Familial Dilated Cardiomyopathy Genotypes Update: An Important Cause of Nonischemic Heart Failure

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INTRODUCTION

Dilated cardiomyopathy (DCM), a disorder characterized by cardiac dilation and reduced systolic function, represents an outcome of a heterogeneous group of idiopathic, inherited and acquired disorders. DCM is a condition in which the heart becomes weakened and enlarged, and cannot pump blood efficiently. The decreased heart function can affect the lungs, liver, and other body systems. It's an entity of poorly defined etiology (possibly idiopathic or primary), which surely comprises a heterogeneous, multifactorial group, with a significant immunological component, viral or genetic-familial, isolated or associated, which is characterized by left, right or global chamber dilatation (cardiomegaly) with alteration of contractile function of the left ventricle (LV), right ventricle (RV) or both. This is translated by systolic dysfunction syndrome, significant decrease of ejection fraction (EF), significant increase of LV end of diastole or both, secondary non-significant ostial mitral or mitro-tricuspid insufficiency, and significant alterations in electrical and autonomous behavior, with a high index of potentially fatal arrhythmic events and frequently accompanied by reactive myocardial hypertrophy. To reach this diagnosis the following should be ruled out: ischemic heart disease, high blood pressure, valvular heart disease, and pulmonary hypertension.

PREVALENCE

Prevalence of DCM usually refers to the estimated population of people who have DCM that is being managed at any given time.

About one in three cases of congestive heart failure (CHF) is due to DCM.

DCM is the most common form of cardiomyopathy and occurs in an estimated 2 out of 100 people. Idiopathic DCM occurs with a prevalence of about 36.5 per 100,000; it accounts for more than 10,000 deaths in the U.S. annually and is the primary indication for cardiac transplantation. Among

cases of idiopathic DCM, familial occurrence accounts for 20 to 25%, with the exception of rare cases resulting from mutations in dystrophin.

Its estimated prevalence is 1:2500 persons have DMC[1].

INCIDENCE

The term 'incidence' of DCM refers to the annual diagnosis rate, or the number of new cases of DCM diagnosed each year.

The first national (United Kingdom and Ireland) prospective national, multicenter study of new-onset HF in children with heart muscle disease showed an incidence of 0.87/100,000. In this study, data were collected on children admitted to a hospital through 2003 with a first episode of HF in the absence of congenital heart disease. Multivariable analysis of survival data indicates a better outcome for younger children and for those with better systolic function at presentation, but overall, 33% of children die or requires transplantation within 1 year of presentation[2].

From a total of 1426 children from the United States and Canada diagnosed as having DCM, younger than 18 years old, the annual incidence of DCM was 0.57 cases per 100,000 per year overall. The annual incidence was higher in boys than in girls (0.66 vs. 0.47 cases per 100,000; P<.001), in blacks than in whites (0.98 vs. 0.46 cases per 100,000; P<.001), and in infants (<1 year) than in children (4.40 vs. 0.34 cases per 100,000; P<.001). The majority of children (66%) had idiopathic disease. The most common known causes were myocarditis (46%) and neuromuscular disease (26%). The 1- and 5-year rates of death or transplantation were 31% and 46%, respectively. Independent risk factors at DCM diagnosis for subsequent death or transplantation were older age, CHF, lower LV fractional shortening Z score, and cause of DCM (P<.001 for all).

In children, DCM is a diverse disorder with outcomes that depend largely on cause, age, and HF status at presentation. Race, sex, and age affect the incidence of disease. Most children do not have a known cause of DCM, which limits the potential for disease-specific therapies[3].

GENDER

Men are more commonly afflicted with DCM, but women with DCM tend to present with a more advanced disease[4]. In the EuroHeart Failure Survey II trial that evaluates the gender differences in patients hospitalized for acute HF, women more frequently had new-onset acute HF, hypertension

and valvular disease; and less frequently coronary heart disease or DCM compared with men. Smoking, chronic obstructive pulmonary disease, peripheral arterial disease and renal failure were less common, but diabetes and anemia significantly were more frequent in women. Atrial fibrillation (AF) and preserved LV function were more common in women. Men were more often non-compliant with medication. After adjustment for indications and age, there were no significant gender differences in prescription of HF medication. All-cause readmission rate during the one-year follow-up was lower in women[5].

In children younger than 18 years the annual incidence was higher in boys than in girls (0.66 vs. 0.47 cases per 100,000; P<.001).

AGE

It can affect anyone at any age, although it is most common in adult men. DCM may manifest clinically at a wide range of ages is most common between the ages of 20 and 60 years but also in young children. Survival in children with DCM is variable; 30% of infants die within 2 years of diagnosis, but 5-year survival for childhood DCM is 60% to 84%[4].

The first national prospective study of new-onset HF in children has shown an incidence of 0.87/100,000. Multivariable analyses of survival data indicates a better outcome for younger children and for those with better systolic function at presentation, but overall, 30% of children die or require transplantation within 1 year of presentation[2].

ETHNIC GROUP

The disease is more common in African-Americans than in whites[6].

For many affected individuals, DCM is a condition which will not limit the quality or duration of life. A minority, however, experience significant symptoms and there is sometimes a risk of SCD. Evaluation by a cardiologist is recommended to confirm the diagnosis and to assess the outlook and particularly the risk of complications. In some patients symptoms of left- and right-sided CHF develop gradually. LV dilatation may be present for months or even years before the patient becomes symptomatic.

Vague chest pain may be present, but typical angina pectoris is unusual and suggests the presence of concomitant ischemic heart disease. Systemic embolism may occur.

Syncope is due to arrhythmias: Syncope occurring in patients with DCM has several causes: ventricular tachycardia (VT), a major severe cause of this diagnosis, occurring however only in ≈

30% of cases. The other causes are supraventricular tachycardia, bradycardia and vagal hyperactivity[7].

Family members, especially first degree relatives, might benefit from screening for DCM. Among affected relatives, symptoms can be quite variable.

Familial dilated cardiomyopathy (**FDC)** demonstrates incomplete penetrance, variable expression, and significant locus and allelic heterogeneity, making diagnosis complex. Echocardiographic and electrocardiographic screening of first-degree relatives of individuals with IDC and FDC is indicated, as detection and treatment are possible prior to the onset of advanced, symptomatic disease. Genetic counseling for IDC and FDC may also be appropriate. It is anticipated that a great deal of additional genetic information yet to be discovered will add greatly to our understanding of the genetics of DCM[8]. Relatives of DCM patients have been found to show preclinical, asymptomatic heart-muscle changes[9].

POSSIBLES ETIOLOGIES

DCM may be mainly idiopathic, familial/genetic (in up to 50% of cases, familial aggregation is observed[10]) viral, and/or autoimmune. In a significant percentage of patients, myocarditis and DCM are different stages of an organ-specific autoimmune disease that represents the final common pathogenesis pathways of infectious and noninfectious myocardial injuries in genetically predisposed individuals.

In table 1 we show the main causes of DCM.

Table 1

DILATED CARDIOMYOPATHIES: ETIOLOGICAL CLASSIFICATION

1) Idiopathic
2) Familial/Hereditary/Genetic (FDCM)
   - (2A) Autosomal dominant: > 95% of cases
   - (2B) Autosomal recessive
   - (2C) X-Linked FDCM, (XLDC) or XLDCM
   - (2D) Mitochondrial (MT) DNA/RNA MUTATIONS
3) Infectious: Late sequel of viral myocarditis
4) Autoimmune response to viral infection
5) Other secondary forms: Drugs**:** heavy metals, emetine, anthracyclines (daunorubicin and doxorubicin), cocaine, methamphetamine, cobalt etc.

1) IDIOPATHICS FORMS: In the cases where the cause of DCM is unknown, the condition is called idiopathic, cryptogenetic, primary, or essential. Idiopathic because their cause remains unknown. To this date in at least 30% of patients, DCM remains idiopathic. Studies have demonstrated that genetic factors are likely to play a major role in the pathogenesis of idiopathic IDC. In clinical surveys, a familial trait has been demonstrated in 20 to 30% of idiopathic DCM patients (familial DCM or FDCM).

2) FAMILIAL/GENETIC FORMS OF FAMILIAL DILATED CARDIOMYOPATHIES (FDCM): FDCM are caused by rare mutations showing Mendelian inheritance conferred by genes encoding the structural proteins of the myocardium. Epidemiologically, these rare familial forms play a minor role in the overall population and are characterized mainly by an autosomal dominant pattern of inheritance with age-related penetrance, rarely recessive or X-linked. It presents with development of ventricular dilatation and systolic dysfunction usually in the second or third decade of life. Genetic studies have mapped multiple loci for DCM, which is a major cause of nonischemic heart failure (HF); however, the genes responsible for the majority of cases have yet to be identified. About 50% of patients have FDCM of the disease, with mutations of genes encoding cytoskeletal, contractile, or other proteins present in myocardial cells[11]. Among the most frequently encountered mutations in DCM are those in the lamin A/C (LMNA) gene. LMNA screening should be considered in

patients with DCM or familial lone conduction disease[12]. Genotype-phenotype relationships revealed a high rate of sudden death (SD) and cardiac transplants in carriers of the p.N195K mutation. The p.R225X mutation leads to cardiac conduction disease with late or no development of DCM, underscoring the importance of this mutation in putative familial "lone conduction disease." Nearly 30% of LMNA mutation carriers had experienced a thromboembolic event because of clinical variability, including the development of associated symptoms in time.

Possible transmission patterns on Familial Dilated Cardiomyopathy (FDCM) forms:

AUTOSOMAL DOMINANT

The disease is genetically heterogeneous, but the autosomal dominant form is considered to be the most frequent form of inherited idiopathic DCM. Several of the mutant genes linked to autosomal dominant DCM encode the same contractile sarcomeric proteins that are responsible for hypertrophic cardiomyopathy, including α-cardiac actin; α-tropomyosin; cardiac troponin T, I, and C; and β- and α-myosin heavy chain. Research to determine further disease loci is ongoing.

AUTOSOMAL RECESSIVE

This pattern of inherence is found, for example, in the TNNI3 gene (Cardiac troponin I **CMD2A**). TNNI3 is the first recessive gene identified for DCM. It is on chromosome 19q13.4. The OMIM number is 611880[13].

X-LINKED FDCM, (XLDC) OR XLDCM

In families with X-linked DCM, the disease gene has been identified as the dystrophin gene. The 5' end of the gene appears to be the critical region for the development of DCM without clinical evidence of muscle dystrophy. X-LINKED FDCM is a clinical phenotype of dystrophinopathy characterized by preferential myocardial involvement without any overt signs of skeletal myopathy. It is a familial myocardial disease that presents with severe CHF in young males with symptoms occurring between ages 15 and 21 years old. Progressive CHF develop gradually over a period of ≈10 years. A significant portion of XLDC-patients carry mutations in the dystrophin gene. Alström syndrome, X-linked, is also found[14].

MITOCHONDRIAL (MT) DNA/RNA MUTATIONS

Mitochondrial inheritance of the disease is also found[14]. Mahjoub et al[15], *identified a novel heteroplasmic mitochondrial DNA (mtDNA) (m.4322dupC) mutation in the tRNA gene associated*

with isolated DCM as maternal trait. Recently, Van Hove et al[16] identified a 6-week-old child that presented with hypotonia, myopathy, and a rapidly worsening DCM with severe atrial and ventricular arrhythmias and pulmonary hypertension, which proved fatal at age 3 months. Biochemical analysis showed a combined deficiency of the enzymatic activities of complexes I and IV and T14709C mutation in the mitochondrial tRNA glutamic acid gene.

Inherited DCM is a genetically and phenotypically very heterogeneous disease. DCM is caused by mutations in multiple genes encoding proteins that are involved in force generation, force transmission, energy production and several signaling pathways. Additionally, the mutation could occur in mitochondrial DNA and mitochondrial tRNA.

The main FDCM are:

1) CMD1A CARDIOMYOPATHY, DILATED, 1A

It is the most common form of autosomal dominant CMT1, however CMD1A, is listed as a "rare disease" by the Office of Rare Diseases of the National Institutes of Health. This means that CMD1A, or a subtype of CMD1A, affects less than 200,000 people in the US population. Mutation is located on chromosome 1p1-1q1. The entity has autosomal-dominant inheritance. Clinically is manifested by DCM and conduction system defect. It is a progressive disorder that both perturbs atrioventricular conduction and depresses cardiac contractility.

SCD is an important late outcome in heritable (chromosome 1p1-1q1) cardiac conduction and myocardial disease. Pacemaker therapy is important for the treatment of symptomatic bradycardia, but it does not prevent SCD. Family members who are beyond the third decade of life with reduced functional capacity, LV dysfunction, pacemakers and who are the offspring of a parent with SCD appear to be at greatest risk[17]. The authors speculate that gap junction protein connexin 40 is a candidate for mutations that result in conduction system disease and DCM[18].

The OMIM locus designated is #115200. A number sign (#) is used with this entry because this form of dilated cardiomyopathy can be caused by mutation in the lamin A/C gene LMNALAMIN, CLMNC. The mutation is observed in the lamin A/C gene (LMNA; 150330) on chromosome 1q11-21. The protein is Lamin A/C150330. Allelic disorders include the autosomal dominant forms of Emery-Dreifuss muscular dystrophy (181350), and Hutchinson-Gilford progeria syndrome (176670), among others[19].

2) CMD1B CARDIOMYOPATHY, DILATED, 1B

The mutation is observed in the CARDIOMYOPATHY, DILATED, 1B; CMD1B on chromosome 9q13-22 with autosomal dominant inheritance[20].

The OMIM locus designated is 600884.

3) CMD1C CARDIOMYOPATHY, DILATED, 1 CARDIOMYOPATHY, DILATED, WITH LEFT VENTRICULAR NONCOMPACTION, INCLUDED

The mutation is ZASP/LBD3 in the LDB3 gene on chromosome 10q22-q23.3. The transmission has autosomal dominant inheritance. The protein is in cypher/LIM binding domain 3. Its function is cytoskeletal assembly; involved in targeting and clustering of membrane proteins.

The OMIM locus designated is #601493 with or without LV noncompaction (605906) of the LV myocardium[21]

4) CMD1D; CARDIOMYOPATHY, DILATED, 1D

The gene map locus is TNNT2 TROPONIN T2, CARDIAC cTnT2. The mutation is observed on chromosome 1q32. It is a sarcomeric protein of muscle contraction essential for calcium-regulated myofibrillar ATPase activity. The protein is named cardiac troponin T[22].

The OMIM loci designated are 191045 and 601494

Additionally, Fernandez et al[23] described in a South African Caucasian family of Northern European descent, an autosomal dominant cardiac disorder characterized by progressive familial heart block type II (PFHBII) and DCM, (OMIM 140400).

5) CMD1E; CARDIOMYOPATHY, DILATED, 1E

The mutation is observed in the SCN5A gene on chromosome 3p21 and 3p22-p25. This gene has been implicated in congenital Long QT syndrome type 3 (LQT3), Brugada syndrome, idiopathic ventricular fibrillation, sick sinus syndrome, conduction system disease, and DCM with atrial arrhythmias[24-25].

The OMIM loci designated are #601154 and 600163.

6) CMD1F, CARDIOMYOPATHY, DILATED, 1F

The mutation is observed in the long arm of chromosome 6q22-23 with autosomal dominant transmission. Clinically is characterized by DCM, cardiac conduction-system disease, and adult-onset limb-girdle muscular dystrophy (FDCM, conduction disease, and myopathy [FDCM-DCM)[26].
The OMIM locus designated is 602067.

7) CMD1G CARDIOMYOPATHY, DILATED, 1G

The mutation is observed in the TTN gene (188840) on chromosome 2q31.
The protein is a giant titin. This protein has a role in the elastic properties of active muscles.
Clinically, it is characterized by DCM with early-onset and CHF during the third decade of life[27].
The OMIM loci designated are 188840 and # 604145.

8) CMD1H CARDIOMYOPATHY, DILATED, 1H

The mutation is observed in the CARDIOMYOPATHY, DILATED, 1H; CMD1H on chromosome 2q14-q22 with autosomal dominant transmition[28].
The OMIM locus designated is 604288.

9) CMD1I CARDIOMYOPATHY, DILATED, 1I

The mutation is observed in the DES gene on chromosome 2q35.
The protein affected is desmin. It is a type III intermediate filament found near the Z line in sarcomeres. Desmin is a protein that polymerizes to form the intermediate filaments of muscle cells and used as a marker of these cells. The entities that affect desmin are named desminopathies. Transmission is autosomal dominant. Mutations in desmin can cause DCM[29] or restrictive cardiomyopathy with atrioventricular conduction block[30].
The OMIM loci designated are 125660 and 604765.

10) CMD1J CARDIOMYOPATHY, DILATED, 1J

The mutation is observed in the EYA4 gene, Eyes-absent 4 eyes absent (EYA) gene, in chromosome 6q23-q24. The protein is a key regulator of ocular development in Drosophila and transcriptional coactivators (of Six and Dach) via phosphatase activity. The DCM is associated with sensorineural hearing loss[31].
The OMIM loci designated are 125660, 605362 and 603550.

11) CMD1K, DILATED CARDIOMYOPATHY, 1K

The mutation is observed in the CMD1K gene on chromosome 6q12-q16. The entity has autosomal-dominant inheritance[32].

The OMIM locus designated is 605582.

12) CMD1L CARDIOMYOPATHY, DILATED, 1L

The mutation is observed in the SGCD gene on chromosome 5q33-34. The protein affected is delta-sarcoglycan or Sarcoglycan, delta (35kDa dystrophin-associated glycoprotein), also known as SGCD, is a human gene dystrophin-associated glycoprotein complex. The protein encoded by this gene is one of the four known components of the sarcoglycan complex, which is a subcomplex of the dystrophin-glycoprotein complex (DGC). DGC forms a link between the F-actin cytoskeleton and the extracellular matrix. This protein is expressed most abundantly in the skeletal and cardiac muscles. Clinically, it can cause Hypertrophic cardiomyopathy and DCM[33].

The OMIM loci designated are 601411 and 606685.

13) CMD1M CARDIOMYOPATHY, DILATED, 1M

The mutation is observed in the MLP/CSRP3 gene on chromosome11p15.1. The protein affected is the muscle LIM protein a sarcomere stretch sensor/Z discs. Its mutation causes DCM. LIM protein interacts with and colocalizes with telethonin (T-cap), a titin interacting protein. The mutation causes DCM that results in a marked defect in T-cap interaction/localization[34].

The OMIM loci designated are 607482 and 600824.

14) CMD1N CARDIOMYOPATHY, DILATED, 1N

The mutation is observed in the Titin-cap TCAP gene on chromosome 17q12. The protein is the Titin-cap or telethonin. It is a Z-disc protein that associates with titin; aids sarcomere assembly[35].

The OMIM loci designated are 607487 and 604488.

15) CMD1O CARDIOMYOPATHY, DILATED, 1O

The mutation is observed in the ABCC9 gene on chromosome12p12.1. Mutation is observed in ABCC9, which encodes the regulatory SUR2A subunit of the cardiac K(ATP) channel. It is a regulatory subunit of Kir6.2, an inwardly rectifying cardiac KATP channel. Missense and frameshift mutations were mapped to evolutionarily conserved domains adjacent to the catalytic ATPase pocket within SUR2A. Mutant SUR2A proteins showed aberrant redistribution of conformations in

the intrinsic ATP hydrolytic cycle, translating into abnormal K(ATP) channel phenotypes with compromised metabolic signal decoding. Defective catalysis-mediated pore regulation is thus a mechanism for channel dysfunction and susceptibility to DCM[36].
The OMIM loci designated are 608569 and 601439.

16) CMD1P CARDIOMYOPATHY, DILATED, 1P

The mutation is observed in the PLN gene on chromosome 6q22.1. The protein affected is Phospholamban, a transmembrane phosphoprotein that inhibits the cardiac sarcoplasmic reticular Ca2+-adenosine triphosphatase (SERCA2a) pump. Clinically it manifests by DCM with refractory CHF[37].
The OMIM loci designated are 609909 and 172405.

17) CMD1Q CARDIOMYOPATHY, DILATED, 1Q

The mutation is observed in chromosome 7q22.3-q31. Transmission is autosomal-dominant with age-related penetrance[38].
The OMIM locus designated is 609915.

18) CMD1R CARDIOMYOPATHY, DILATED, 1R

The mutation is observed in the cardiac actin gene (ACTC) or ACTIN, ALPHA, CARDIAC MUSCLE; ACTC1 on chromosome15q14. The protein affected is a sarcomeric protein important in muscle contraction. Defective transmission of force in cardiac myocytes is a mechanism underlying HF[39].
The OMIM locus designated is +102540.

19) CMD1S CARDIOMYOPATHY, DILATED, 1S

The mutation is observed in the MYH7 gene on chromosome 14q12. The protein affected is the beta-myosin heavy chain. It's a sarcomeric protein muscle contraction. It's clinically associated with a typical DCM phenotype[40].
The OMIM locus designated is 160760.

20) CMD1T CARDIOMYOPATHY, DILATED, 1T

The mutation is observed in the Thymopoietin or TMPO gene (it's an alternative gene symbol, LAP2) on chromosome 12q22.
The protein affected is the LAP2alpha protein that interacts with lamin A/C[41].
The OMIM locus designated is +18838.

21) CMD1U CARDIOMYOPATHY, DILATED, 1U

The mutation is observed in the Presenilin 1 or PSEN1 gene on chromosome 14q24.3. The protein affected is the Presenilin. It is one of four proteins (including nicastrin, Aph-1, and Pen-2) that comprise the active gamma-secretase complex. Presenilin is believed to be the actual enzymatic component. It is capable of cleaving numerous single-transmembrane proteins within the membrane domain after initiating a cleavage by different proteases within the extracellular domain close to the transmembrane region. Presenilins are cleaved by an unknown protease to yield N- and C-terminal fragments which co-assemble into an active heterodimer. Mutations in presenilin have been associated with early-onset forms of Alzheimer's disease. Presenilin 1 is a critical component of the g-secretase complex and plays an essential role in the production of the amyloid-beta peptide. This peptide has been strongly associated with the pathophysiology of the disease[42].

The OMIM locus designated is +104311.

22) CMD1V CARDIOMYOPATHY, DILATED, 1V

The missense mutations are observed in the Presenilin 2 or PSEN2 gene (Ser130Leu) on chromosome 1q31-q42. The proteins affected are the presenilins. They are expressed in the heart and are critical to cardiac development. Presenilin 2. The PSEN2 mutation showed partial penetrance, milder disease, and not a bad prognosis[42].

The OMIM locus designated is 600759.

23) CMD1W CARDIOMYOPATHY, DILATED, 1W

The mutation is observed in the VINCULIN VCL gene on chromosome 10q22-q23. The protein affected is Metavinculin. It's a sarcomere structure on intercalated discs[43].

The OMIM loci designated are 611407 and 193065.

24) CMD1X CARDIOMYOPATHY, DILATED, 1X

The mutation is observed in the FUKUTIN; FKTN or FCMD GENE on chromosome 9q31. The protein affected is alpha-dystroglycan. It's an indispensable molecule for intra-extra cell membrane linkage. FKTN mutations could cause much wider spectrum of clinical features than previously perceived, including familial DCM and mildest limb girdle muscular dystrophy[44].

The OMIM locus designated is 607440.

25) CMD1Y CARDIOMYOPATHY, DILATED, 1Y

The mutation is observed in the TROPOMYOSIN 1 or TPM1 gene on chromosome 15q22.1. The protein affected is alpha-tropomyosin. It is a sarcomeric protein of muscle contraction[45].
The OMIM loci designated are 611878 and 191010.

26) CMD1Z CARDIOMYOPATHY, DILATED, 1Z

The mutation is observed in the TROPONIN C, SLOW or TNNC1 gene in chromosome 3p21.3-p14.3. The protein affected is Cardiac troponin C. It is a sarcomeric protein with regulation of myocardial contractility[46].
The OMIM loci designated are 611879 and 191040.

27) MYOSIN-BINDING PROTEIN C, CARDIAC; MYBPC3

The missense mutation is observed in the (Asn948Thr) in the myosin-binding protein Cardiac MYBPC3 gene on chromosome 11p11.2. Cardiac myosin-binding protein C is arrayed transversely in sarcomere A-bands and binds myosin heavy chain in thick filaments and titin in elastic filaments. Phosphorylation of this protein appears to modulate contraction.
The protein affected is Myosin-binding protein C. It is a sarcomeric protein of muscle contraction[47].
The OMIM locus designated is 600958.

29) CMD2A

The missense mutation is observed in the TNNI3 gene. TNNI3 is the first recessive gene identified for DCM on chromosome 19q13.4. The protein affected is Cardiac troponin I (cTnI). It's a part of the troponin complex. It binds to actin in thin myofilaments to hold the troponin-tropomyosin complex in place[13].
The OMIM loci designated are 611880 and 191044.

30) APO-DYSTROPHIN 1

The mutation occurs in chromosome X21.2. Transmission: X-Linked FDC genes inheritance. It affects only males. The protein is dystrophin. The muscle dystrophin isoform is critical for myocardial function[48].
The OMIM locus designated is 300377.

31) TAFAZZIN; TAZ/G4.5 Barth syndrome (BTHS)

The mutation occurs in chromosome Xp28. Transmission: X-Linked FDC genes inheritance. Clinically characterized by the associated features of cardiac and skeletal myopathy, short stature, and neutropenia. HF occurs as a consequence of infantile DCM and hypertrophy[49].

The OMIM loci designated are 300394 and 302060.

32) Mitochondrial (mt)DNA mutations

The mtDNA encodes 13 polypeptides that are essential for oxidative phosphorylation, upon which the heart relies for energy. The mtDNA variant (T16189C) and A3243G mutation of the mitochondrial DNA[50], is clinically characterized by DCM associated with diabetes and deafness. Raised serum lactic acid, abnormal lactate/pyruvate ratio are observed[51].

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