfunction, separating DCM from the two other classic cardiomyopathy categories, HCM or re-

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Table 1 Characteristics of dilated (DCM), hypertrophic (HCM), or restrictive (RCM) cardiomyopathies

Type of cardiomyopathy	Characteristics	Comments
DCM	LV dilatation Systolic dysfunction	Can also be accompanied by RV dilatation or atrial and ventricular (four chamber) dilatation Usually defined as ejection fraction <50 or 45%; the ejection fraction may be 10–20% with advanced disease
HCM	LV hypertrophy No dilatation May be hypercontractile In late stage may occasionally resemble DCM	May show asymmetric septal hypertrophy or concentric LV hypertrophy Hypertrophy occurs commonly with LV wall thickness >15 mm but can be severe (>20 mm) or very severe (>>20 mm), where normal LV wall thickness is ≤12 mm. Normal to smaller LV cavity Ejection fraction at times >80% The "burned out" phase in late-stage disease may show a diminished ejection fraction and at times some dilatation. It is unusual for "true" HCM to present in the "burned out" DCM phase.
RCM	Mild LV hypertrophy Systolic function normal to mildly decreased	RCM is usually defined physiologically, where an elevated left ventricular end diastolic pressure is required to reach a normal left ventricular end diastolic volume. The ejection fraction may be normal and is usually not less than 40%.

Normal ejection fraction usually considered 55–75%. Usual LV wall thickness is 9–11 mm. RCM at times can be difficult to categorize clinically; it can commonly overlap with HCM, and part of this is phenotypic plasticity with genetically mediated HCM/RCM.
LV, left ventricle; RV, right ventricle.

strictive cardiomyopathy (RCM) (Table 1).[11] Further, it has become common practice within heart failure clinical trials to assign patients into categories of "ischemic" or "nonischemic" DCM. The former category includes anyone with ischemic heart disease, most commonly from prior myocardial infarction and/or CAD, defined most stringently for research purposes as at least one epicardial coronary artery with >50% narrowing. However, this research standard may be too stringent for clinical (or clinical trial) purposes, as it is not uncommon to observe DCM with CAD and coronary narrowing of 50–70% (and at times involving multiple vessels) without evidence of prior myocardial infarction that may be adjudicated by cardiovascular specialists as "nonischemic cardiomyopathy with incidental CAD." Nonischemic cardiomyopathy is used to categorize all other causes of DCM (Table 2), although the majority com-

Table 2 Selected reported causes of nongenetic DCM[6–8]

- Ischemic
  - Coronary heart disease, myocardial infarction, and associated conditions
- Toxins
  - Ethanol/alcohol
  - Cobalt
  - Carbon monoxide/smoking
  - Lead
  - Cadmium
  - Mercury
  - Chemotherapeutic agents
    - Anthracyclines (e.g., doxirubucin)
    - Trastuzumab
  - Other drugs
    - Cocaine
    - Sympathomimetics
- Metabolic
  - Nutritional deficiencies: Thiamin, selenium, and carnitine
  - Electrolyte disturbances: Hypocalcemia and hypophosphatemia
- Endocrine
  - Hypothyroidism
  - Acromegaly
  - Thyrotoxicosis
  - Cushing disease
  - Pheochromocytoma
- Inflammatory or infectious causes
  - Infectious
    - Viral (enteroviruses, influenza, and HIV)
    - Rickettsiual
    - Bacterial
    - Mycobacterial
    - Fungal
    - Parasitic (toxoplasmosis, trichinosis, and Chagas disease)
  - Noninfectious
    - Hypersensitivity myocarditis
- Infiltrative
  - Sarcoidosis
  - Amyloidosis
- Other
  - Tachycardia mediated

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prises DCM of unknown etiology. This latter category, termed IDC, is a diagnosis of exclusion. IDC is used to describe the phenotype (Table 3). Assignment of IDC requires a careful and complete medical and at least a three-generation family history, a comprehensive physical examination, an electrocardiogram, an echocardiogram, and further testing as indicated (see later).

Familial DCM

A diagnosis of familial DCM (FDC) is assigned when IDC occurs in at least two closely related family members.[4,5] This is a phenotypic diagnosis (Table 3). Of these cases, we have recently shown that approximately 28% have nonsynonymous rare variants in 14 genes previously shown to cause DCM.[13] Most genes implicated in genetic DCM/FDC are autosomal with dominant transmission, although a few follow an autosomal recessive, X-linked, or mitochondrial pattern of inheritance[4,11,14] (Table 4).

DCM nomenclature: Genetic DCM

The genetic basis of IDC has recently emerged, and hence at this time, the terminology of "genetic DCM," (Table 3) much less a more specific gene-based diagnosis (e.g., *LMNA* cardiomyopathy), is not part of the common diagnostic lexicon. However, we propose this approach (Table 3).

IDC epidemiology

IDC affects all ethnic groups. An epidemiologic study conducted in Olmsted County, Minnesota, in 1989, estimated the incidence of IDC at 6/100,000, and prevalence was estimated at 36.5 per 100,000.[76] That same study found that the prevalence of HCM was 19.7 per 100,000.[76] This study may have significantly underestimated both IDC and HCM prevalence, as subsequent studies have estimated HCM prevalence to be 1/500,[77] (or 200/100,000, 10 times more prevalent than the Olmsted County study). From a variety of sources, it is likely that the incidence and prevalence of DCM have also been significantly underestimated. Heart failure experts suggest that IDC is at least as common as HCM, with estimates ranging up to twice that of HCM, but no further published studies are available.

LVE and systolic dysfunction

The DCM diagnosis by definition requires the presence of LVE and reduced systolic function, both most commonly evaluated by transthoracic echocardiography. The echocardiographically determined upper limits of normal of the left ventricular (LV) chamber size have historically been defined using an algorithm based on body surface area.[78] More recently, echocardiographic data from 1099 normal subjects from the Framingham heart study led to more rigorous definitions of echocardiographic normals using a height- and gender-based approach,[79] which has been used in our DCM research.[80,81] Defining the upper limits of normal LV size is imperative for clinical interpretation, so that mildly dilated left ventricles will not be missed, particularly in females of shorter stature. Regardless of approach, genetics professionals conducting family-based evaluations of early DCM in at-risk relatives must insist on careful LV measurements in end diastole using current tables or algorithms for determining upper limits of normal. This concept, however, has not been incorporated into echocardiogram reports on a regular basis.

We note, however, that in familial studies that include cardiovascular screening of asymptomatic relatives of individuals with IDC, systolic dysfunction has been observed to precede LVE or vice versa. A key IDC/FDC phenotyping study[82] observed that LVE preceded systolic dysfunction in a number of cases and proposed LVE as an early sign of DCM. In other cases, the opposite has been observed, where reduced systolic function precedes LVE.

Systolic function is almost always estimated by a measure of the LV ejection fraction, most commonly by echocardiography, nuclear studies, or cardiac magnetic resonance (CMR) imaging. Systolic function, measured by EF provided in EF percentage units, can be most accurately assessed with high reliability with nuclear studies performed in good laboratories. For example, a multiuptake gated acquisition study can provide measures of LV ejection fraction (±3% EF units) that are considered superior to that of echocardiography (±5–10% EF units). The mean EF by nuclear studies in a population of normal subjects in most laboratories is approximately 65% ± 10% representing two standard deviations. The normal EF for echocardiographic studies is also 65% ± 10%, but because of issues of precision, an echocardiographically derived EF of 50–55% is considered a gray zone, and an echocardiographic EF $< 50\%$ is considered abnormal.

Another measure of systolic function, fractional shortening (FS), is a ratio of the LV end dimension in systole (LVEDs) compared with the LV dimension in end diastole (LVEDd) that can be simply calculated from echocardiographic LV measurements (FS = [LVEDd − LVEDs]/LVEDd). A FS of <25–28% is also indicative of systolic dysfunction.

CMR, because of its superior imaging capabilities, is recently considered the gold standard for measures of chamber size, function, mass, and other parameters, and with expert interpretation, is always reasonable to consider in the initial evaluation of cardiomyopathy. However, compared with echocardiography, CMR is not universally available, CMR is more expensive

Table 3 Proposed phenotype and genotype nomenclature for DCM

		Genotype[b]	
	Phenotype[a]	Nonspecific	Specific[c]
Sporadic	IDC—Idiopathic dilated cardiomyopathy	Genetic dilated cardiomyopathy (genetic DCM)	*TNNT2*-DCM, *LMNA*-DCM, *MYH7*-DCM, etc.
Familial	FDC—Familial dilated cardiomyopathy		

[a]We note that IDC and FDC are phenotypic terms.
[b]Whether all FDC has a genetic basis is still not fully resolved. However, for clinical care purposes, it may be reasonable to assume that most of FDC is genetic because of its familial basis and thus inferred heritable nature and the extensive genetic data to support this (Table 4). How much of IDC is caused by genetic disease remains unanswered at this time—other hypotheses have included a variety of endogenous or exogenous environmental causes (e.g., hypertension, hormones, ethanol, viruses, and other environmental toxins).
[c]The "specific genotype" category means that a genetic diagnosis has been made. If a specific genetic cause is found in a patient with IDC/FDC, we suggest a nomenclature where the "disease gene" is appended with "DCM."

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Table 4 Genes reported in association with (nonsyndromic) dilated cardiomyopathy

Genes[a]	Protein	Function	Estimated frequency[b]	References
Autosomal-dominant FDC				
Dilated cardiomyopathy phenotype				
ACTC	Cardiac actin	Sarcomeric protein; muscle contraction	0.005	15–20
DES	Desmin	DAGC; transduces contractile forces	0.003	18, 21, 22
SGCD	δ-sarcoglycan	DAGC; transduces contractile forces	0.003	22–24
MYH7	β-myosin heavy chain	Sarcomeric protein; muscle contraction	0.042	25–28
TNNT2	Cardiac troponin T	Sarcomeric protein; muscle contraction	0.029	25–27, 29–32
TPM1	α-tropomyosin	Sarcomeric protein; muscle contraction	0.006	13, 33, 34
TTN	Titin	Sarcomere structure/extensible scaffold for other proteins	?	35
VCL	Metavinculin	Sarcomere structure; intercalated discs	0.01	27, 36
MYBPC3	Myosin-binding protein C	Sarcomeric protein; muscle contraction	0.02	13, 28
CSRP3	Muscle LIM protein	Sarcomere stretch sensor/Z discs	0.003	25, 37
ACTN2	α-Actinin-2	Sarcomere structure; anchor for myofibrillar actin	0.009	38
PLN	Phospholamban	Sarcoplasmic reticulum Ca++ regulator; inhibits SERCA2 pump	?	27, 39, 40
LDB3	Cypher	Cytoskeletal assembly; targeting/clustering of membrane proteins	0.01	25, 41
MYH6	α-Myosin heavy chain	Sarcomeric protein; muscle contraction	0.043	13, 42
ABCC9	SUR2A	Kir6.2 regulatory subunit, inwardly rectifying cardiac KATP channel	0.006	43
TNNC1	Cardiac troponin C	Sarcomeric protein; muscle contraction	0.004	13, 30
TCAP	Titin-cap or telethonin	Z-disc protein that associates with titin; aids sarcomere assembly	0.01	25, 44
TNNI3	Cardiac troponin I	Sarcomeric protein, muscle contraction; also seen as recessive	0.004	13, 45
EYA4	Eyes-absent 4	Transcriptional coactivators (Six and Dach)	?	46
TMPO	Thymopoietin	Also LAP2; a lamin-associated nuclear protein	0.011	47
PSEN1/2	Presenilin 1/2	Transmembrane proteins, gamma secretase activity	0.01	48
CRYAB	Alpha B crystalin	Cytoskeletal protein	0.007	49
PDLIM3	PDZ LIM domain protein 3	Cytoskeletal protein	0.005	50
MYPN	Myopalladin	Sarcomeric protein, Z-disc	0.035	51
LAMA4	Laminin a-4	Extracellular matrix protein	0.011	52
ILK	Integrin-linked kinase	Intracellular serine-threonine kinase; interacts with integrins	0.005	52
ANKRD1	Ankyrin repeat domain-containing protein 1	cardiac ankyrin repeat protein (CARP); localized to myopalladin/titin complex	?	53
RBM20	RNA binding protein 20	RNA binding protein of the spliceosome	0.019	54, 55

(*Continued*)

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Table 4 *Continued*

Genes[a]	Protein	Function	Estimated frequency[b]	References
Conduction system disease with dilated cardiomyopathy phenotype				
LMNA	Lamin A/C	Structure/stability of inner nuclear membrane; gene expression	0.06	56–68
SCN5A	Sodium channel	Controls sodium ion flux	0.026	25, 69–71
X-linked FDC				
DMD	Dystrophin	DAGC; transduces contractile force	?	72, 73
TAZ/G4.5	Tafazzin	Unknown	?	74, 75

[a]Genes ordered by publication year.
[b]Estimated frequency from the literature.
DAGC, dystrophin-associated glycoprotein complex.

and time intensive for conduct and analysis, and CMR is contraindicated for most existing pacemakers and implantable cardiac defibrillators (ICDs) because of concern of disruption of circuitry and heating of endocardial leads. However, new generations of pacemakers and ICDs will be CMR compliant. Ongoing CMR research may also provide unique parameters to help detect very early clinical disease (e.g., Ref. 83), but given the financial, accessibility, and device-related limitations of CMR, echocardiography remains the usual initial approach to clinical evaluation.

Disease presentation—IDC

Although IDC may be asymptomatic for months to years, it almost always presents late in its clinical course, usually with serious and/or life-threatening advanced disease such as heart failure, sudden cardiac death (SCD), or stroke from mural thrombus. However, early medical intervention can be highly effective to ameliorate disease and in some cases to reverse the phenotype. This provides the compelling rationale for presymptomatic diagnosis, warranting clinical and molecular screening of at-risk relatives.

Age of onset or diagnosis

IDC commonly presents in the 4th–6th decades of life; however, onset in infancy and early childhood has been reported, as well as in the elderly.[11] When advanced disease presents in a proband with no prior knowledge of risk for DCM, its presentation may include heart failure with symptoms of congestion (edema, orthopnea, and paroxysmal nocturnal dyspnea) and/or reduced cardiac output (fatigue, shortness of breath, dyspnea, on exertion); arrhythmia and/or conduction system disease (CSD), including syncope or presyncope, bradycardia, tachycardia, supraventricular or ventricular arrhythmias including atrial flutter or atrial fibrillation, ventricular tachycardia (VT), or SCD; or stroke or other embolic phenomena from mural thrombus.[4,84,85] DCM can also be present in asymptomatic individuals and is discovered from preventive screening or serendipitously from medical evaluation for other reasons.[4,84,85]

Disease presentation in FDC

The age of onset, presentation, and disease course in a proband will not necessarily be helpful to predict prognosis in other family members, even those shown to carry the same mutation.[81]

DCM presenting in pregnancy

DCM may also occur during pregnancy and is commonly termed peripartum cardiomyopathy (PPCM) or pregnancy-associated cardiomyopathy (PACM). We have recently shown that some women with PPCM or PACM carry rare mutations in established DCM genes.[86] PPCM has been traditionally defined as DCM onset during the last month of pregnancy to 5 months postpartum. This is an arbitrary definition, and a related term, PACM, refers to onset occurring before the last month of pregnancy.[87] Although considered a different clinical entity by some,[87,88] we did not observe any clinical differences in the 45 cases assigned as either PACM or PPCM from our cohort of 520 families with DCM.[86] Of these 45 cases, 19 had been sequenced for known DCM genes, and six of these carried a mutation in a gene previously observed to carry mutations causing DCM (*MYBPC3, MYH7, TNNT2, SCN5A, MYH6,* and *PSEN2*). All 45 cases were embedded in FDC/IDC families.[86]

DCM with CSD that may be associated with prominent arrhythmias

A subset of individuals with DCM also exhibit CSD and/or cardiac arrhythmias,[81] particularly those with *LMNA* or *SCN5A* mutations (Table 4). In a subset of cases, CSD with or without arrhythmia may be the presenting clinical feature, and in some families with a known genetic cause, individuals have been shown to exhibit only CSD and arrhythmia.[56] Family studies (see references in Table 4) suggest that CSD commonly precedes the development of DCM in these individuals by a few years to more than a decade.

CSD includes first, second, or third degree heart block, usually identified by a resting electrocardiogram (ECG) or bundle branch blocks.[56] CSD involvement commonly starts with disease of the sinus node and/or atrioventricular node that can manifest as sinus bradycardia, sinus node arrest with junctional rhythms, or heart block.[89] Associated cardiac arrhythmias

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include the presence of paroxysmal or sustained atrial flutter or fibrillation, paroxysmal or sustained supraventricular arrhythmias, symptomatic brady-tachy syndrome (sick sinus syndrome), VT or ventricular fibrillation (VF), or resuscitated SCD.[56]

The use of a permanent pacemaker or ICD is indicated for CSD or to prevent or treat lethal cardiac arrhythmias. When taking a family history, the presence of a pacemaker or ICD in relatives can be helpful to indicate cardiovascular disease.[56] SCD due to arrhythmia tends to occur with progressive disease, although SCD as the presenting manifestation has been reported in *LMNA*-related DCM,[89] as well as other DCM genetic etiologies, particularly from *SCN5A*-related DCM (see references in Table 4).

Nuances of the term "sudden cardiac death" and implications for family history

We clarify in this review that the SCD term in the cardiovascular literature does not necessarily imply a vital status outcome of the subject, that is, an individual who has suffered SCD may remain alive, having been resuscitated and his/her rhythm successfully treated. In this way, the SCD term denotes either a lethal life-threatening arrhythmia (usually fast VT or VF) that required medical intervention for survival or the occurrence of death of the individual, suddenly, that has been attributed to cardiovascular cause (and in the clinical trial literature, in most cases, arrhythmic death). We also clarify that when taking a cardiovascular family history, relatives can "die suddenly" from acute myocardial infarction, which in almost all cases results from VT or VF associated with the myocardial ischemia occurring during the acute myocardial infarction, triggering the arrhythmia. Although this death technically results from arrhythmia as a consequence of an acute event from CAD, and although such history may be informative for other genetic and/or familial causes of coronary atherosclerosis, including familial hypercholesterolemia, it is not useful for purposes of ascertaining whether the subject has genetic DCM because of its fundamentally different etiology. On the other hand, the incidence and prevalence of CAD are high in a first world population, and therefore, it is not uncommon for a DCM gene carrier to also have CAD, confounding family history assessments. Because of the age dependency of CAD, we treat any unexpected death of men younger than 40 years and women younger than 45 years as suspicious for DCM. For those older individuals who had an episode of SCD or died suddenly of cardiac cause, CAD needs to be ruled out for the SCD to be suggestive of an underlying DCM mutation.

Syndromic DCM

Although most genetic DCM involves only the heart, a number of syndromic genetic conditions include DCM as a feature. Selected examples are provided (Table 5). For this reason, careful attention should be paid to the family history and physical examination to rule out syndromic disease. In most cases of syndromic disease involving DCM, multiple tissues and/or organ systems are involved, the most common of which is skeletal muscle.[11] The ratio of syndromic compared with nonsyndromic DCM is unknown.

DCM GENETICS

Clinical genetics

Cardiovascular screening in family members of IDC probands has revealed FDC in 20–35% of cases.[82,96–99] Using LVE alone as an early indicator of IDC, familial disease has been found in up to 48% of probands.[82] In general, the clinical cardiovascular characteristics of those with IDC[6] and those with FDC do not differ.[4,5,81,84,100]

Estimates suggest that IDC is inherited in an autosomal dominant pattern in about 90% of kindreds and shows reduced, age-dependent penetrance and variable expressivity.[4,5,11,81,84,96,100] Exact penetrance estimates are not available, although one study calculated 90% penetrance after the age of 40 years in autosomal dominant forms[99] and as high as 100% in *LMNA* mutation carriers older than 30 years.[101] Autosomal recessive and X-linked inheritance has also been reported in 1–2% and 5–10% of cases, respectively.[14]

Molecular genetics of IDC/FDC: Marked locus heterogeneity

FDC is a genetically heterogeneous disease. More than 30 genes, almost all autosomal, encoding proteins of diverse roles have been identified (Table 4), demonstrating a degree of locus heterogeneity that is comparable with few other genetic disorders. Genetic DCM differs from HCM and arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) most notably in the number of genes associated with disease and the diversity of gene/protein function. For instance, in HCM, two genes, *MYH7* and *MYBPC3*, account for 40–60% of cases or 80–90% of genetic cause when a genetic basis can be established.[102,103] In ARVD/C, three genes, *PKP2* (plakophilin 2), *DSP* (desmoplakin), and *DSG2* (desmoglein 2) account for 40–50% of cases.[104,105] Further, although mutations in genes encoding proteins of diverse function have been identified in FDC, most HCM and ARVD/C mutations occur in genes encoding sarcomeric or desmosomal proteins, respectively (see Refs. 11 and 14). A predominant LV ARVD/C phenotype has also been described that presents with prominent arrhythmias that can present phenotypically as DCM.[106,107]

To date, a subset of 14 genes, screened by bidirectional Sanger sequencing for mutations, collectively accounted for approximately 28% of likely or possible cause in a series of 312 probands with IDC/FDC.[13] The fraction of cause of DCM attributed to nonsynonymous, splice site, and small insertion/deletion mutations in coding regions and intron/exon boundaries of these genes is shown (Table 4). The remainder of the genetic cause has been estimated from single gene reports in various cohorts (Table 4). These data indicate that, to date, mutations in *LMNA*, *MYH7*, *MYBPC3*, *TNNT2*, *SCN5A,* and *MYH6* account for approximately 75% of known genetic cause of DCM.[13] From all publications, we estimate that approximately 30–35% of DCM genetic cause has been identified (Table 4).

DCM shows marked allelic heterogeneity

Numerous mutations have been identified in FDC. Unlike cystic fibrosis, in which, despite large allelic heterogeneity, 70% of cases are caused by the [Delta]F508 mutation,[85] almost all DCM mutations are private. Although there are some mutations that have been reported in multiple families, such as a *TNNT2* lysine210 deletion (see references in Table 4), the vast majority of DCM mutations are private to a given family.[13,25,29,30,56,57] Although most variants are missense, a few nonsense, small insertion/deletions, and splice site variants have also been reported.[25,56,108] Exceptions to date include a 2 kb deletion in the *EYA4* gene[46] and a large *LMNA* deletion.[109]

Mitochondrial disease

Mitochondrial mutations, because of the high energy requirements of myocardium and the key role of mitochondria to synthe-

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Table 5 Selected causes of syndromic dilated cardiomyopathy

Syndrome	Locus	OMIM	Gene symbol	Gene product	Inheritance pattern	Additional clinical features
Emery-Dreifuss muscular dystrophy types 2 and 3 (EMD2 and EMD3), limb girdle muscular dystrophy (LGMD 1B)	1q21.2	150330	*LMNA*	Lamin A/C	EMD 2: AD; EMD3: AR; LGMD1B: AD	Joint contractures (more severe in EMD); arrhythmias; childhood muscle weakness (shoulder/hip-girdle in LGMD1B)
Hemochromatosis	6p21.3	235200	*HFE*	Hereditary hemochromatosis	AR	Cirrhosis, diabetes, hypermelanotic pigmentation, increased serum iron and ferritin
Laing distal myopathy	14q12	160760	*MYH7*	β-myosin heavy chain	AD	Childhood onset weakness of ankles and great toes, then finger extensors. Neck flexors and facial weakness.
Carvajal syndrome	6p24	125647	*DSP*	Desmoplakin	AR	Woolly hair and keratoderma
Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD)	Xp21.2	300377	*DMD*	Dystrophin	XL	DMD: men with elevated CK, childhood muscle weakness, wheelchair bound by the age of 12 years, DCM after the age of 18 years; BMD: elevated CK, skeletal muscle weakness in 20s or later; women can be affected with milder phenotype or DCM alone
Barth syndrome	Xq28	300394	*TAZ/G4.5*	Tafazzin	XL	Growth retardation, intermittent lactic acidemia, granulocytopenia, recurrent infections
Kearns-Sayre syndrome	mtDNA multigene deletion	530000	Variable (e.g., *MTND5*, *MTND4*, *MTND3*, *MTCD3*, *MTATP3*, and *MTATP8*)	NADH dehydrogenase subunit 3, 4, and 5; Cytochrome c oxidase subunit 3	De novo	Progressive external ophthalmoplegia, muscle weakness, cerebellar ataxia, and diabetes mellitus

Adapted from *Circ Heart Fail*.[11]
See text for additional comments on mitochondrial mutations.[90–95]
AD, autosomal dominant; AR, autosomal recessive; XL, X linked; OMIM, Online Mendelian Inheritance in Man; mtDNA, mitochondrial DNA.

size ATP, have been hypothesized to cause DCM. Although ascertaining whether mtDNA mutations actually cause DCM has been challenging, some mtDNA mutations have been reported in DCM.[90–95] Syndromic disease associated with DCM resulting from mitochondrial mutations (e.g., Kearns-Sayre syndrome, OMIM, #530000) has also been recognized (Table 5). We are not yet aware of next generation sequencing technologies that have been used to rigorously evaluate heteroplasmic mitochondrial DNA variation in large cohorts of patients with DCM or the evaluation of genomic sequences encoding mitochondrial proteins for nonsynonymous variants, although commercial testing panels that include mitochondrial DNA are currently available.

IDC/FDC pathology and pathogenesis: Multilocus pathways resulting in a final common phenotype

Despite dramatic locus and allelic heterogeneity, a relatively homogeneous DCM phenotype results. Histologic findings of IDC include the relatively nonspecific findings of myocyte hypertrophy, myocyte loss, and interstitial fibrosis.[110] DCM has been proposed to result from a "final common pathway."[111] Alternatively, we have proposed a multilocus pathway hypothesis, where DCM is a final phenotype resulting from a variety of different disease genes or genetic injury pathways.[13] In this paradigm, DCM may also result from a variety of other nongenetic causes noted earlier, such as ischemic cardiomyopathy. Because of the marked locus heterogeneity involving multiple gene networks, this hypothesis suggests that many different genetic pathways may lead to DCM. This multilocus pathway hypothesis is relevant because if many different disease genes or gene networks cause DCM, then specific interventions, targeted to these genes or gene cascades, may be relevant for therapy. Testing this hypothesis will require identifying and characterizing these genetically active pathways or gene cascades in DCM.

Genotype/phenotype correlations

No clear genotype-phenotype correlations exist in genetic DCM. Possible exceptions, as noted earlier, include the prominent CSD and arrhythmia that precede the onset of LVE and/or systolic dysfunction for *LMNA* and *SCN5A* mutations. Particularly for *LMNA*, the CSD consists of heart block, sustained atrial

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flutter/fibrillation, paroxysmal supraventricular arrhythmias, atrial flutter/fibrillation, symptomatic brady-tachy syndrome, VT/fibrillation, and SCD.[4,11,56] *LMNA* cardiomyopathy may also show relatively less LVE compared with the degree of systolic dysfunction, particularly early in its course (see references in Table 4). *SCN5A* mutations also commonly present with CSD during adolescence progressing to LV dysfunction.[69]

We[25,29,108] and others[30,26,27,31] have also observed that *TNNT2* mutations are commonly associated with DCM of early and aggressive onset, often in the 2nd and 3rd decades of life. Despite this, we have also more recently documented disease in a 70-year-old woman with onset at the age of 69 years, who was found to have a *TNNT2* mutation shown to be likely pathogenic through functional studies (Morales et al., unpublished data). This illustrates the uncertainties of relying on any specific phenotype/genotype association in genetic DCM.

Phenotypic heterogeneity and plasticity

Phenotypic heterogeneity has been observed for several genes associated with DCM. *LMNA* mutations have shown dramatic phenotypic heterogeneity (e.g., Hutchison-Gilford progeria, partial lipodystrophy, mandibular acral dysplasia, Charcot-Marie-Tooth type 2B1, and others),[112] with skeletal myopathy and CSD with or without DCM the most relevant to this topic. Other heterogeneity has been observed in genes encoding sarcomeric proteins, most commonly with DCM or HCM from mutations in *MYH7,*[25] *TNNT2,*[25,32,113] or *MYBPC3*.[13] One multiplex family showed DCM, HCM, and RCM phenotypes in different family members harboring a single mutation in *TNNT2*.[113]

"Apparently sporadic" IDC

Most genetic discovery research in the 1990s and early 2000s targeted large FDC kindreds. Thus, the extent of genetic causation in sporadic IDC remains an open question. We emphasize the term "apparently sporadic IDC" to mean phenotype studies where the available data were derived from probands reporting a negative family history, as their relatives were not systematically screened clinically (echocardiogram and ECG) to rule out DCM. Ruling out FDC by clinical cardiac screening, especially imaging studies to assess LV size and function, is essential given that early signs of DCM, even to the extent of meeting full criteria for IDC, can be present in completely asymptomatic individuals. We again emphasize that the family history is known to be insensitive to detect FDC and that a family member may have a completely normal history, examination, and ECG but still be affected when an echocardiogram or equivalent cardiac imaging is performed.

The currently available studies of systematic resequencing in sporadic IDC cohorts are limited. To date, no major prospective study (including our prior work in this area[13,25,48,54,56]) has systematically resequenced the most common DCM genes in a cohort of sporadic IDC patients where first-degree relatives were screened clinically (history, examination, ECG, and echocardiogram) to rule out familial DCM. Despite this caveat, our resequencing studies suggest that apparently sporadic IDC may also have a genetic basis.[13,25,54,56] For example, in our *LMNA* resequencing study, we identified mutations in 3.6% of apparently sporadic IDC and 7.5% of FDC.[56] Further, our resequencing study of six genes (*MYH7, TNNT2, SCN5A, CSRP3, LBD3,* and *TCAP*) in 313 DCM probands identified mutations in 10.8% with apparently sporadic IDC and in 9.8% with FDC.[25] A follow-up resequencing study of five additional genes (*MYBPC3, MYH6, TPM1, TNNC1,* and *TNNI3*) in 312 subjects (311 from the previous cohort and one additional case) identified mutations in 9.2% with apparently sporadic IDC and in 11.6% with FDC.[13] Confirming that sporadic DCM has a genetic basis will require formal studies with clinical screening to confirm sporadic DCM, followed by comprehensive genetic studies.

MANAGEMENT APPROACHES TO DCM

Treatment

Treatment of individuals with symptomatic DCM is recommended, per American Heart Association/American College of Cardiology guidelines[114,115] for DCM and heart failure: in brief, ACE-inhibitors, beta blockers, and ICDs when indicated.[114,115] Guidelines for genetic cardiomyopathies have also been recently prepared by the Heart Failure Society of America.[11] For patients with advanced heart failure, the above measures in addition to diuretics and inotropes, as indicated, and for end-stage disease, consideration of ventricular assist devices and/or cardiac transplantation.[114,116] Treatment of asymptomatic LV dysfunction from any cause with beta blockers and ACE-inhibitors will delay onset of symptoms, improve LV function, and will likely improve mortality.[14,114] Formal studies have not yet been completed with asymptomatic and very early genetic DCM, but most cardiovascular experts suggest that treatment will likely improve outcomes.[117] Resolution of this question is one that deserves carefully designed gene-specific clinical trials.

Management of asymptomatic CSD in someone with suspected or proven FDC requires close surveillance. At times, progressive but asymptomatic CSD in family members harboring *LMNA* mutations may require prophylactic pacemaker or ICD placement, an issue that requires expert electrophysiological consultation in concert with other cardiovascular and genetics assessments. This important issue has been noted in the 2009 Heart Failure Society of America guideline document.[14]

Genetic counseling

As per guidelines, genetic counseling is recommended for all patients and families with cardiomyopathy,[14] particularly in light of the complexity and rapidly evolving options for genetic testing in DCM. Multidisciplinary medical care involving genetic counselors and cardiologists, medical geneticists, or other experts in the field of cardiovascular genetics is ideal.

Genetic counseling includes obtaining a careful and comprehensive family history, education regarding disease transmission, advice on potential risks and benefits of cardiac screening and genetic testing, assistance in interpreting genetic test results, and helping patients and their families adapt to the psychosocial consequences of genetic disease.[14,84,100]

A targeted three- to four-generation pedigree is essential in the medical evaluation of DCM.[4,14,84,100] Key questions include age at the onset of symptoms, as IDC onset at a young age is suggestive of a strong genetic component.[84,100] Infantile onset of cardiomyopathy is often consistent with autosomal recessive, X-linked, or mitochondrial inheritance.[4,14,84,100] Inquiry is important regarding symptoms of heart failure (edema, orthopnea, paroxysmal nocturnal dyspnea, dyspnea on exertion, and fatigue) and arrhythmia (palpitations, presyncope, syncope, and SCD).[4,14,84,100] Symptoms of heart failure in the peripartum period can be indicative of PPCM[86,118] and should also be noted.

Documentation of SCD, unexplained death at a young age, and history of other heart conditions such as "heart attack" (myocardial infarction) should also be documented. This attribution ("heart attack") is commonly used by many patients to describe any CV condition that caused a CV hospitalization in a family member. Follow-up questions to ascertain whether the family member in question underwent stent placement or had a

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coronary artery bypass grafting operation can help identify ischemic versus nonischemic disease. Results from other tests and procedures such as a coronary angiogram, echocardiogram, multiuptake-gated acquisition, electrocardiogram, 24-hour ECG recording (commonly referred to as a "Holter monitor"), endocardial biopsy, and others should be documented.

Assessment for possible syndromic forms of DCM (Table 5) requires careful attention to the history and examination. For example, noting sensorineural hearing loss, which may be observed in people with FDC and an *EYA4* mutation should be noted (Table 4). DCM can be a part of the spectrum of disease for several mitochondrial syndromes.[11] Muscle weakness and elevated CPK levels suggests *DMD*-related Duchenne or Becker muscular dystrophy or *LMNA*-associated myopathy. Short stature, neutropenia, and congenital DCM suggest Barth syndrome. Findings with *LMNA*-DCM associated with Emery-Dreifuss muscular dystrophy include skeletal muscle weakness, contractures, a waddling gait, and toe walking among others.[100] Basic knowledge of signs and symptoms of other types of cardiomyopathy, particularly HCM (Table 1), and other arrhythmia syndromes such as the Long QT syndrome, is also important, as symptoms and at times genetic cause can overlap with those seen in FDC.[100]

Clinical cardiovascular screening of relatives

Clinical screening is recommended for first-degree relatives of probands with IDC.[14] The standard for cardiac screening in those at risk for DCM includes a careful medical and family history, an echocardiogram, an electrocardiogram, and a physical examination. If any cardiovascular abnormalities are detected, a full cardiovascular evaluation by a cardiovascular specialist is indicated. This is particularly relevant when symptoms or signs of DCM are identified in those whose coronary disease risk is increasing (men older than 40 years, women older than 45 years, modified to earlier ages with added coronary risk factors such as cigarette smoking, diabetes, hypertension, a positive family history of early CAD, or hyperlipidemia). CMR mentioned earlier can also be useful, especially for questions of overlap of DCM with HCM, RCM, or ARVD/C.

Screening asymptomatic relatives

It is imperative to understand that genetic DCM can occur in individuals who are completely asymptomatic. Presymptomatic diagnosis of FDC emphasizes the importance of preventive screening in first-degree relatives of individuals with IDC.[14] Presymptomatic diagnosis allows for early intervention and may result in the prevention or delayed onset of heart failure or SCD.[14]

Screening intervals for asymptomatic relatives

Regardless of genetic testing status in the family (i.e., an established mutation, genetic testing that is negative or has shown a variant of unknown significance, or no genetic testing), asymptomatic relatives with any evidence suggestive of DCM on cardiac screening studies should be rescreened on a regular basis.[14] This group should be followed up by cardiovascular specialists with expertise in DCM diagnosis and treatment.

Follow-up for asymptomatic individuals who carry a putative disease-causing DCM mutation but who have thus far had negative clinical cardiac screening is recommended yearly in childhood and then every 1–3 years in adulthood.[14] For families in which a mutation has not been identified in a proband, relatives with negative clinical cardiac screening should be rescreened every 3–5 years beginning in childhood.[14] Similarly, for families with a family history of IDC in which no genetic testing has been pursued, individuals with negative cardiac screening should seek rescreening every 3–5 years.[14]

At this time, continued screening has not been recommended[14] for those family members who test negative for their family's DCM-causing mutation. However, they should be informed of the symptoms associated with DCM (arrhythmia, heart failure, etc.) and should be instructed to bring such symptoms promptly to medical attention should they occur. In relatives who do not carry the putative family DCM mutation, the residual risk of developing DCM has not yet been assessed, but the marked locus heterogeneity and the estimate that only 30–35% of genetic cause has been identified for DCM make this a concern.

Genetic testing guidelines

Clinical genetic testing for DCM has been evolving rapidly, from testing one or two genes, such as *LMNA,* at selected laboratories, on a gene-by-gene basis, to panels containing 10–30 genes. The recently published guidelines (2009) for the evaluation of genetic cardiomyopathies[14] recommended a stepwise genetic testing process, beginning with the three genes accounting for approximately half of DCM risk (*LMNA, TNNT2,* and *MYH7*) and, if negative, reflex to the remainder of genes available for testing.[14] These guidelines have already become outdated, as molecular genetic testing laboratories now offer DCM genetic testing panels of 12–30 genes using next generation sequencing methods.

Testing approach within a family

Following family-based genetic testing principles, genetic testing should begin with an affected family member available for testing and ideally the one who is the most severely affected. In addition to the common genes associated with DCM, the large, currently available genetic panels also include syndromic disease genes and genes with limited association data with DCM. This reinforces the emphasis on a careful physical examination and family history to rule out syndromic disease. Pretest genetic counseling should also include a thorough discussion of the likelihood of finding a variant of unknown significance (VUS), the meaning of a VUS, and the need for cooperation among family members to assess the pathogenicity of a VUS. Because a genetic cause is likely to be identified in only 15–25% of cases, genetic testing of an unaffected family member has not been recommended. If an affected family member is unavailable, investigations should be conducted to identify stored tissue suitable for DNA analysis from an affected, deceased family member. In the absence of an affected relative or stored tissue, testing of an unaffected family member may be considered with expert counseling and communication of the limitations of this testing approach. Insurance coverage is also variable and can be a limiting factor in deciding where to begin testing in the family.[11,14]

FUTURE DIRECTIONS: A MORE COMPLETE MODEL FOR DCM GENETICS?

Limitations of current DCM genetic studies

Current research has only scratched the surface of DCM genetics. Most recent efforts have been devoted to DCM gene discovery or to preliminary studies of mutation frequency and character in modest sized DCM cohorts, with almost exclusive focus on mutation detection in coding sequence. We estimate that only 30–35% of DCM genetic cause has been identified. The limited research into mutations of genomic or mitochondrial DNA encoding mitochondrial proteins has been noted earlier. No systematic study of structural variants has been published for any

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DCM cohort. Although our resequencing studies[13,25] have examined some intronic and 5′- and 3′-untranslated regions in 11 genes (unpublished data), in general such noncoding sequence has not been reported in DCM gene studies. Similarly, the search for rare variants in near or far upstream regions harboring promoter sequences have not been reported. We also note the lack of investigation of epigenetic mechanisms that may also be key to understanding DCM genetics.

Molecular research has been framed within a Mendelian, rare variant paradigm disregarding common variants, although a recent study[119] of our first resequencing dataset[25] suggested that such analyses were feasible and may contribute to understanding potential genetic modifiers. Common polymorphisms in DCM genes may be highly relevant for disease expression, as illustrated by *SCN5A* variants affecting *SCN5A* disease-causing mutations (Cheng et al., unpublished data). These issues will need to be addressed with exome or whole genome sequence analysis in DNA specimens from hundreds of IDC and FDC probands.

A complex rare variant DCM genetic disease model

DCM genetics has been viewed through the lens of Mendelian genetics, specifically where high penetrance mutations in a few genes cause disease.[3] Most of the published evidence (Table 4) supports this model and particularly for highly penetrant nonsynonymous variants in sarcomeric proteins (e.g., *TNNT2* and *MYH7*). However, aspects of our resequencing data, although quite preliminary, suggest a more complex genetic DCM model.[3] In our *LMNA* resequencing study, at least one individual with DCM in 6 of 19 (32%) FDC kindreds with a putative disease-causing *LMNA* mutation showed nonsegregation, that is, at least one affected family member was negative for the family mutation.[56] These findings suggest that in DCM, multiple mutations may be at play more commonly than anticipated, perhaps underlying penetrance, expressivity, or even causation. Additional complexity is possible in that multiple rare (allele frequencies $<0.001–0.005$) or "not so rare" variants (allele frequencies of 0.002–0.01) may be relevant.[3] These issues have also been recently explored for other conditions.[120,121]

A related question is whether familial or sporadic IDC lie on a genetic continuum, resulting from different degrees of genetic influence. A corollary of this question is the fact that the genetic factors underlying penetrance and variable expressivity in FDC are still unknown. The genetic basis of sporadic IDC remains to be determined, whether from rare, single, de novo high penetrance mutations or from the cumulative effects of more than one rare, moderate to low penetrance variants. In our preliminary studies, we have observed that approximately 3% of our DCM probands (our unpublished data), when resequenced for multiple genes,[13,25] have multiple rare nonsynonymous variants. Similar findings have been observed in other cardiovascular genetic phenotypes, including 5% of HCM,[102,103,122,123] 5–8% of the long QT syndrome,[124,125] and in ARVD/C.[126] However, unlike HCM, the long QT syndrome, and ARVD/C, where approximately 65%, 75%, and 50% of genetic cause has already been identified, respectively, we estimate that only approximately 25–30% of genetic cause has been found in DCM spanning more than 30 genes. Hence, we suggest that it may be possible that rare variants in many additional genes may be relevant to cause or modify the DCM phenotype. It has been postulated that most rare missense mutations may be deleterious in humans,[127] and thus far, the available data show that IDC arises from rare variants, which remain the foundation for interpreting DCM genetic data.[121,128] Therefore, an oligogenic model[120] may more appropriately describe some aspects of DCM than a Mendelian model.[3,120,121] Other genetic models are possible, especially those informed from untapped research areas (e.g., structural variants, 3′- or 5′-untranslated regions, and epigenetics).

Exome sequencing[129,130] now and whole genome sequencing soon will provide the basis to identify additional variants, both rare and common, that may act in concert to modulate the DCM phenotype. Functional studies (e.g., strengthening association with disease, for examples, see Refs. 108 and 131 and Morales et al., submitted) of such variants will be imperative to draw firm conclusions.

CONCLUSION

Although a great deal of progress for IDC and FDC has been made in discovering genetic cause and providing guidelines for its management, much more extensive research is needed, including genetic discovery and medical management of specific types of genetic DCM. As important, awareness that IDC and FDC are conditions with significant underlying genetic etiology is imperative for both the genetics and cardiovascular communities. Much greater understanding of DCM genetics will be required, including discovery of the remaining major portion of genetic cause and determining the frequency and spectrum of multiple mutations. Resolution on the issue of whether sporadic (IDC) disease has a genetic basis, and if so, how it differs from familial disease is also key. Finally, we hope that new strategies, including those devoted to gene-specific or genetic pathways, will lead to novel approaches to the prevention and treatment of DCM.

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