Familial Dilated Cardiomyopathy – an Overview

Introduction

Idiopathic dilated cardiomyopathy (DCM), with a prevalence of at least 1 in 2500, is characterized by left ventricular dilatation and systolic dysfunction leading to progressive heart failure (1). DCM-related heart failure is one of the most common indications for heart transplantation, and DCM is also associated with cardiac arrhythmias that can lead to stroke or sudden cardiac death (2). Without treatment, DCM has a five year-mortality rate of up to 50%. Since lifestyle changes and/or pharmacological treatment with ACE inhibitors and/or β-blockers may delay DCM progression, early diagnosis is important (3). In cases of familial DCM, which accounts for roughly 30-60% of DCM, screening of at-risk relatives of known patients can facilitate early diagnosis and may help to identify affected individuals before overt symptoms develop. Importantly, at-risk family members must maintain regular cardiac screenings throughout their lives to ensure early detection of DCM, since DCM may develop at any age (4). Since familial DCM has been associated with mutations in any one of at least 24 genes (Table 1), genetic testing can facilitate the diagnosis of familial DCM, even in the absence of a known or conclusive family history. Once a familial mutation is known, genetic testing can also identify family members predisposed to or presymptomatically affected with DCM at any age and exclude an increased risk of DCM in family members not carrying the familial mutation, obviating the need for continual screening of non-mutation carriers (5). In addition, identification of the underlying genetic cause of DCM can alert patients and physicians to the risk of additional manifestations such as cardiac conduction disease that are associated with some forms of DCM (6).

Molecular Pathophysiology

Familial DCM is a genetically heterogeneous disease caused by mutations in any one of at least 24 genes, many of which encode components of the cardiac sarcomere or proteins that regulate sarcomeric functions (5). Autosomal dominant mutations in the genes LMNA, MYH7, TNNT2, and MYBPC3 are the four most common genetic causes of familial DCM (7-10). LMNA encodes lamins A and C, which assemble to form a highly conserved two dimensional matrix located in the nucleus, adjacent to the inner nuclear membrane. The nuclear lamins are involved in maintaining nuclear stability and chromatin structure, as well as regulating transcription, nuclear pore functions, and heterochromatin organization (reviewed in (11)). MYH7, TNNT2, MYBPC3, ACTC, TPM1, and TNNI3 encode components of the cardiac sarcomere – the contractile unit of the heart muscle. The sarcomere consists of thick and thin filaments, which are aligned and arranged in an overlapping fashion. Thick filaments are composed primarily of myosin, along with associated myosin binding proteins C, H, and X. Thin filaments are composed of cardiac actin, α-tropomyosin, and troponins C, I, and T. A giant protein, titin, provides a scaffold for the thick and thin filaments. When thick filaments slide along thin filaments, the muscle shortens. This contractile motion is driven by interaction of the myosin motor protein with actin and triggered by transient increases in intracellular Ca²⁺ concentration. Several other genes identified in association with familial DCM are also listed in Table 1.

Clinical Presentation

Onset of DCM is typically in the fourth or fifth decade of life, but can occur at any age (16). Affected individuals usually present with signs and symptoms of congestive heart failure, often of New York Heart Association (NYHA) class III or IV (3). Fatigue, chest pain, often during exercise, and/or palpitations are common. Thromboembolisms in the pulmonary or systemic circulation are the initial manifestation in up to 5% of patients and can lead to stroke. Initial presentation with syncope or SCD is also possible, although rare. LMNA-related DCM may present with cardiac conduction defects and/or musculoskeletal dis-
ease (8) and has been associated with a high penetrance and high risk of sudden cardiac death (12, 13).

### Diagnosis

Diagnosis of idiopathic DCM is most commonly based on the observation of unexplained left ventricular dilation and systolic dysfunction, both of which can be observed by echocardiography (37). Diagnosis of familial DCM requires exclusion of secondary DCM, which may be related to a number of different conditions such as congenital heart disease or hypertension (see Table 2 for more complete list), as well as independent diagnoses of DCM in two first or second degree relatives or occurrence of SCD under age 35 in a first or second degree relative of an affected individual (3). Once a diagnosis of familial DCM has been established, additional family members are diagnosed according to the criteria outlined in Table 2 (1). Since DCM symptoms can develop at any age, “unknown” and “unaffected” relatives are still at risk of developing the disease later in life and should be screened periodically for signs of DCM. Since published studies have established a causal relationship between certain variants in the genes listed in Table 1 and familial DCM, a diagnosis of familial DCM can be established or confirmed through genetic testing, even in the absence of a known or conclusive family history (18). Once the familial mutation is known, genetic testing can distinguish family members who harbor the mutation and should be monitored for manifestations of DCM from family members who do not harbor the mutation and do not require the same level of extensive monitoring.

### Table 1

<table>
<thead>
<tr>
<th>Gene (Protein)</th>
<th>% Familial DCM</th>
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<tbody>
<tr>
<td>LMNA (lamin A)</td>
<td>5-10 (6, 8, 14)</td>
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<tr>
<td>MYH7 (cardiac myosin heavy chain, beta)</td>
<td>5-10 (9, 15, 16)</td>
</tr>
<tr>
<td>TNNT2 (cardiac troponin T)</td>
<td>1-10 (9, 14-17)</td>
</tr>
<tr>
<td>MYBP3 (myosin binding protein C)</td>
<td>2-10 (14, 18)</td>
</tr>
<tr>
<td>ACTC (α-cardiac actin)</td>
<td>1.5 (19, 20)</td>
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<tr>
<td>TPM1 (α-tropomyosin)</td>
<td>&lt;1 (19)</td>
</tr>
<tr>
<td>TNNT3 (cardiac troponin I)</td>
<td>&lt;1 (21)</td>
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<tr>
<td>PLN (phospholamban)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>LDB3 (LIM domain-binding 3)</td>
<td>1-6 (16, 23, 24)</td>
</tr>
<tr>
<td>SCN5A (sodium channel, voltage-gated, type V, α subunit)</td>
<td>2.5 (16)</td>
</tr>
<tr>
<td>TTN (titin)</td>
<td>&lt;1 (25)</td>
</tr>
<tr>
<td>ABCC9 (ATP-binding cassette, sub-family C (CFTR/MRP), member 9)</td>
<td>&lt;1 (26)</td>
</tr>
<tr>
<td>ACTN2 (actinin, α 2)</td>
<td>&lt;1 (27)</td>
</tr>
<tr>
<td>CSRP3 (cysteine and glycine-rich protein 3)</td>
<td>&lt;1 (16, 27-29)</td>
</tr>
<tr>
<td>FCMD (fukutin)</td>
<td>&lt;1 (30)</td>
</tr>
<tr>
<td>DES (desmin)</td>
<td>2 (20, 31)</td>
</tr>
<tr>
<td>SGCD (sarcoglycan, delta)</td>
<td>&lt;1 (32)</td>
</tr>
<tr>
<td>TCAP (titin-cap)</td>
<td>&lt;1 (16, 28)</td>
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<tr>
<td>VCL (vinculin)</td>
<td>&lt;1 (33)</td>
</tr>
<tr>
<td>EYA4 (eyes absent homolog 4)</td>
<td>&lt;1 (34)</td>
</tr>
<tr>
<td>TNNT1 (troponin C type 1)</td>
<td>&lt;1 (17)</td>
</tr>
<tr>
<td>PSEN1 (presenilin 1)</td>
<td>&lt;1 (35)</td>
</tr>
<tr>
<td>PSEN2 (presenilin 2)</td>
<td>1.5 (35)</td>
</tr>
<tr>
<td>TMPO (thymopoietin)</td>
<td>1 (36)</td>
</tr>
</tbody>
</table>

### Treatment

Treatment of DCM depends on the extent of heart failure and the risk of stroke or SCD (38). DCM patients are advised to restrict their intake of salt, fluids, and alcohol; control their weight; monitor their blood pressure; and engage in moderate aerobic exercise, preferably in a controlled environment (3). Congestive heart failure is treated pharmacologically with ACE inhibitors and/or β-blockers (39). It is also believed that these medications will delay DCM progression in presymptomatic affected individuals (5). In patients who have frequent arrhythmias and are thus at risk of stroke and/or SCD, treatment can involve pharmacologic therapy, biventricular pacing, cardiac resynchronization therapy, and the use of an implantable cardioverter-defibrillator (37). Patients with end stage progressive heart failure may require heart transplantation.

Of note, autosomal dominant mutations in TNNT2, TPM1, MYBP3, MYH7 and ACTC are also associated with familial hypertrophic cardiomyopathy, and autosomal dominant
mutations in TNNI3 are also associated with both familial hypertrophic cardiomyopathy and familial restrictive cardiomyopathy (7, 40-44). Autosomal dominant mutations in LMNA are also associated with several other diseases generally called laminopathies, which may or may not include cardiac manifestations (Table 3) (45).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Criteria for Diagnosis of Familial Dilated Cardiomyopathy</th>
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| **Affected** | - Both major criteria **OR**  
- Left ventricular dilation of >117% of the predicted value and one minor criterion  
- Three minor criteria  

**Unaffected** | - No major or minor criteria met  

**Unknown** | - Some criteria met, but not enough for “affected”  

**Major Criteria** | - Left Ventricular Dilation: End diastolic diameter >117% of predicted value based on patient age and body surface area.  
- Left Ventricular Systolic Dysfunction: Fractional shortening <25% of predicted value and/or ejection fraction <45% of predicted value.  

**Minor Criteria** | - Unexplained frequent and/or repetitive arrhythmias before age 50  
- Left Ventricular dilation with end diastolic diameter 112-117% of predicted value  
- Left Ventricular Systolic Dysfunction with fractional shortening 25-28% of predicted value and/or ejection fraction 45-50% of predicted value  
- Unexplained cardiac conduction disease  
- Unexplained stroke or sudden cardiac death before age 50  
- Segmental wall motion abnormalities in the absence of intraventricular conduction defect or ischemic heart disease  

**Exclusion Criteria (causes of secondary DCM)** | - Hypertension of 160/110  
- Coronary Artery Disease with >50% blockage of at least one major branch of a coronary artery  
- Excessive alcohol consumption  
- Persistent high rate supraventricular arrhythmias  
- Pericardial disease  
- Systemic disease  
- Congenital heart disease  
- Cor pulmonale  
- Myocarditis  

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<th>Table 3</th>
<th>LMNA-related Laminopathies</th>
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| **Disease or Disorder** | **OMIM number**  

**Autosomal dominant disorders** |  
Dilated cardiomyopathy with cardiac conduction abnormalities (CMD1A) | 115200  
Emery-Dreifuss muscular dystrophy (AD-EMD2) | 181350  
Early onset atrial fibrillation (EOAF) | 607554  
Limb-girdle muscular dystrophy (LGMD1B) | 159001  
Hutchinson-Gilford progeria syndrome (HGPS) | 151660  
Restrictive dermopathy (RD) | 150330.0036  
Atypical Progeria Syndromes |  
- Atypical HGPS (AHGPS) | 150330  
- Atypical Werner syndrome (AWRN) | 150330.0030  
Ols1-Ols5: include combinations of the following phenotypes: |  
- lipodystrophy (LD) | OLS1 (LiRLLC): 608056  
- muscle weakness (MW) | OLS2 (LD+MW+DCM+CMA): no OMIM number  
- dilated cardiomyopathy (DCM) | OLS3 (LD+DCM+CMA): 150330.0005  
- OLS4 (CMD1A+QM): 150330.0017  
- OLS5 (LD+MD+CMA): 150330.0003 |
• cardiac conduction abnormalities (CCA)
• quadriiceps myopathy (QM)
• syndromic lipodystrophy (LIRLLC) which includes insulin-resistant diabetes, disseminated leukemelano dermic papules, liver steatosis, and cardiomyopathy

| Autosomal recessive disorders |  
|------------------------------|-------------------|
| Emery-Dreifuss muscular dystrophy (AR-EMD2) | 604929  
| Charcot Marie Tooth disease (AR-CMT) | 605588  
| Mandibuloacral dysplasia (MAD) | 248370  

Table adapted from (45)

References


