Genetics of Dilated Cardiomyopathy: Risk of Conduction Defects and Sudden Cardiac Death

Samer Arnous, MBBS, MRCPI[a], Petros Syrris, PhD[b], Srijita Sen-Chowdhry, MRCP, MD, FESC[b,c], William J. McKenna, MD, DSc, FRCP, FESC[a,b,*]

KEYWORDS

• Arrhythmia • Familial dilated cardiomyopathy
• Sudden cardiac death • Conduction defect • Laminopathy
• Left ventricular arrhythmogenic cardiomyopathy

Dilated cardiomyopathy (DCM) is a chronic progressive myocardial disorder with an annual incidence of 6 to 8 cases/100,000 population and prevalence of 36.5 cases/100,000 population.[1] It remains a leading cause of heart failure in people younger than 35 years and the most common indication for cardiac transplantation worldwide.[2,3] The reported frequencies probably represent an underestimate, however, because most studies focus on index cases presenting with clinical heart failure. Recognition of the familial and genetic basis of DCM is relatively recent.

In index cases, DCM is diagnosed in the presence of depressed fractional shortening (<25%) or reduced left ventricular ejection fraction (LVEF) (<45%), and a dilated left ventricle (end-diastolic diameter >117% of the predicted value corrected for age and body surface area).[4] Incomplete phenotypic expression is common among relatives, contributing to underrecognition of familial disease. Nevertheless, nearly a third of asymptomatic relatives of patients with DCM have echocardiographic abnormalities on screening (eg, depressed fractional shortening, left ventricular enlargement), and more than a quarter of these patients develop overt DCM.[5] Furthermore, cardiac-specific autoantibodies were present in more than 30% of asymptomatic relatives of patients with DCM,[6,7] and are weak independent predictors of DCM development at 5-year follow-up.[7,8]

In a longitudinal study of families with DCM, 23% of 767 asymptomatic relatives were found to have echocardiographic evidence of depressed fractional shortening or left ventricular dilation, and these patients were eight times more likely to develop overt DCM than those with normal echocardiograms.[9] Additional studies in the asymptomatic relatives showed that the 25% of relatives with left ventricular enlargement (LVE) without systolic dysfunction had histologic findings consistent with DCM,[10] significant reduction

This work was undertaken at UCLH/UCL, which received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme.
The authors have nothing to disclose.

[a] Inherited Cardiovascular Disease Group, University College London Hospitals NHS Trust, The Heart Hospital, 16-18 Westmoreland Street, Westminster, London W1G 8PH, UK
[b] Inherited Cardiovascular Disease Group, Institute of Cardiovascular Science, University College London, Paul O'Gorman Building, 72 Huntley Street, Camden, London WC1E 6DD, UK
[c] Department of Epidemiology, Imperial College- St Mary's Campus, Norfolk Place, London W2 1NY, UK
* Corresponding author. Inherited Cardiovascular Disease Group, University College London Hospitals NHS Trust, The Heart Hospital, 16-18 Westmoreland Street, Westminster, London W1G 8PH, UK.
E-mail address: william.mckenna@uclh.org

Card Electrophysiol Clin 2 (2010) 599–609
doi:10.1016/j.ccep.2010.09.008
1877-9182/10/$ – see front matter

in exercise capacity,[5,11] and a prolonged QRS complex on signal-averaged ECG, in contrast to normal relatives.[5] This finding suggests that LVE represents subclinical disease, with incomplete phenotypic expression. Despite reduced penetrance, variable expressivity, and the small nuclear families commonly evaluated in clinical practice, familial disease can be confirmed in up to 50% of DCM cases. Familial DCM is diagnosed in the presence of at least two affected individuals in the same family, or a history of unexplained sudden cardiac death (SCD) before the age of 35 years in a first-degree relative.

The prognosis of DCM is highly variable. Earlier studies reported 5-year mortality rates of 50%, which have declined to 20% in more recent reports. This improvement in survival reflects both advances in heart failure therapy and early disease detection. Previously, most patients in any DCM cohort presented with symptoms of high pulmonary venous pressure and a low cardiac output. Increasingly, DCM is diagnosed as an incidental finding in asymptomatic individuals during routine examination or family screening.[5,12,13]

Currently patients with DCM are treated according to international guidelines for the management of heart failure, which are backed by clinical trials. However, a significant knowledge gap remains. The optimal approach to forestalling progression in relatives with early disease is unresolved. Furthermore, there is an unmet need to individualize standard therapies, which do not factor in the influence of underlying cause on treatment responsiveness. Recent studies suggest that this might result in suboptimal or inappropriate therapy in some patients.[14–16] The influence of genetic factors in determining the response (and timing) of drug therapy is largely unstudied in DCM. Heterogeneity in age of onset, clinical manifestations, and outcome is observed within families, implying that factors other than the primary mutation influence phenotype and prognosis.

An important unsolved challenge in the management of DCM is individual assessment of the lifetime risk of SCD. Scant data exist on the natural history associated with specific genetic mutations and predisposition to arrhythmia. However, recent studies have shown that the arrhythmogenic risk is higher in certain subtypes of DCM, such as the laminopathies.

This article focuses on the heterogeneity of phenotypic expression in familial DCM, with emphasis on the various gene mutations associated with increased risk of high-grade atrioventricular block, malignant ventricular arrhythmias, and SCD.

GENETICS

More than 40 disease-causing genes have been identified in DCM,[17] most of which encode proteins of the sarcolemma,[18–20] cytoskeleton,[21] sarcomere,[22–26] nuclear envelope (eg, Lamin[27–29]), and mitochondrion[30] (**Table 1**). The structural and functional consequences DCM mutations include impairment of myocardial force generation, force transmission, and cell survival (**Fig. 1**).

DCM is inherited as an autosomal dominant trait in 90% of families. This mode of transmission is often associated with reduced and age-related penetrance (**Table 2**), although onset by the fourth decade of life is typical.[13] Expression is also variable and frequently incomplete; although symptomatic disease may not be present, cardiac evaluation may reveal unexplained electrocardiogram (ECG) or echocardiographic abnormalities. Autosomal dominant forms of DCM may be associated with conduction disease[76] or skeletal myopathy.[52,77]

Other modes of inheritance include autosomal recessive, X-linked recessive, and mitochondrial. In autosomal recessive DCM, patients usually present at a younger age than those with the dominant form. The disease course is characterized by more rapid progression to death or cardiac transplantation.[13] X-linked inheritance is characterized by the absence of male-to-male transmission.[13,78] Women may be affected but usually express a milder form of disease expression with onset later in life. Affected patients usually have an increase in creatine kinase (CK)-MM isoform level (eg, mutations in dystrophin that also cause Duchenne and Becker muscular dystrophy).

Matrilineal inheritance is usually associated with signs of mitochondrial-related phenotype, such as lactacidemia, hypoacusia, palpebral ptosis, myopathy with ragged red fibers, ophthalmoplegia, encephalopathy, or retinitis pigmentosa. In this form of inheritance the mother, son, or daughter may be affected, but the affected men do not transmit the disease to their offspring.

DCM WITH ARRHYTHMIA AS INITIAL PRESENTATION

Laminopathies

A large number of mutations have been identified in LMNA, the gene encoding lamins A and C, which is 12 exons in length and located on the long arm of chromosome 1 (1q21.2-q21.3). Phenotypic manifestations are diverse, including an array of rare but dominantly transmitted diseases affecting cardiac and skeletal muscle (laminopathies): Emery-Dreifuss muscular dystrophy,[29,79]