Genetic Ideology of Dilated Cardiomyopathy

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Abstract

Familial cardiomyopathies represent a substantial portion of idiopathic dilated cardiomyopathy in clinical practice. Diversity of clinical presentations and variability in penetrance lead to under-recognition of this disease entity as an inherited disorder. The mechanisms by which mutations in different genes perturb cardiac function and lead to pathologic remodeling help us understand the molecular pathways in disease pathogenesis and define the potential targets for therapeutic interventions. Appreciating when DCM is inherited might spare unnecessary diagnostic efforts and, instead, help give appropriate attention to the timely detection of subclinically affected family members. Establishing preventive therapy in asymptomatic family members showing early signs of cardiac dysfunction might prevent death and slow down progression to end-stage heart failure.

Congestive heart failure is a rapidly expanding epidemic of the 21st century, constituting a major cause of hospitalization, morbidity and mortality with resulting public health expenses. Primary diseases of the myocardium (cardiomyopathies) are second only to coronary heart disease as a cause of heart failure, accounting for approximately 20% of cases in the western world. Cardiomyopathy represents a diverse group of heart-muscle disorders, which are further subdivided according to their anatomic and hemodynamic findings. Diminished systolic contractile function is the critical hemodynamic feature of congestive cardiomyopathy or DCM. More than 80% of cardiomyopathies are classified as dilated, with a prevalence of 1 in about 2,500 individuals. Because a comprehensive medical workup often fails to identify the disease etiology in most of these cases, they are called “idiopathic DCM.”

DCM is often clinically diagnosed with non-invasive cardiac imaging, in particular two-dimensional echocardiography. Measurements obtained throughout the cardiac cycle provide systolic and diastolic dimensions that both determine the extent of chamber enlargement and provide an estimate of contractile function, through calculations of the fractional shortening of the heart muscle, the fraction of the left ventricular blood volume ejected with each beat, and the right ventricular fractional area change.

Inadequate cardiac performance triggers complex neurohumoral responses, which increase circulatory volume to maintain cardiac output. Myocyte enlargement or hypertrophy leads to an increase in both myocardial mass and volume. Eventually the heart becomes thin walled and distended. Excessive neurohumoral responses ultimately become maladaptive and contribute to clinical deterioration by causing myocardial cell necrosis, apoptosis and fibrosis [1]. Idiopathic DCM often presents after many years of asymptomatic, progressive left ventricular dysfunction and adverse remodeling. Typically, an otherwise healthy individual develops signs of heart failure during intercurrent infection or stress, and is found to have a dilated heart with severe biventricular dysfunction. Only 50% of patients with DCM survive more than 5 years after diagnosis. Premature death results from unmitigated pump failure, arrhythmia, and from co-morbidities such as stroke or thromboembolism. Despite contemporary strategies of heart failure management, idiopathic DCM remains a common cause of end-stage heart failure and accounts for about 50% of referrals for cardiac transplantation [2].

Familial dilated cardiomyopathy

Over the past two decades there has been increased recognition of the fact that many “idiopathic” DCMs are familial. Although medical reports of familial cardiomegaly were published as early as 1948, a clinical estimate of prevalence was provided only in 1992 when Michels et al. [3] reported that >20% of individuals with DCM had an affected first-degree relative. Other studies, applying close scrutiny and longer follow-up, found evidence of familial disease in up to 50% [1,4]. Population-based studies have confirmed that there are no prognostic differences between familial and sporadic forms of idiopathic DCM. The cardiac pathology of familial DCM is variable and usually non-specific. The disease can be transmitted as autosomal dominant, X-linked, or mitochondrial traits [4,5]. There are rare reports of DCM with autosomal recessive inheritance, or DCM associated with high levels of parental consanguinity in the population [6,7]. Not only have these observations fostered molecular genetic analyses aimed at the definition of disease-causing mutations, but they have also...
altered clinical practice. Screening evaluations of asymptomatic relatives at risk of inheriting the disease led to the diagnosis of clinically silent DCM in a considerable number of family members whose condition warrants early intervention [8].

Targeting the process of detrimental remodeling reduces symptoms and decreases morbidity and mortality associated with heart failure, arrhythmia or thromboembolic events [9]. Although the early initiation of treatment may both retard progression and prolong the pre-transplantation phase of the disease, more definitive therapies for DCM await better mechanistic understanding of the molecular basis of this disease.

**Molecular mechanisms of familial dilated cardiomyopathy**

There is considerable heterogeneity in the clinical features of heritable DCM resulting from a single gene mutation. Age at disease onset ranges from early childhood to late senescence. Metabolic cardiomyopathies and storage disorders affecting the heart usually predominate in the pediatric population, while most cases of genetically determined DCM in adults become apparent during the second to fifth decade of life. The natural history of the disease can vary considerably with regard to the severity of symptoms and survival, even in affected members of the same family. Genetic studies of DCM are limited by the lethal nature of the disorder, small pedigree size, age-dependent penetrance, and a considerable number of phenocopies (most commonly persons with heart failure due to ischemic heart disease, i.e., ischemic cardiomyopathy).

Table 1 provides an up-to-date list of chromosomal loci and disease-causing genes reported in teenage and adult-onset DCM. Some of these individuals have distinguishing extracardiac manifestations like skeletal myopathy, conduction system disease, hearing loss, and mitral valve prolapse. These features can be useful but are rarely sufficient to establish the genetic diagnosis. The remarkable genetic heterogeneity helps us appreciate the multitude and complexity of different mechanisms that may lead to cardiomyopathy.

Mutations in structural proteins – desmin, sarcoglycan, dystrophin – cause DCM (with or without associated skeletal myopathy) by disrupting the intracellular architecture or loss of the normal anchoring of the cytoskeleton to the sarcolemma [14,17,29]. Defects in force transduction are caused by mutations in proteins attaching the sarcomere assembly to the cytoskeleton: titin, associated proteins including TCAP, LIM and myosin-binding protein C [15,24,25]. Mutations in sarcomeric proteins (myosin, actin, the troponins and tropomyosin) suggest the impairment of force generation as a mechanism of contractile dysfunction [1,6,12,27,28]. Reduced calcium uptake (phospholamban mutation [20]) or disordered calcium release from the sarcoplasmic reticulum (owing to defects in ryanodine receptor in arrhythmogenic right ventricular cardiomyopathy), emphasizes the important role of calcium dysregulation in heart failure. Recent findings add membrane ion channels [16,26], as well as defects in intercellular junction proteins (desmoplakin, plakoglobin, plakophilin-2), to the list of molecular causes of cardiomyopathy [32]. Mutations in mitochondrial DNA represent the potential role of energy metabolism and possibly of accelerated apoptosis in DCM pathogenesis [31]. Alteration in the nuclear architecture and defective nuclear function caused by mutations in a nuclear lamina protein (LAMIN A/C) result in a spectrum of apparently unrelated clinical syndromes [10,11], including DCM with conduction system disease, limb-girdle muscular dystrophy, Emery-Dreifuss muscular dystrophy, familial lipodystrophy, and progeria (premature aging).

<table>
<thead>
<tr>
<th>Locus</th>
<th>Trait</th>
<th>Additional phenotype</th>
<th>Disease gene</th>
<th>Ref.</th>
</tr>
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<td>1q21</td>
<td>AD</td>
<td>Conduction disease</td>
<td>Lamin A/C</td>
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<td>Lamin A/C</td>
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<td>None</td>
<td>Cardiac troponin T</td>
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<td>Conduction disease</td>
<td>?</td>
<td>13</td>
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<td>AD</td>
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<td>Desmin</td>
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<tr>
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<td>Wooly hair and keratoderma</td>
<td>Desmoplakin</td>
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<tr>
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<td>24</td>
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<tr>
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<td>Mitral valve prolapse</td>
<td>Myosin-binding protein C</td>
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<td>Troponin I</td>
<td>33</td>
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<td>Dystrophin</td>
<td>34</td>
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<td>X-linked</td>
<td>Short stature and neutropenia (Barth syndrome) Non-compaction</td>
<td>Talazazin</td>
<td>35</td>
</tr>
<tr>
<td>Mitochondrial DNA</td>
<td>Maternal</td>
<td>Kearns-Sayer, MELAS syndrome</td>
<td>t-RNA mutations, large deletions</td>
<td>36</td>
</tr>
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</table>

AD = autosomal dominant, AR = autosomal recessive, ? = the causative gene was not identified.
Finally, discovering that transcription co-activator EYA4 is a cause of familial DCM (associated with hearing loss) introduces transcription regulation into the list of genetically established mechanisms of human heart failure [21].

**Familial metabolic cardiomyopathy of juvenile or adult onset**

Defects in metabolic pathways often result in infantile or pediatric disease onset with multisystem involvement. Rarely, more subtle enzymatic defects are compatible with long-term survival and lead to a more restricted phenotype, with predominant cardioskeletal involvement. Clinical recognition is important because some of these are directly treatable causes of cardiomyopathy.

Inborn errors of mitochondrial beta-oxidation result in tissue injury due to lipid infiltration, hypoglycemia, neurologic problems, hepatocellular dysfunction, myoglobinuria and cardiomyopathy. Cardiomyopathy (hypertrophic or dilated) is the most common clinical phenotype of VLCAD (very long chain acyl dehydrogenase) deficiency [33]. Myopathic carnitine deficiency or carnitine-palmitoyl transferase II deficiency is another form of lipid storage myopathy with cardiomyopathy [34].

Among the glycogen storage diseases are Pompe (GSDII), caused by acid maltase deficiency, Cori (GSD III), caused by debrancher enzyme deficiency, and phosphorylase kinase deficiency (GSDVIII), which may be associated with long-term survival and cardiomyopathy as a prominent manifestation. Glycogen storage disease type IV is caused by Brancher enzyme deficiency and the accumulation of abnormal glucose polymer – amylopectin. While the classical infantile form causes failure to thrive, hepatosplenomegaly, liver cirrhosis and neuromuscular manifestations, in the juvenile and adult-onset disease muscle and heart involvement predominate and death frequently results from cardiac failure.

Recent reports have drawn attention to a unique X-linked lysosomal storage disease, Danon disease, caused by mutations in lysosomal-associated membrane protein (LAMPII), which manifests as late-onset DCM in females and hypertrophic cardiomyopathy progressing to DCM in males [35].

Disorders in iron metabolism cause cardiac dysfunction concomitant with prominent extracardiac manifestations. Hemochromatosis is a multisystem iron-overload disorder, caused by at least five distinct genetic mechanisms [36]. Patients rarely present with heart failure but develop congestive cardiomyopathy later in life. Friedreich ataxia is caused by recessively inherited mutations in the Frataxin gene required for mitochondrial iron metabolism and antioxidant defense. While progressive neurologic abnormalities are the presenting feature, about one-half of the patients die of heart failure. Patients typically have concentric hypertrophic cardiomyopathy, which often progresses to a hypokinetic dilated form [37].

**Other familial variants**

Hypertrophic cardiomyopathy rarely progresses to the dilated (“burned-out”) phase (about 5%), but such a course appears to be more common with certain gene defects, for instance β-myosin Arg719Trp and tropomyosin mutations. Some of these patients present in a dilated phase with or without residual cardiac hypertrophy. Families with incomplete phenotypic characterization, with numerous individuals suffering from either sudden cardiac death or congestive failure leading to heart transplantation, are often presumed to have familial DCM. Other patients with sarcomere protein mutations present as heart failure with restrictive physiology and no prominent hypertrophy.

Arrhythmogenic right ventricular dysplasia is a familial cardiomyopathy primarily involving the right ventricle [32]. It is a genetic heterogeneous disorder with a dominant or recessive (dependent on the disease gene) mode of inheritance and remarkable phenotypic variability. While electrophysiologic and morphologic manifestations of right ventricular involvement are the characteristic features of the disease, many of those affected have associated left ventricular pathology. Moreover, some of the affected family members require clinical attention as DCM patients with biventricular failure [38].

Left ventricular non-compaction is characterized by deep trabeculations of the left ventricular endocardium in association with hypertrophy or dilatation. The familial autosomal dominant form may be associated with congenital heart defects, including hypoplastic left ventricle, myocardopathy and α-dystrobrevin gene defects [39]. Isolated X-linked non-compaction with infantile or later presentation was reported in association with tafazzin mutations [30].

Some pediatric familial (recessive or X-linked) heart failure patients are diagnosed as endocardial fibroelastosis (on endo-myocardial biopsy or autopsy). Fibroelastosis may be associated with congenital heart malformations, with Barth syndrome [Table 1], or with carnitine deficiency caused by mutations in the gene of sodium ion-dependent carnitine transporter [40].

**Clinical implications**

The European Research Group [9] formulated the following guidelines for diagnosis and management of familial DCM. Idiopathic DCM will be diagnosed in the presence of the following major criteria:

1. Ejection fraction <45% and/or shortening fraction <25%
2. Left ventricular end-diastolic dimension >117% upper limit of the norm (i.e., 2SD of the predicted + 5%) after considering repeated measures or evidence of end-organ damage
3. Moderate or severe sustained hypertension (>160/100 on repeated measures or evidence of end-organ damage)
4. Alcohol abuse (>40 g/day for females and >80 g/day for males) with remission of DCM after 6 months of abstinence of alcohol consumption

**Consider familial disease during the clinical workup of every patient with non-ischemic dilated cardiomyopathy**
d. Sustained and rapid supraventricular arrhythmia
e. Pericardial disease
f. Systemic disease
g. Congenital heart disease
h. Cor pulmonale.

Familial DCM will be diagnosed by the presence of two or more affected individuals in a single family or in a patient with “idiopathic” DCM, who had a first-degree family member with well-documented unexplained sudden death at <35 years age.

In a patient suspected of familial DCM, particular attention will be paid to unique features, neuromuscular dysfunction, laboratory screening including creatine phosphokinase values and meticulous pathologic analysis of tissue specimens, when available. Detailed (and possibly repeated) family history with pedigree construction is indispensable. Screening of asymptomatic first-degree family members by physical examination is essential, and ECG and echocardiogram are mandatory and must be repeated every 3 years [8,9]. Distinguishing the affected from non-affected family members among individuals with minor cardiovascular abnormalities is not trivial and might require an extended follow-up.

To facilitate clinical diagnosis in family members, the working group defined the following minor criteria for DCM:

1. Unexplained atrial fibrillation, sustained supraventricular arrhythmia or non-sustained ventricular tachycardia before 50 years of age
2. Left ventricular dilatation >112% of predicted value
3. Left ventricular ejection fraction <50% or shortening fraction <28%
4. Unexplained complete left bundle branch block, second or third-degree atrioventricular block or sinus node dysfunction
5. Unexplained sudden death or stroke before 50 years of age
6. Segmental wall abnormalities in the absence of coronary disease or intraventricular conduction defect

DCM in a family member will be diagnosed by the presence of either two major criteria (systolic dysfunction and dilatation) as stated above: left ventricular dilatation >117% plus one minor criterion, or by three minor criteria.

Considering familial disease in the differential diagnosis of cardiomyopathy should be integrated into the clinical evaluation of newly diagnosed DCM [Figure 1]. Evaluation, genetic counseling and follow-up of families with DCM require a dedicated team experienced in heart failure clinical management, as well as clinical and molecular genetic analysis. Genetic diagnosis, per se, currently plays a limited role in the routine clinical management of DCM, excluding several metabolic cardiomyopathies. Nearly every family has its own “individual” gene mutation. Results from studies that performed a serial mutation screen in DCM cohorts [1,10,12] indicate that the known disease genes currently account for less than 30% of DCM families. However, the rapidly expanding list of novel disease genes [Table 1] suggests an ongoing change. The progress in genetic technology and bioinformatics might eventually turn genetic analysis into a major component in the clinical investigation of familial DCM. Integrating basic science into clinical practice is the way to try and define the disease-causing mutation or the disease-associated haplotype (in families large enough to qualify for linkage analysis). Once available, genetic diagnosis and genotyping of family members will be valuable tools for genetic counseling, risk stratification, clinical follow-up, and the early institution of preventive therapy in the affected relatives. Finally, those who genotype negative will be spared repeated clinical studies and lifelong uncertainty for both themselves and their offspring.

For further details on disease − causing mutations, gene function, clinical features and literature, the reader is advised to visit the site of Online Mendelian Inheritance in Man (OMIM) at http://ncbi.nlm.nih.gov.

Figure 1. Proposed scheme for evaluating inherited dilated cardiomyopathies.

- While no edge-to-edge consensus exists on routine studies in first-degree family of individuals diagnosed with idiopathic DCM, these are the contemporary ACC/AHA/ASE guidelines for the clinical application of echocardiography.
- Transforming lymphocytes from an individual creates a cell line that can be used as an “eternal” source of DNA, RNA and protein.
Reviews

References


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