

For Professionals

This page provides information most commonly sought by health care professionals and scientists regarding dilated cardiomyopathy (DCM) and familial dilated cardiomyopathy (FDC). Please refer your patients and their families with FDC who are willing and interested to participate in this research project.

Referring Patients for Research Purposes provides guidelines and instructions for referring patients and families with IDC/FDC to us for research purposes.

Background on DCM provides an introduction to dilated cardiomyopathy for clinical and research professionals who are not familiar with the topic.

The Genetics of DCM provides a brief overview of the genetics of dilated cardiomyopathy.

Clinical Recommendations provides screening, diagnosis, counseling and treatment recommendations for patients diagnosed with IDC, and for patients and families with FDC.

A Comprehensive Review of FDC Research provides a review of FDC clinical reports, and a **GeneTable** lists FDC genes and provides links to additional information. Gene locations are provided in a **LocusTable**.

Genetic Evaluation of Cardiomyopathy: A Heart Failure Society of America Practice Guideline is the title of the practice guidelines for the genetic evaluation of cardiomyopathy, including dilated cardiomyopathy, which was published in March 2009 in the Journal of Cardiac Failure (**Journal of Cardiac Failure Vol. 15 No. 2, 2009**). If you would like to obtain a reprint of this publication but are not able to, please **contact us** and we will assist you.

We hope you find this information useful. If you have questions that have not been addressed here, please **contact us**. We are updating and improving this website continuously. We have not been able to include all of the literature in this rapidly expanding field, and we apologize to our many colleagues if we did not integrate your reports into this website.

Referring Patients for Research Purposes

Please screen your patients with IDC for FDC (see **Clinical Recommendations**), and please refer your patients and their families with IDC/FDC to us for research purposes.

The most important aspect of our success is your patient's enthusiasm and willingness, and that of their affected family members, to participate in our research efforts. In 2009, we have broadened our recruitment to DCM patients beyond those with identifiable familial disease. Therefore, we now seek out both FDC and IDC (apparently sporadic DCM). For families with FDC, we will accept families of any size as long as we are able to establish a diagnosis of FDC. For patients with IDC, we will accept them into our study if they have first degree relatives who will participate, especially parents and/or siblings.

We only need the following information from you or your office:

- 1) assurance that your patient has agreed that we may contact them to discuss participation in our research program, and
- 2) their contact information (name, and phone number or email address).

Please also provide your contact information. We will do the rest.

After contacting your patient (the index patient), we will first inform them about our research program and request their written informed consent. We will then obtain a 3-4 generation family history, seek a release of medical information and request copies of their pertinent cardiovascular medical records regarding IDC/FDC. We will also express mail a blood collection kit to the patient (which contains all necessary blood tubes, instructions, and a prepaid Fed Ex return mailer). We will also request your patient to contact their family members and obtain verbal consent for us to contact their closely related family members and other affected family members. Upon obtaining the verbal consent of additional family members, we will obtain their contact information and request their participation.

If a family is very large with multiple affected members, we may consider doing a full family screening, where we travel to screen an entire kindred by exam, ECG and echocardiography.

We track all referrals for research purposes and keep you updated every 6-12 months with progress reports of the families that you refer to us.

Background on DCM

What is dilated cardiomyopathy? Dilated cardiomyopathy is a descriptive term that refers to heart muscle disease where the left ventricle dilates, or enlarges, and has reduced systolic (pumping) function. Thus, the key diagnostic features of dilated cardiomyopathy are left ventricular enlargement (LVE) with decreased systolic function.

What are the causes of dilated cardiomyopathy? The most common cause of dilated cardiomyopathy in the US is termed "ischemic cardiomyopathy." Ischemic cardiomyopathy results from loss of myocardium from myocardial infarction (heart attack) which may lead to a myopathy in the remaining heart muscle. After ischemic cardiomyopathy, the next most common cause of dilated cardiomyopathy is idiopathic dilated cardiomyopathy (IDC). By definition, the etiology of IDC is unknown. Other identifiable causes of cardiomyopathy include valvular abnormalities that cause volume or pressure overload, such as mitral regurgitation or aortic stenosis, respectively, or toxic cardiomyopathies from alcohol or anthracycline antibiotics, rheumatic heart disease, viral infections, infiltrative cardiomyopathies such as hemochromatosis and other unusual causes.

An **IDC diagnosis** is based upon an increased left ventricular end diastolic dimension combined with decreased systolic function, usually defined as an ejection fraction of less than 0.50 after other causes of cardiomyopathy have been excluded. This includes the exclusion of significant (>50% obstruction) coronary artery disease and/or previous myocardial infarction, the most common cause of dilated cardiomyopathy. Other diagnoses to be excluded include valvular, inflammatory or infiltrative cardiomyopathies.

What is familial dilated cardiomyopathy, and what are diagnostic criteria for FDC? Familial dilated cardiomyopathy (FDC) is dilated cardiomyopathy that occurs in families. The usual diagnostic criterion for FDC is an index patient with a formal diagnosis IDC who has one first degree or two second degree relatives who have also met the diagnostic criteria for IDC.

How does FDC present, and are there any key findings? The clinical presentation of FDC is as variable as the presentation of IDC, and thus there are no singular or key findings. The index patient usually presents with symptomatic cardiac disease such as clinical heart failure, arrhythmia, sudden cardiac death or stroke. The diagnosis of FDC is frequently not considered until another close family relative is also diagnosed independently with IDC, and the same diagnoses are brought to the attention of health care providers.

Once a diagnosis of FDC is established for a family, and in our research program with prospective screening of otherwise asymptomatic subjects, we have found that some families may have a predisposition to a pattern of presentation. Such patterns include similar ages of onset (within decades) or the presence and type of arrhythmia (for example, atrial fibrillation or sudden cardiac death). However, the expression of FDC can also be quite variable both within and between families. Families often have a combination of mild and severe disease across all generations; within the same family, the disease may be manifest as subtle clinical symptoms or mild arrhythmias, but also

may exhibit sudden death or dilated cardiomyopathy leading to heart failure and/or heart transplantation.

What is the relationship of familial dilated cardiomyopathy to heart failure?

Familial dilated cardiomyopathy is a diagnostic term to describe one of several causes of cardiomyopathy, and thus FDC (as other cardiomyopathies) may cause heart failure. **Heart failure** is a clinical syndrome or symptom complex from multiple etiologies that results when cardiac output is not sufficient to meet the metabolic needs of the body. Symptoms commonly include dyspnea on exertion, edema, shortness of breath, and paroxysmal nocturnal dyspnea.

As such, the diagnosis of heart failure requires symptoms to have occurred at some time. In previous decades, the use of the term "heart failure" was usually restricted to the time during acute symptomatic exacerbations, and when acute symptoms resolved the patient was thought to be "out of heart failure." More common current usage of the "heart failure" term is applied to subjects who have had symptomatic heart failure in the past with ongoing left ventricular dysfunction and intermittent symptoms, even if symptoms are present only with vigorous activities (e.g., early Class II New York Heart Association classification).

Familial (or idiopathic) dilated cardiomyopathy may also reflect one etiological cause of left ventricular enlargement with symptomatic systolic dysfunction. This is in contrast to left ventricular enlargement (LVE) without systolic dysfunction, which can be identified in some asymptomatic family members in FDC pedigrees by echocardiography.

The Genetics of Dilated Cardiomyopathy

Recognition that from one-quarter to one-half of IDC has a familial basis: From scattered case reports prior to 1985 it was suggested that 1-2% of patients with idiopathic dilated cardiomyopathy (IDC) had family members with a similar condition, termed familial dilated cardiomyopathy (FDC). FDC was therefore thought to be infrequent and genetic factors were considered an unusual cause of IDC. However, systematic studies in the mid 1980s to early 1990s, usually using family history, suggested rates from 2-10%. However, family history is quite insensitive to identify FDC, and when first-degree relatives of individuals with IDC were examined prospectively with echocardiography (echo) and electrocardiography (ECG), FDC rates were observed to be 10-33% (for references, please see **Section A** of the Comprehensive Review, which follows this section). A key prospective study published in the New England Journal of Medicine in 1992 (**The Michels study, 1992**) using the most stringent diagnostic criteria (a formal diagnosis of IDC in relatives) demonstrated

that FDC was present in 20% of patients with IDC. In that study, only 5% of familial disease was identified by family history alone. When less stringent diagnostic criteria other than a formal diagnosis of IDC in relatives was used (such as isolated left ventricular enlargement, or explained heart failure and/or sudden cardiac death in young relatives), two of the largest studies suggested that 35-48% of all patients with IDC have relatives with a similar condition (**The McKenna and co-workers report, London, 1998; The Heidelberg report, 1998**).

Inheritance. FDC most commonly exhibits familial transmission consistent with autosomal dominant (AD) inheritance (approximately 90%), but X-linked (5-10%) and much less commonly autosomal recessive (AR) or **mitochondrial** inheritance have been reported. Preliminary data from our research suggests that DCM-causing mutations may be present in the absence of a family history (apparently sporadic DCM).

Autosomal Dominant FDC. Mutations in greater than 20 autosomal genes (all autosomal dominant (AD) transmission except 1 autosomal recessive (AR) and 2 X-linked genes have been suggested to be causative. These genes and the proteins they encode have been provided in the **GeneTable**. References and additional information is provided in the section which follows, **A Comprehensive Review of FDC Research**. Autosomal dominant FDC has been linked to additional loci which are also reviewed below. Gene locations have been provided in a **LocusTable**.

Clinical Genetic Testing and Genetic Counseling. The development of a comprehensive genetic test for DCM is currently complicated by (1) locus and allelic heterogeneity and (2) the finding that a significant proportion of cases are not attributable to any of the known genes. Despite this clinical genetic testing is now available. Larger series of patients will be required to understand gene penetrance, genotype-phenotype correlations, and the true incidence and prevalence of FDC, which will greatly augment genetic counseling. Our reviews "**Clinical and Genetic Issues in Familial Dilated Cardiomyopathy**" and "**Progress With Genetic Cardiomyopathies: Screening, Counseling, and Testing in Dilated, Hypertrophic, and Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy**" also have sections that review a variety of genetic counseling issues.

Clinical Recommendations: Screening, Diagnosis, Treatment and Counseling

1. Overview. This section provides screening, clinical cardiovascular diagnosis, counseling and treatment recommendations for patients with IDC and families discovered to have FDC (**Clinical Genetic Testing** is covered elsewhere). We initially published these recommendations in September, 1999 in the Journal of the American College of Cardiology (Crispell K, Wray A, Ni H, Nauman D, Hershberger R. Clinical

profiles of four large pedigrees with familial dilated cardiomyopathy: preliminary recommendations for clinical practice. **J Am Coll Cardiol 1999;34:837-847, PMID: 10483968**). These recommendations were updated in 2005 (Burkett E, Hershberger RE. State of the Art: Clinical and Genetic Issues in Familial Dilated Cardiomyopathy. **J Am Coll Cardiol 2005;45:969-81, PMID: 15808750**). In March 2009, the Heart Failure Society of America (HFSA) published medical guidelines that reiterate these recommendations (Hershberger, RE et al. Genetic Evaluation of Cardiomyopathy : A Heart Failure Society of America Guideline. **J Cardiac Failure, 2009; 15:83-97 PMID: 19254666**). Further, genetic testing to assist with diagnosis is available, and its role and indications are comprehensively addressed on the page entitled **Clinical Genetic Testing**.

a. The rationale for these recommendations rests on the following points.

First and foremost, FDC is a potentially serious, life-threatening disease. Second, screening to detect FDC may be successful, as FDC is much more common than recently thought -- the likelihood of FDC in a patient diagnosed with IDC is from 35-50%. Third, effective treatment is available. Extensive clinical trial data supports improved outcomes with medical treatment. Fourth, similar recommendations have been made for other genetic and familial cardiovascular diseases, such as hypertrophic cardiomyopathy, even though medical treatment may not be as effective for hypertrophic cardiomyopathy. Finally, diagnostic, therapeutic, counseling or other interventions assume the voluntary and informed consent of the subject.

b. The diagnosis of IDC most commonly rests on left ventricular enlargement accompanied by systolic dysfunction after ruling out other possible causes of dilated cardiomyopathy. Most commonly, this includes an increased left ventricular end diastolic dimension (LVEDD) at echocardiography adjusted for height or BSA in combination with evidence for systolic dysfunction (ejection fraction <50%). Other causes of dilated cardiomyopathy should be excluded, and includes most importantly ischemic heart disease which causes ischemic dilated cardiomyopathy, the leading cause of dilated cardiomyopathy in the US. Coronary heart disease should be definitively excluded in patients who appear to have IDC but who are at risk for ischemic heart disease (age > 40 years in men, age > 45 years in women, cigarette smoking, diabetes, hypertension, hypercholesterolemia and other risk factors). Other less common causes of dilated cardiomyopathy can usually be excluded by history, exam, EKG and echocardiography, and include valvular heart disease, rheumatic heart disease, hypertensive heart disease, congenital heart disease, and toxic or drug induced cardiomyopathies such as anthracycline cardiomyopathy.

c. Other non-dilated cardiomyopathies may also be familial such as hypertrophic cardiomyopathy or arrhythmogenic right ventricular dysplasia. It is usually easy to differentiate IDC/FDC from these other non-dilated cardiomyopathies, but occasionally classification becomes difficult. In these situations comprehensive review of all cardiovascular data from all affected family members can usually lead to the correct diagnostic assignment.

2. Screen patients with IDC for FDC. Whether a new or established diagnosis, we recommend that all patients with IDC should undergo clinical cardiovascular screening for FDC. This is accomplished by taking a careful family history of a patient with IDC, and by recommending that a history, an exam, an EKG and an echocardiogram be performed for first degree relatives (parents, siblings, children) of the patient with IDC.

a. Obtain a careful family history. The family history includes a careful and thorough cardiovascular family history for heart failure or "dropsy," the colloquial term used in previous generations to label heart failure, sudden death not associated with known coronary disease, premature stroke or other history suggestive of heart failure. Other common historical features are sudden death and/or history of heart failure in the peripartum period. Although the family history has been shown to be much less sensitive to detect FDC than echo screening of first degree relatives, it is painless, inexpensive and relatively easy to an experienced clinician.

b. Screen first-degree relatives for IDC/FDC. We recommend that a history (including a careful and thorough cardiovascular family history), an exam, an EKG and an echocardiogram be completed for all first degree relatives of patients with an established diagnosis of IDC. This assumes the informed consent of both patients and their first degree family members. Patients with IDC should be informed about the 35-50% risk of FDC with IDC. We then recommend that they inform their first degree relatives of their IDC diagnosis, of the possible familial nature of the disease, and that they should undergo IDC/FDC screening.

3. Establish a Clinical Diagnosis of FDC. The FDC clinical diagnosis is established most simply by diagnosing two (or more) family members with IDC in first or second degree family members. An FDC diagnosis can be established with an IDC diagnosis in more distant relatives (third degree and greater) with greater reliability when three or more family members are diagnosed with IDC. We would emphasize that we recommend that the diagnosis of FDC, that is, the establishment of the diagnosis of heart muscle disease in a family is best made with a *bona fide* IDC diagnosis in two family members. This is in distinction to the assignment of affected status to additional family members, once the FDC diagnosis has been established in a kindred, with less stringent criteria than those used to diagnose idiopathic dilated cardiomyopathy or the assignment of genetic cardiovascular disease based on genetic testing. If you are a cardiovascular specialist and would like further review and discussion of this quite technical, but important point, please see our FDC **Publications**.

4. Once FDC is diagnosed, pursue additional stepwise screening. Stepwise screening is progressive screening of first degree relatives of those shown to be affected with FDC. Thus, with at least two family members diagnosed, their first degree relatives should be advised to undergo screening (history, exam, EKG, echo) by their physician. If cardiac abnormalities are discovered in any of these relatives (step one of stepwise screening), a full cardiovascular evaluation should follow. For any additional relatives discovered to have FDC, progressive stepwise screening (step 2) should be advised for their first-degree relatives. Thus, it is possible that progressive stepwise

screening will identify affected individuals throughout an extended family. A more detailed example of stepwise screening is also given in the For Families section. This clinical recommendation may also identify large kindreds for research. (See **Referring Patients for Research Purposes**).

The diagnostic criteria used to diagnose additional members of a kindred as "affected" may be less rigorous than the criteria used for the formal diagnosis of IDC. This depends on the clinical presentation, signs, symptoms, ECG and echocardiographic findings for the family. For example, specific clinical findings on echocardiography (e.g., mitral valve prolapse, or on ECG or Holter monitor with heart block or atrial fibrillation) may be a distinctive marker of disease in the pedigree which may permit a diagnosis of "affected" status to be made in a close relative family without meeting the formal diagnostic criteria for IDC (reduced systolic function and cardiac enlargement). In some larger families the most appropriate method to assign affected status in relatives may be to use left ventricular end-diastolic dimension, with or without some measure of fractional shortening (e.g., see Hershberger RE, Ni H, Crispell KA. Familial dilated cardiomyopathy: new echocardiographic diagnostic criteria for classification of family members as affected. **J Cardiac Failure 1999;5:203-212, PMID:10496193**). Other diagnostic criteria have also been proposed (Mestroni L, Maisch B, McKenna W, et al. Guidelines for the study of familial dilated cardiomyopathies. **Eur Heart J 1999;20:93-102. PMID:10099905**).

Routine screening beyond first-degree relatives of affected individuals is probably not indicated for clinical purposes, based on our experience. However, affected individuals in some extended families could easily be missed, and thus we suggest the following: (1) comprehensive medical evaluations of any family members with unexplained cardiovascular symptoms should always be undertaken, and (2) screening of some second and/or third degree relatives for FDC may be appropriate in some families with particularly troublesome, aggressive or life-threatening disease in the setting of variable age of onset.

5. Treatment intervention. We recommend the use of ACE inhibitors and/or beta blockers in family members determined to be affected with FDC. This is based on the knowledge that ACE inhibitors improved survival in patients with left ventricular enlargement (LVE) and symptomatic heart failure and demonstrated less progression to symptomatic heart failure in subjects with asymptomatic LVE (SOLVD prevention trial). The SOLVD and other trials with ACE inhibitors were performed in patients with both ischemic and idiopathic dilated cardiomyopathies, but the responses to therapy were similar with both etiologies, and from one-third to one-half of these patients (assigned as IDC) had FDC. Thus, these studies support the use of conventional medical treatment with ACE inhibitors for FDC to improve survival and prevent progression of disease. For FDC this may be particularly relevant for screening of family members with asymptomatic LVE. The use of beta-blockers in combination with ACE inhibitors may also be appropriate in these settings.

6. FDC Counseling. According to the HFSA guidelines, genetic and family counseling is recommended for all patients with DCM and their family members. Genetic counseling involves obtaining a family history. The educational component of genetic counseling involves informing the patient and family regarding the disease transmission and family risks. Family members with FDC should be counseled that the clinical course of FDC is unpredictable, and ranges from one that is relatively benign with conventional treatment to one of progressive heart failure, and advanced disease resulting in heart transplantation or sudden cardiac death. Affected family members should also be informed that they have a heritable disease with a genetic risk to their offspring (up to a 50% probability with Mendelian autosomal dominant inheritance). Finally, those who are genetically at risk but have no evidence of LVE should be counseled about the age-dependent penetrance, the possibility of future disease presentation, and clinical recommendations including future surveillance screening or screening at any time with symptoms of cardiac dysfunction. Our reviews "***Clinical and Genetic Issues in Familial Dilated Cardiomyopathy***" and "***Progress With Genetic Cardiomyopathies: Screening, Counseling, and Testing in Dilated, Hypertrophic, and Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy***" also have sections that review a variety of genetic counseling issues.

7. Ongoing Periodic Surveillance Clinical Screening. According to the HFSA guidelines, surveillance screening (history, exam, ECG, echo) is indicated at the following intervals or at any time that symptoms occur:

Interval if genetic testing is negative and/or if clinical family screening is negative	Screening interval if a mutation is present
Every 3-5 years beginning in childhood	Yearly in childhood; every 1-3 years

8. Clinical Genetic Testing. According to the HFSA guidelines, clinical genetic testing should be considered for patients with DCM. Any patient with IDC and/or FDC may benefit from clinical genetic testing. One quarter to one half of patients with idiopathic dilated cardiomyopathy (IDC) will likely have familial dilated cardiomyopathy (FDC), which is defined as two or more close relatives with IDC. Patients with IDC (apparently sporadic disease) and/or FDC may benefit from clinical genetic testing. Data from our recent publications "***Lamin A/C mutation analysis in a cohort of 324 unrelated patients with idiopathic or familial dilated cardiomyopathy***" and "***Coding sequence mutations identified in MYH7, TNNT2, SCN5A, CSRP3, LBD3, and TCAP from 313 patients with familial or idiopathic dilated cardiomyopathy***" (*Clin Trans Sci* 2008; 1:21-26(6)) support this recommendation.

The first family member to be tested should be the family member with the clearest diagnosis of IDC. This patient is usually the index patient, but in some families the index patient is deceased and no DNA is available. Considering clinical genetic testing in a patient with a questionable IDC diagnosis or those with little or no evidence of cardiovascular disease will decrease the sensitivity of clinical genetic testing and may confuse the issue.

A positive genetic test result may aid in a more accurate diagnosis, thus impacting management decisions, surveillance, and therapy. A positive genetic test result may also be important in the management of your patient's family. First degree relatives of an individual with an autosomal dominant FDC gene mutation each have a 50% chance of carrying the same gene mutation, therefore at-risk relatives may wish to undergo genetic testing to determine if screening and surveillance for clinical disease are indicated. Because of incomplete penetrance and variable expressivity, the symptoms, age of onset, disease features and severity can be very different among members of the same family. Some gene mutation carriers in a family may have severe disease, while others may have only minor heart muscle and/or rhythm problems. Still others may have no cardiac symptoms or signs of heart problems. "Unaffected" gene carriers of an autosomal dominant FDC gene mutation (those who have the mutation but have no evidence of clinical disease) still have a 50% chance of passing the mutation on to each of their offspring, who again could fall anywhere in the clinical spectrum.

A negative test result in the index patient only rules out genetic disease caused by the gene(s) tested. In this case, genetic testing of asymptomatic family members for that gene(s) is not useful. As more genes become available for clinical genetic testing for IDC/FDC, the sensitivity of the test will increase but may never reach 100%.

We know that testing for lamin A/C cardiomyopathy is almost always indicated for IDC or FDC that presents with prominent conduction system disease. We don't yet know how frequently lamin A/C cardiomyopathy underlies IDC/FDC with minimal or no conduction system disease, so testing any patient with IDC or FDC is reasonable until we have much better data to sort out this latter point.

A Comprehensive Review of FDC Research

This section provides a comprehensive review of clinical and genetic research on FDC with references. This section has been extensively updated and reorganized (2009) to make it easier to add new material.

A. Clinical Familial Dilated Cardiomyopathy (FDC) Reports:

Introduction – Early Clinical Reports. A genetic basis for idiopathic dilated cardiomyopathy (IDC) in 1-2% of subjects with the diagnosis had been postulated since scattered reports of families with IDC first appeared in the literature over the past 3-4 decades. Hereditary dilated cardiomyopathy had been reported most commonly with autosomal dominant inheritance, but reports of autosomal recessive and sex-linked inheritance had been reported, as well as mitochondrial mutations.

Key clinical studies published in the 1990s provided clear evidence that FDC was much more common than previously thought, accounting for 20-50% of cases of idiopathic dilated cardiomyopathy, and that a genetic basis was likely. These reports can be reviewed by following the links below:

Earlier Clinical Reviews.

The Michels study, 1992.

The McKenna and co-workers report, London, 1998.

The Heidelberg report, 1998.

The Mestroni report, 1999.

Additional clinical reports have been reviewed in a recent publication from our group (Burkett E, Hershberger RE. State of the Art: Clinical and genetic issues in familial dilated cardiomyopathy. **J Am Coll Cardiol** 2005;45:969-81, PMID:15808750). If you are unable to obtain the pdf of this publication, please **contact us**.

B. A Review of FDC Genetic Reports: Approximately 30 genes have been implicated in FDC since the first report in 1998. Autosomal dominant, X-linked, autosomal recessive and mitochondrial mutations have been reported. Reports have been summarized in the **GeneTable** by general phenotype, either dilated cardiomyopathy or conduction system disease with DCM. Links active from the **GeneTable** will take the reader to the gene discovery publication reference. For the genes that are relatively more common in DCM, a list of the most relevant publications is provided. For those more interested in genetic locations of known disease genes and reported loci, a **LocusTable** has been provided.

GeneTable

Gene	Protein	Function	OMIM	Links to Information/References
AUTOSOMAL DOMINANT FDC				
Dilated cardiomyopathy phenotype:				

<i>ACTC</i>	cardiac actin	sarcomeric protein; muscle contraction	*102540	→
<i>DES</i>	desmin	dystrophin- associated glycoprotein complex; transduces contractile forces	*125660	→
<i>SGCD</i>	delta-sarcoglycan	dystrophin- associated glycoprotein complex; transduces contractile forces	*601411	→
<i>MYH7</i>	beta-myosin heavy chain	sarcomeric protein; muscle contraction	*160760	→
<i>TNNT2</i>	cardiac troponin T	sarcomeric protein; muscle contraction	*191045	→
<i>TPM1</i>	alpha- tropomyosin	sarcomeric protein; muscle contraction	*191010	→
<i>TTN</i>	titin	sarcomere structure/extensible scaffold for other proteins	*188840	→
<i>VCL</i>	metavinculin	sarcomere structure; intercalated discs	*193065	→
<i>MYBPC3</i>	myosin-binding protein C	sarcomeric protein; muscle contraction	*600958	→
<i>MLP/CSRP3</i>	muscle LIM protein	sarcomere stretch sensor/ Z discs	*600824	→
<i>ACTN2</i>	alpha-actinin-2	sarcomere structure; anchor for myofibrillar actin	*102573	→
<i>PLN</i>	phospholamban	sarcoplasmic reticulum Ca ⁺⁺ regulator; inhibits SERCA2 pump	*172405	→
<i>ZASP/LDB3</i>	Cypher/LIM binding domain 3	cytoskeletal assembly; involved in targeting and clustering of	*605906	→

		membrane proteins		
<i>MYH6</i>	alpha-myosin heavy chain	sarcomeric protein; muscle contraction	*160710	
<i>ABCC</i>	SUR2A	regulatory subunit of Kir6.2, an inwardly rectifying cardiac KATP channel	*601439	->
<i>TNNC1</i>	cardiac troponin C	sarcomeric protein; muscle contraction	*191040	->
<i>titin-cap TCAP</i>	titin-cap or telethonin	Z-disc protein that associates with titin; aids sarcomere assembly	*604488	->
<i>EYA4</i>	eyes-absent 4	transcriptional coactivators (of Six and Dach) via phosphatase activity	*603550	->
<i>PDLIM3</i>	PDZ and LIM domain protein 3	Cytoskeletal protein	*605889	->
<i>TMPO/LAP2</i>	thymopoietin	lamina-associated nuclear protein	*188380	->
<i>PSEN1</i>	presenilin 1	Transmembrane protein, gamma secretase activity	*104311	->
<i>PSEN2</i>	presenilin 2	Transmembrane protein, gamma secretase activity	*600759	->
<i>CRYAB</i>	alpha B crystallin	Cytoskeletal protein	*123590	->
<i>MYPN</i>	myopalladin	Sarcomeric protein, z-disc	*608517	->
<i>LAMA4</i>	laminin a-4	Extracellular matrix protein	*600133	->
<i>ILK</i>	integrin-linked kinase	Intracellular serine-threonine kinase; interacts with integrins	*602366	->
<i>ANKRD1/CARP</i>	cardiac ankyrin	titin-associated	*609599	->

	repeat protein	sarcomere stretch sensor at I band; transcriptional repressor		
<i>RBM20</i>	RNA binding protein 20	RNA spliceosome protein; pre-RNA splicing	NA	->
Conduction system disease with dilated cardiomyopathy phenotype:				
<i>LMNA</i>	lamin A/C	inner leaflet, nuclear membrane protein; confers stability to nuclear membrane; gene expression	*150330	->
<i>SCN5A</i>	sodium channel	controls sodium ion flux	*600163	->
X-LINKED FDC			*300377	
<i>DMD</i>	dystrophin	primary component of dystrophin-associated glycoprotein complex; transduces contractile force	*300377	->
<i>TAZ/G4.5</i>	tafazzin	unknown	*300394	->
RECESSIVE FDC				
<i>TNNI3</i>	cardiac troponin I	sarcomeric protein, muscle contraction	*191044	->

LocusTable

Locus	OMIM	Gene	Protein	Links to Information/References
AUTOSOMAL FDC GENES				

1q21.2-.3	*150330	<i>LMNA</i>	lamin A/C	→
1q31-q42	*600759	<i>PSEN2</i>	presenilin 2	→
1q32	*191045	<i>TNNT2</i>	cardiac troponin T	→
1q42-q43	*102573	<i>ACTN2</i>	alpha-actinin-2	→
2q14-22	*604288	?	?	Jung
2q31	*188840	<i>TTN</i>	titin	→
2q35	*125660	<i>DES</i>	desmin	→
3p21.3-p14.3	*191040	<i>TNNC1</i>	cardiac troponin C	→
4q35	*605889	<i>PDLIM3</i>	PDZ LIM domain protein 3	→
5q33-34	*601411	<i>SGCD</i>	delta-sarcoglycan	→
6q21	*600133	<i>LAMA4</i>	laminin a-4	→
6q22.1	*172405	<i>PLN</i>	phospholamban	→
6q22-23	*602067	?	?	Messina
6q23	*603550	<i>EYA4</i>	eyes-absent 4	→
9q13-22	*600884	?	?	Krajinovic
10	*609599	<i>ANKRD1</i>	cardiac ankyrin repeat protein	→
10q21-23	*601493	?	?	Bowles
10q22.1-23	*193065	<i>VCL</i>	metavinculin	→
10q22.2-23.3	*605906	<i>ZASP/LDB3</i>	Cypher/LIM binding domain 3	→
10q25.2 NA		<i>RBM20</i>	RNA binding protein 20	→
11p11.2	*600958	<i>MYBPC3</i>	myosin-binding protein C	→
11p15.1	*600824	<i>MLP/CSRP3</i>	muscle LIM protein	→
11p15.5-p15.4	*602366	<i>ILK</i>	integrin-linked kinase	→
11q22.3-q23.1	*123590	<i>CRYAB</i>	alpha B crystallin	→
12p12.1	*601439	<i>ABCC</i>	SUR2A	→
12q22	*188380	<i>TMPO</i>	thymopoietin	→
14q12	*160710	<i>MYH6</i>	alpha-myosin heavy chain	
14q12	*160760	<i>MYH7</i>	beta-myosin heavy chain	→
14q24.3	*104311	<i>PSEN1</i>	presenilin 1	→
15q14	*102540	<i>ACTC</i>	cardiac actin	→

15q22.1	*191010	<i>TPM1</i>	alpha-tropomyosin	->
17q12	*604488	<i>titin-cap</i> <i>TCAP</i>	titin-cap or telethonin	->
19q13.4	*191044	<i>TNNI3</i>	cardiac troponin I	->
X-LINKED FDC GENES				
Xp21.2	*300377	<i>DMD</i>	dystrophin	->
Xq28	*300394	<i>TAZ/G4.5</i>	tafazzin	->

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