1. Clinical Characteristics

1.1 Definition and prevalence

Dilated cardiomyopathy (DCM) is a myocardial disorder characterised by dilatation and contractile dysfunction of the left ± right ventricles. DCM may be caused by a diverse range of conditions that promote cardiomyocyte injury or loss, e.g. coronary artery disease, viral myocarditis, alcohol excess. In approximately 50% cases, an underlying cause is unable to be identified. This group has traditionally been termed “idiopathic” DCM. It is now recognised that approximately one-third to one-half of cases of “idiopathic” DCM have a positive family history, suggesting that an inherited gene defect might be the cause of the disorder (“familial DCM”).

1.2 Clinical presentation

Familial DCM may be inherited as an autosomal dominant, autosomal recessive, maternal or X-linked trait; autosomal dominant inheritance is present most commonly. In autosomal dominant inheritance, each child of an affected parent has a 50% chance of inheriting a disease-causing gene mutation, with males and females equally at risk. Clinically-affected individuals generally present with symptoms and signs of heart failure or arrhythmias. Some families have a clinical presentation (phenotype) that is characterised by DCM alone, while in others, DCM may be associated with additional cardiac manifestations e.g. conduction-system disorders, valve defects, atrial/ventricular septal defects, left ventricular non-compaction, or with non-cardiac manifestations e.g. skeletal myopathy, partial lipodystrophy, sensorineural deafness.

1.3 Clinical diagnosis

The diagnosis of familial DCM is made when DCM (with or without associated features) is present in the setting of a positive family history (at least 2 family members affected). There are no specific clinical features that reliably distinguish familial from non-familial DCM.
Family history: A detailed family history and a high level of clinical suspicion are essential. While inherited gene defects alone may be sufficient to cause disease, some individuals in families may have concurrent risk factors for DCM that may confound the recognition of familial disease. In addition, familial clustering may not be immediately apparent if the clinical presentation differs between members of the same family. For example, in DCM with conduction-system disease, some individuals may present with heart failure, while others may have a history of arrhythmia symptoms, pacemaker implantation or sudden death. The severity of disease, and the age of onset, may differ between families and within members of the same family. While familial DCM generally shows high penetrance, some individuals may remain non-penetrant (i.e. genotype-positive but with no clinical manifestations of disease) throughout life.

Family screening: It is currently recommended that all first-degree family members of individuals with “idiopathic” DCM, and of individuals with suspected familial DCM on the basis of a positive family history, should undergo clinical screening with physical examination, 12-lead ECG and transthoracic echocardiography to identify familial disease and to determine the number of affected individuals within families. Measurement of CK levels is useful to identify subclinical skeletal muscle abnormalities and provides supportive evidence for the presence of an inherited myopathic disorder. Exercise treadmill testing and/or coronary angiography may be indicated in family members aged over 50 years who are found to have a new diagnosis of DCM, to distinguish a familial from a non-familial cause.

2. Molecular Genetics

2.1 Familial DCM disease genes

Familial DCM is a genetically-heterogeneous disorder. To date, nearly 40 chromosomal loci have been associated with various forms of autosomal dominant DCM, with the disease-causing genes identified in >30 of these loci. These disease genes encode a variety of proteins in the cardiomyocyte sarcomere, cytoskeleton, sarcolemma, and nucleus. These findings indicate that diverse molecular mechanisms may underlie familial DCM.

2.2 Genetic testing

Despite the relatively large number of genes identified, mutations in the majority of these genes are uncommon and collectively account for a minority of cases of familial DCM. Furthermore, families with DCM generally have unique mutations. Hence, screening for mutations in the known disease genes would require evaluation of the entire coding sequence of a large numbers of genes, which has been prohibitively time-consuming and costly. With the advent of high-throughput sequencing technologies, however, it is now feasible to more efficiently screen panels of the known DCM genes and there are several commercial laboratories, mainly based overseas, that offer this service. The interpretation of DNA sequence variants identified in individual patient samples is not straightforward however and the discovery of a novel DNA sequence variant per se does not imply pathogenicity. Factors that need to be considered include whether the variant segregates with disease status in families, its presence/absence in control subjects, whether it is a novel or known variant in a novel or known disease gene, and whether there are predicted or experimentally validated functional consequences. It is highly recommended that the results of genetic testing are reviewed by experienced molecular cardiology personnel, and that testing is carried out in an appropriate setting that includes pre-test and post-test genetic counselling. Since the yield of mutation testing, even with the aid of high-throughput technologies, is relatively low (25-
30%), the role of genetic testing in familial DCM remains uncertain. The yield of genetic testing will be higher in specific patient subgroups in which there are distinct genotype-phenotype correlations, for example, \textit{LMNA} testing in families with DCM and conduction-system disease. Rapid progress in this field can be anticipated and recommendations for genetic testing will evolve accordingly.

3. Management

3.1 Affected individuals

Clinically-affected family members with DCM should receive standard pharmacological management as indicated by the severity of symptoms and signs of heart failure. In families with DCM and conduction-system disease, young family members who present with conduction-system disturbances (sinus bradycardia, atrioventricular conduction block, ± atrial fibrillation) should be followed for arrhythmias that might necessitate pacemaker implantation and for the onset of DCM in later life. Electrophysiological studies ± AICD implantation should be considered in individuals with syncopal episodes, and/or a strong family history of sudden death. The natural history of familial DCM can vary within families and between members of the same family. It is likely that family genotype will be a very important determinant of prognosis. Genotype-phenotype correlations in large populations of family members will be a useful guide in the future for patient therapy and counselling.

3.2 Asymptomatic family members

\textit{Longitudinal follow-up:} Periodic cardiac screening (ECG and transthoracic echocardiography) of family members of probands with familial DCM is recommended, to identify arrhythmias and asymptomatic abnormalities of left ventricular size and function. The frequency of follow-up assessments should be determined in each individual case by factors such as the typical age of onset of disease in symptomatic family members, and “suspicious” echocardiographic changes (eg. borderline normal, or suggestive of early disease [see below]), and may range from 6-12 months to 5 years. Familial DCM exhibits age-related penetrance, i.e. family members who are born with a gene defect may not develop manifestations of disease until later in life. The age of onset of disease in families is variable, with clinical signs appearing from the second to ninth decades. Young family members with a normal ECG and echo, particularly offspring of an affected parent, should not be dismissed as “unaffected” and require ongoing medical surveillance.

\textit{Early disease:} As part of clinical screening for molecular genetics studies, a previously unrecognised subgroup of family members with asymptomatic echocardiographic changes (left ventricular dilation and/or mild impairment of contractile function) has been identified. Although left ventricular dilatation is not specific for early disease and may result from unrelated pathologies, or physiological variation, particularly in young, fit individuals engaged in competitive sporting activity, several studies have suggested that at least one third of these individuals have latent cardiomyopathy, indicated by the presence of myocardial histological changes, reduced maximal exercise oxygen consumption, or cardiac autoantibodies. Detailed characterisation of left ventricular function using a range of echocardiographic techniques and/or magnetic resonance imaging may help to better differentiate individuals with early cardiomyopathy, but sensitive and specific markers of early disease have yet to be established. Longitudinal studies have shown that approximately 10% of individuals with left ventricular dilation and/or mild impairment of contractile function will develop DCM over a 5-year period. The development of risk stratification
algorithms to reliably identify those individuals at greatest risk of disease progression is still required. The ability to recognise early disease has important management implications, since early intervention may prevent, or attenuate progression to symptomatic heart failure. Large-scale clinical trials with long-term follow-up are needed to evaluate the role of pharmacologic intervention in this subgroup of family members. Such trials would ideally be performed in genotyped familial DCM populations.

### 3.3 Counselling

All family members potentially at risk of disease should receive lifestyle modification advice, e.g. avoidance of alcohol excess, regular moderate exercise, etc. Female family members who are considering pregnancy should have initial cardiological review and regular follow-up during pregnancy, since familial DCM may be unmasked or accelerated in the peripartum period, especially in the last trimester and first 6 months postpartum. The diagnosis of a genetic disorder in a family and the possibility of testing for the disorder raises a number of issues that are best addressed by experienced cardiovascular genetics counsellors.

**Key references:**


