

# Familial dilated cardiomyopathy

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## Abstract

*Dilated cardiomyopathy (DCM) is a heart muscle disease characterized by ventricular dilatation and impaired systolic function. Patients with DCM suffer from heart failure, arrhythmia, and are at risk of premature death. In many cases the disease is inherited and is called familial DCM (FDC). FDC is caused by genetic mutations in FDC genes that encode cytoskeletal and sarcomeric proteins in cardiac myocytes. Family history analysis is an important tool for identifying families affected by FDC. Standard criteria for evaluating FDC families have been published and such criteria are increasingly used. Clinical genetic testing is being developed and is expected to be utilized for evaluating FDC families in the near future. The treatment of patients affected by FDC is based on currently accepted treatment guidelines for DCM. Family screening by pedigree analysis (and soon by genetic testing) makes it possible to identify patients at earlier stages of their disease. This represents an opportunity to invoke lifestyle changes and to provide pharmacological therapy earlier in the course of disease. Genetic counseling is used to identify additional asymptomatic family members who are at risk to develop symptoms, allowing for regular screening for these persons. FDC may account for between 35-48% of seemingly idiopathic DCM.*

## Key-words

Dilated cardiomyopathy, Familial dilated cardiomyopathy, *Lamin A/C* gene, Heart failure, Arrhythmia, Conduction defects.

## Disease name and synonyms

Dilated cardiomyopathy (DCM) is a disease of the heart muscle characterized by ventricular dilatation and impaired systolic function (1). DCM is a leading cause of heart failure and

arrhythmia. Due to its significant prevalence, high mortality and morbidity, including frequent hospitalizations, DCM is a major health concern for adults. Despite improvements in the treatment of heart failure introduced in the last

10 years including the general availability of cardiac transplantation and better medical treatment, clinical outcome following the onset of symptoms has not substantially changed. Mortality remains high, the disease is progressive and unrelenting, and disability and morbidity are among the highest of any disease or syndrome.

DCM is defined as *idiopathic* when appearing sporadically, *isolated* when appearing in a single member of a family and without known cause or *familial* when occurring in two or more related family members (1,2).

### Excluded diseases

DCM differs from other forms of secondary dilatation and dysfunction of the ventricles due to known cardiac or systemic processes (1). These are referred to as *specific cardiomyopathies*, named after the disease process with which they are associated, such as ischemic cardiomyopathy, valvular heart cardiomyopathy, hypertensive cardiomyopathy, alcoholic cardiomyopathy, and myocarditis. Less common forms of *specific cardiomyopathies* are peripartum cardiomyopathy and cardiomyopathies developing in patients with amyloidosis, hemochromatosis, sarcoidosis, and due to toxicity from agents like doxorubicin. In the pediatric population, metabolic cardiomyopathies are encountered with greater frequency.

It should be noted that cases of myocarditis and peripartum cardiomyopathy can occur as familial forms, in patients in whom DCM can also be present, and therefore, it may be difficult to differentiate these forms (3).

### Definition of DCM and diagnostic criteria of familial DCM

The diagnosis of DCM is made according to criteria provided by the World Health Organization/International Society and Federation of Cardiology (WHO/ISFC) (4), the guidelines of the National Heart, Lung, and Blood Institute Workshop on the Prevalence and the Etiology of Idiopathic Dilated Cardiomyopathy (4), and the more recent *Guidelines for the study of familial dilated cardiomyopathies* (2), designed to improve the sensitivity and specificity of the old classification criteria.

DCM is diagnosed in the presence of:

- a) fractional shortening (FS) less than 25% (> 2SD – standard deviations-) and/or ejection fraction less than 45% (> 2SD); and
- b) left ventricular end diastolic diameter (LVEDD) greater than 117% (>2SD of the predicted value of 112% corrected for age and body surface area, BSA), (5) excluding any known cause of myocardial disease. In the context of familial

DCM, these criteria are used to diagnose the proband in a family.

FDC is defined by the presence of:

- a) 2 or more affected relatives with DCM meeting the above-mentioned criteria; or
- b) a relative of a DCM patient with unexplained sudden death before the age of 35 years (2). In FDC, family members may be classified as *affected*, *unaffected* or *unknown* (2). This classification is based on major and minor criteria that have been developed to account for the high frequency of minor cardiac abnormalities within families with FDC and the need for more sensitive criteria (3,6).

In relatives, the *affected* status is defined by the presence of:

- a) 2 major criteria consisting of left ventricular systolic dysfunction (fractional shortening < 25% and/or ejection fraction < 45%) and dilatation (LVEDD > 117% of the predicted value corrected for age and BSA) (5) or
- b) left ventricular dilatation (as defined above) and one minor criterion; or
- c) 3 minor criteria. The *unknown* status is defined by the presence of 1 or 2 minor criteria and the *unaffected* status is defined by the presence of a normal heart or the determination of other causes of myocardial dysfunction.

Minor criteria of disease are:

- 1) unexplained supraventricular arrhythmias (atrial fibrillation or sustained arrhythmias), or frequent (>1000/24 h) or repetitive (3 or more ectopic beats with a heart rate > 120 beats/min) ventricular arrhythmias before the age of 50;
- 2) left ventricular dilatation (> 112% of the predicted value);
- 3) left ventricular dysfunction (ejection fraction < 50% or fractional shortening < 28%); unexplained cardiac conduction system disease (grade II or III atrioventricular blocks, complete left-ventricular bundle branch block, or sinus nodal dysfunction);
- 4) unexplained sudden death or stroke before 50 years of age;
- 5) segmental wall motion abnormalities (>1 segment, or 1 if not previously present) in the absence of intraventricular conduction defect or ischemic heart disease.

### Differential diagnosis

Exclusion criteria for *idiopathic/familial* DCM are:

1. blood pressure higher than 160/110 mmHg, documented and confirmed through repeated measurements;
2. obstruction (more than 50%) of a major branch of the coronary artery;
3. alcohol intake more than 100g/day;
4. persistent high rate supraventricular arrhythmia;
5. systemic diseases;
6. pericardial diseases;

7. congenital heart diseases;
8. cor pulmonale;
9. myocarditis.

Table 1 shows the diagnostic tools available for differentiating the different forms of DCM.

**Table 1. Etiology and diagnostic tools in DCM.**

Causes	% of cases	Diagnostic tools
Frequent DCM		
Idiopathic/Familial DCM	20 – 50	Family history, echocardiogram, detailed evaluation of first-degree relatives, coronary angiography, endomyocardial biopsy
Ischemic DCM	50 - 70	History, coronary angiography
Valvular DCM	1.5 – 4	Echocardiogram, physical exam
Hypertensive DCM	2 – 4	Physical exam, echocardiogram showing hypertrophy
Alcoholic	3 – 40	History of excessive alcohol use
Myocarditis	5 – 10	History compatible with viral myocarditis, endomyocardial biopsy
Rare DCM		
Peripartum	2-3	History
Amyloidosis		Echocardiogram, endomyocardial biopsy, rectal/fat pad biopsy
Hemochromatosis		Extra-cardiac signs, endomyocardial biopsy, iron studies
Sarcoidosis		Extra-cardiac signs, endomyocardial biopsy
Doxorubicin toxicity		History of exposure to doxorubicin
Other toxic substances		History
Metabolic DCM		Laboratory tests, pediatric age

### Frequency

DCM has a prevalence of one case out of 2,500 individuals (7) with an incidence of 7/100,000/year (8). However, DCM is probably underdiagnosed and is now believed to account for a much larger number of cases, owing to the fact that subjects may remain asymptomatic until marked ventricular dysfunction has occurred.

Prior to 1990, FDC was not widely recognized and genetic contributions to the development of dilated cardiomyopathy were rarely implicated in disease models. In 1981, a retrospective review of 104 patients with DCM at the Mayo clinic estimated that approximately 2% of cases were potentially familial in nature (9). The paradigm changed dramatically in 1992 when it was reported that by carefully collecting the family history and by screening relatives by physical examination and echocardiography 20% of cases of FDC were likely to be familial (6). More recent studies support that FDC may account for between 35-48% of seemingly idiopathic DCM (10-13). Unfortunately, there are no reliable clinical or morphologic parameters that can predict the familial form from non-genetic causes of cardiac dilatation. A result of this circumstance is that family history data has become critical to the evaluation of these patients and families.

### Clinical description

Initially patients present with signs and symptoms of heart failure, due either to volume overload or to low cardiac output. Usually, by the time of the diagnosis, probands (here referring to the first individual diagnosed within a family) have severe impairment of the left ventricular ejection function and are in New York Heart

Association (NYHA) functional class III-IV. Affected relatives, on the other hand, can be asymptomatic with mild ventricular dilatation and dysfunction. Twenty to thirty-five percent of patients present with chest pain, mostly during exercise, and the electrocardiogram may show pseudo-infarction Q waves. Angina is thought to be due to limited coronary vascular reserve. Fatigue is present in almost one third of patients. Palpitations are very common, due to ventricular arrhythmias, nevertheless, syncope and sudden death rarely constitute the first symptom of the disease. Pulmonary and systemic thromboembolisms occur, as the first manifestation of the disease, at a rate of 1 to 6% per year. Most of them can be found in cases with severe left ventricular dilatation and dysfunction. A particular form of familial DCM due to mutation of the *lamin A/C* gene (14,15) presents with mild dilatation and severe dysfunction of the left ventricle conduction defects, supraventricular arrhythmias, variable skeletal muscle involvement and variable serum creatine phosphokinase (CPK) levels. Prognosis for many of these patients is not favorable. X-linked FDC, due to mutations in the dystrophin gene, has a less severe prognosis and presents with increased CPK, muscular abnormalities, and the typical signs of *dystrophinopathy* at the skeletal muscle biopsy (16-19).

### Management and treatment of familial dilated cardiomyopathy

The management of FDC focuses on limiting the progression of heart failure and controlling arrhythmia. *General measures* include patient education, salt and fluid restriction, treatment of hypertension, limitation of alcohol intake, control

of body weight, and encouraging moderate exercise, preferably aerobic in a controlled environment. *Pharmacological therapy* includes a multitude of agents (20) that are included into the standard approaches to heart failure. Only few of them in each class will be mentioned here.

Angiotensin converting enzyme (ACE) inhibitors reduce mortality, hospitalization and progression of heart failure, as noted in several trials including CONSENSUS, (21) SOLVD (22) and SAVE (23). These drugs are generally started at low doses and are gradually titrated up to doses equivalent to those showing efficacy in randomized trials. Captopril is increased to a maximum of 50 mg three times/day. Maximum for enalapril dose is 20 mg twice/day and that of lisinopril is 40 mg once/day. Lower doses (if high doses are not tolerated) provide most of the benefit. In patients who are intolerant to these agents, angiotensin receptor blockers (ARBs) provide a reasonable alternative to ACE inhibitors. Their use is based on trials such as ELITE-I and II, (24) Val-HeFT (25) and OPTIMAAL (26). The dose of losartan used in these trials was around 50 mg once/day. Maximum dose for valsartan is 160 mg twice/day. The addition of an ARB to an ACE inhibitor likely offers little additional benefit based on the Val-HeFT trial.

First-generation calcium channel blockers are not recommended in patients with heart failure. Trials using endothelin antagonists have been disappointing to date and these agents are not recommended in standard guidelines (20).

Diuretics have not been assessed in a randomized study to verify their effect on survival in heart failure. Furosemide is used at daily doses of 20 mg to 600 mg daily. Bumetanide and ethacrynic acid are other loop diuretics currently in use. Torsemide has better bioavailability when taken orally and is used in some patients who do not respond to oral furosemide. Frequently, the dose is half of that of furosemide for a similar effect. When high doses of loop diuretics are needed and, especially if the patient has diuretic resistance, metolazone is added, usually at a dose of 2.5 mg once/day to 5 mg twice/day.

Acetazolamide is used at a dose of 250 to 500 mg daily in some patients with metabolic alkalosis.

Aldosterone inhibitors such as spironolactone and eplerenone reduce mortality, as noted in RALES (27) and EPHEBUS (28) respectively. Spironolactone is used at doses varying from 12.5 to 50 mg once/day. Eplerenone was started with a dose of 25 mg orally once/day, which was increased to 50 mg once/day as tolerated. Eplerenone is more selective for the aldosterone

receptor and avoids some of the side effects associated with spironolactone, such as gynecomastia. Vasopressin antagonists are still under investigation. Natriuretic peptides are available only intravenously for acute decompensation.

The only inotrope whose use is widely accepted in chronic heart failure is digoxin. It is dosed at 0.125- 0.25 mg once/day and is adjusted to renal function. A recent *post-hoc* analysis of the Digitalis Investigators Group (29) divided the patients based on their digoxin serum level and showed that all-cause mortality was reduced by 6.3% in the subgroup of patients whose level was between 0.5 and 0.8 ng/ml.

Beta-adrenergic blockers are considered a major advance in the therapy of heart failure. CIBIS-II30 and MERIT-HF (31) showed a 34% relative reduction in all-cause mortality using bisoprolol and metoprolol succinate (both beta-1 selective blockers). Carvedilol, a non-selective beta-blocker with alpha-blocking properties reduced mortality by 35% in severe heart failure (COPERNICUS) (32). Beta-blocking agents must be titrated gradually towards their target doses. The target dose of carvedilol is 25 mg twice/day in patients less than 70 kg, and 50 mg twice/day in heavier patients.

The use of anticoagulants, of antiplatelet agents is a controversial subject and more studies are underway to identify which therapy to use and in whom. In clinical practice, anticoagulation is often used in patients with a left ventricular ejection fraction less than 30%.

#### *Mechanical devices*

The use of cardiac resynchronization therapy (CRT) with biventricular pacing improves symptoms in advanced heart failure and reduces hospitalizations. In the COMPANION trial (33) CRT significantly reduced mortality in patients with DCM. In the treatment of arrhythmia, the use of implantable defibrillators is being progressively expanded as they are proving to be useful in reducing mortality from sudden death compared to antiarrhythmic drugs. The use of left ventricular assist devices (LVAD) was evaluated in REMATCH (34). All-cause mortality was 52% at one year in the LVAD group versus 25% in the medical group. The benefits of LVADs are tempered by a multitude of device-related complications.

Finally, patients with severe heart failure, severe reduction of the functional capacity and depressed left ventricular ejection fraction have a low survival rate and may require heart transplant. In this setting, heart transplantation improves survival and quality of life.

#### *Asymptomatic left ventricular dysfunction*

So far, no trial has been carried out on the usefulness of therapy in asymptomatic affected

relatives. However, based on studies on ischemic heart disease, it is believed that an early use of ACE inhibitors and/or beta adrenergic blockers could be very important in slowing down the progression of the disease.

### Etiology

In FDC, there is clear evidence of Mendelian segregation of disease phenotype. FDC is a heterogeneous entity (Table 2). Different forms have been identified and should be distinguished based on patterns of transmission and characteristics of the phenotype. When classifiable, the clinical patterns encountered include: autosomal dominant FDC without extracardiac manifestations; autosomal recessive FDC; FDC with X-linked transmission; autosomal dominant FDC with subclinical skeletal muscle involvement; autosomal dominant FDC with conduction defects; autosomal dominant left ventricular non-compaction; unclassifiable FDC with retinitis pigmentosa and hearing loss (3,13). Right ventricular cardiomyopathy/or arrhythmogenic right ventricular dysplasia is considered as a distinct entity (1). There is clear evidence of incomplete penetrance as well as age-dependent penetrance exemplified by the fact that FDC is typically an adult onset disease and many persons carrying mutations do not develop overt disease until their fifth or sixth decade of life (35).

Carefully designed studies of larger FDC families by genetic linkage analysis and other methods have implicated 22 chromosomal loci as containing FDC genes (reviewed in Fatkin and Graham) (36). Several different genes at these loci have been identified to date (Table 2). The majority of these genes encode proteins that have cytoskeletal and/or contractile properties and most mutations described to date are "private" mutations and are not shared between unrelated families. To date, studies have primarily focused on highly selected families and/or on relatively small numbers of families. Consequently the genetic epidemiology of mutations in FDC genes across all FDC families remains unknown. Furthermore, as mutations have now been described in seemingly non-familial cardiomyopathies (*sporadic or truly "idiopathic" DCM*) the contribution of FDC gene mutations to isolated, or sporadic, dilated cardiomyopathies is not well-defined.

### Diagnostic methods

The basic evaluation in the proband (2) consists of an accurate family history, physical examination with specific attention to the neuromuscular apparatus, laboratory examination including CPK, chest X-ray, ECG and echocardiogram. In selected cases, an

exercise stress test or a pharmacological test, such as dobutamine echocardiography, may be indicated to induce ischemia and unmask ischemic cardiomyopathy. More specific diagnostic tests include hemodynamic and coronary angiographic study, radionuclide ventriculography and endomyocardial biopsy. In the presence of neuromuscular abnormalities, needle skeletal muscle biopsy is indicated. Molecular genetic diagnosis should be performed when the test is available and may impact clinical management.

### Genetic counseling

Genetic counseling approaches for familial FDC are still under developed and consensus guidelines are lacking. The high degree of genetic heterogeneity, uncertainty as to which familial DCM genes are commonly mutated, and the propensity to uncover private mutations, have combined to hinder the development of clinical testing. As the disease is of relatively late onset, many individuals in older generations may be unavailable for examination or may be deceased. Limited knowledge of FDC and thorough evaluation of relatives at risk by practicing generalists and cardiologists also likely contributes to under-recognition of this condition.

An accurate family history and screening of first-degree relatives has fundamental importance in FDC. This approach is not yet widely practiced in the United States. Each first-degree relative should undergo detailed physical examination, ECG, and echocardiogram. Signal averaged electrocardiography (SAECG) has also been suggested as an additional diagnostic tool (37). The thorough evaluation of relatives of patients is standard for the research studies of FDC.

For families where a pathogenetic mutation has been detected, the evaluation of relatives at risk can include molecular testing to confirm the presence or absence of the pathologic mutation. This information can be integrated into the genetic counseling provided to each individual within that family. Non carriers may be reassured that they are not at increased risk of developing FDC. Asymptomatic carriers who are at increased risk of disease may be considered for regular evaluations (including echocardiogram) to screen for the development of early disease. As significant non penetrance has been reported, the counseling session should focus on the *increased risk* of developing FDC for mutation carriers, rather on models that implies a *certainty* of disease for all mutation carriers.

In families where a pathologic mutation has not been detected, genetic counseling is understandably less precise. A detailed examination and analysis of the pedigree is essential to define, if possible, the likely mode of

inheritance. Implicit in this exercise is that historical information provided about relatives should be confirmed through either the direct evaluation of relatives or by reviewing medical records and/or autopsy reports. In performing genetic counseling, careful attention to the problems of age-dependent and incomplete penetrance should be integrated into the discussion. Relatives considered to be at significantly increased risk of developing a cardiomyopathy should be considered, as above, for regular screening.

### Antenatal diagnosis

The use of molecular genetic testing to test fetuses for adult-onset disease has been the subject of a number of ethical discussions. Despite widespread reluctance to embark upon testing in this setting a number of recent examples are challenging this paradigm. Such discussions are likely to ensue in the context of familial DCM once clinical genetic testing becomes more widely available.

### Unresolved questions

There are many aspects of familial DCM that remain poorly understood. Clear and comprehensive understanding of the genetic epidemiology of gene mutations in both FDC and sporadic DCM is needed. Such knowledge will provide a foundation for the development of genetic testing, which will likely be panel-based to simultaneously test multiple genes. Animal models of FDC have been developed to better characterize the pathogenesis of how the underlying genetic defects initiate and/or propagate the disease process. Ultimately this work may suggest novel approaches to target the underlying molecular defects. There is evidence of substantial variability in phenotype within families, suggesting that environmental and/or modifying genetic factors may interact with the underlying FDC mutations. Pilot studies to explore these hypotheses are now underway. Finally, experimental approaches to explore how conventional cardiovascular therapies impact the disease process are desperately needed.

### Research Projects

A large number of investigators are studying various aspects of FDC to study many of the unresolved questions mentioned above. Our group is part of an international collaborative registry dedicated to describing the natural history and genetic epidemiology of FDC. A systematic approach to screening for mutations in the FDC genes in over 150 families with FDC is included in this effort. The National Institutes of Health, the American Heart Association, and the Muscular Dystrophy Association support this

work. Additional information is available at: <http://www.uchsc.edu/cvi>.

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