



The Cardiac Society of Australia and New Zealand

Diagnosis and Management of Familial Dilated Cardiomyopathy – Position Statement

This position statement was reviewed and revised by Prof Diane Fatkin, Dr Renee Johnson, A/Prof Julie McGaughran, Dr Robert G Weintraub and A/Prof John J Atherton on behalf of the CSANZ Cardiovascular Genetics Diseases Council Writing Group. No authors have any relevant Conflict of Interest to disclose.

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KEY POINTS:

- Genetic factors have an important role in the pathogenesis of dilated cardiomyopathy (DCM) and can be a primary cause of disease.
- *Clinical presentation:* The clinical presentation of familial DCM can be variable. In most kindreds, affected individuals present with symptoms and signs attributable to left ventricular dysfunction. In some cases, the family phenotype may include additional cardiac or extra-cardiac manifestations, including conduction-system abnormalities or skeletal myopathy. These features may provide clues to the underlying disease genes.
- *Clinical diagnosis:* The diagnosis of DCM is made using echocardiography or other imaging modalities such as magnetic resonance imaging. Approximately 25% patients with “idiopathic” DCM are likely to have a genetic basis for disease and a detailed three-generation family history needs to be taken in all newly-diagnosed cases. First-degree family members of individuals with known or suspected familial DCM should undergo clinical screening with physical examination, 12-lead ECG and transthoracic echocardiography. A detailed medical history needs to be taken to identify any co-morbidities or acquired factors that might contribute to DCM development or exacerbate disease severity. In female family members, DCM may present during pregnancy or in the postpartum period.
- *Genetic testing:* DCM is genetically heterogeneous with more than 40 genes associated with familial and sporadic disease. To date, the cost and relatively low yield (~20%) of screening known disease genes has limited the role of genetic testing for DCM patients in routine clinical practice. Current international guidelines recommend (i) selective testing of the *LMNA* and *SCN5A* genes in patients

with DCM and conduction-system disease and/or a family history of premature unexpected sudden death, and (ii) cascade testing of relatives in families in which a likely disease-causing variant is identified in the index case. Over recent years, the introduction of next-generation sequencing technologies has been a major advance that allows comprehensive and unbiased evaluation of an individual's genetic makeup. In DCM, these technologies have already increased the yield of potential mutations up to 50%. Surprisingly, truncating variants in the *TTN* gene have been identified in 15-25% of adult DCM cases, but whether these variants are sufficient alone to cause DCM remains to be clarified. As genetic testing becomes more affordable and available, it can be expected to play an increasingly important role in patient management. Interpretation of test results and understanding the clinical significance of genetic variants remains a major challenge.

- *Management:* In most families, treatment choices are not currently altered by the discovery of a causative gene mutation and clinically-affected individuals should receive standard pharmacological and device management. Asymptomatic family members should have baseline cardiac assessment and ongoing periodic cardiac screening for early detection of pre-clinical disease. When a pathogenic genetic variant has been identified in an affected individual, appropriate family members should be offered predictive genetic testing and genetic counselling. Genetic testing and family management is ideally undertaken by experienced personnel in the setting of a multidisciplinary clinic.

CHANGES FROM 2013 DOCUMENT

These guidelines have been revised overall with expanded sections on the molecular genetics of DCM and sequencing options for genetic testing. The document now includes recommendations for paediatric DCM.

1. CLINICAL CHARACTERISTICS

1.1 Definition and prevalence

Dilated cardiomyopathy (DCM) is a myocardial disorder characterised by dilatation and systolic dysfunction of the left \pm right ventricles. It is one of the most common forms of heart muscle disease with an estimated prevalence of 1:2500 [1]. DCM can be caused by diverse conditions that promote cardiomyocyte injury or loss, including viral myocarditis, alcohol excess, and chemotherapeutic drugs. In approximately 50% cases, an underlying cause is unable to be identified and the condition is referred to as “idiopathic” DCM [2]. It is now recognised that approximately 1 in 4 patients with “idiopathic” DCM have a positive family history, which suggests a potential genetic aetiology [3]. A similar prevalence of familial disease (15-20%) has been observed in cohorts of children with DCM [4,5]. In kindreds in which

DCM segregates with a Mendelian inheritance pattern, there is a high probability that a single inherited genetic variant is the primary cause of disease and this is termed “familial” DCM.

1.2 Clinical presentation

Familial DCM may be inherited as an autosomal dominant, autosomal recessive, maternal or X-linked trait. Autosomal dominant is the most common pattern, with each child of an affected parent having a 50% chance of inheriting a disease-causing gene mutation, and 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 eg. conduction-system disorders, valvular abnormalities, congenital heart defects, left ventricular non-compaction, or with extra-cardiac manifestations eg. skeletal myopathy, partial lipodystrophy, sensorineural deafness.

1.3 Clinical diagnosis

A diagnosis of familial DCM generally requires the presence of DCM in two or more affected individuals in a single family in the absence of another heritable cardiac or systemic cause of left ventricular dysfunction. Familial DCM should also be considered in kindreds in which first-degree relatives of DCM cases have unexplained sudden death at a young (<35 years) age [2,3]. Apart from family history, there are no specific clinical features that reliably distinguish familial from non-familial DCM [2,6].

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 families may include individuals who 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 family size is small, or if the clinical presentation differs between members of the same family. For example, in DCM with conduction-system disease due to *LMNA* mutations, family members may variably present with heart failure, arrhythmias, or sudden death [7,8]. The severity of disease and age of onset may differ between families and between members of the same family [9,10]. This may be influenced by sex, genetic modifier variants, comorbidities, and lifestyle factors. DCM may be unmasked prematurely in genetically-predisposed females during the peripartum period [11]. While familial DCM generally shows high penetrance, some individuals may remain non-penetrant (ie. genotype-positive but with no clinical manifestations of disease) throughout life.

Family screening: It has been 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 [12]. Measurement of creatine kinase levels is useful to identify subclinical skeletal muscle abnormalities and provides supportive evidence for the presence of an inherited myopathic disorder. Consideration of other causes of left ventricular dysfunction, including 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. In children, a full diagnostic work-up includes baseline investigations directed toward potential viral, metabolic, endocrine and infective causes. Endomyocardial biopsy may be useful in the diagnostic work-up of patients with idiopathic DCM, particularly those with suspected myocarditis [13,14] but is not required for family screening.

2. MOLECULAR GENETICS

2.1 Familial DCM disease genes

Molecular genetics studies performed to date indicate that DCM is genetically heterogeneous with more than 40 genes associated with adult-onset familial and sporadic forms of disease [15]. These genes encode proteins in the cardiomyocyte sarcomere, cytoskeleton, sarcolemma, and nucleus, indicating pleiotropic molecular aetiologies. A similar spectrum of genetic mutations, including mitochondrial gene mutations, has been described in children with sporadic and familial DCM. The latter typically present early and are often associated with multiple non-cardiac abnormalities. In general, the clinical phenotype provides no real clues for identifying the underlying genotype, with a few notable exceptions. These include *LMNA* and *SCN5A* gene mutations in which DCM may be preceded by conduction-system abnormalities, and *LMNA*, *DES*, *DMD*, and *EMD* mutations that may be associated with skeletal myopathy and/or raised creatine kinase levels [15]. The weight of evidence in support of each of the putative DCM disease genes varies widely. For example, there are genes such as *LMNA*, *MYH7*, *RBM20* and *BAG3*, in which numerous mutations that demonstrably alter protein function have been shown to segregate with DCM status in large families and animal models recapitulate disease. For other genes, there may be only single variants with predicted functional effects that are identified in sporadic cases. It is increasingly recognized that function-altering variants are not necessarily disease-causing, and that not all genes on the disease gene “list” will have *bona fide* roles in DCM pathogenesis. Genotype-phenotype correlations are also revealing that mutations in the same gene can give rise to different cardiomyopathy phenotypes. For example, *MYH7* mutations are one of the most common genetic causes of hypertrophic cardiomyopathy and have also been associated with left ventricular non-compaction [15]. The basis for these phenotypic differences is incompletely understood but may relate to distinctive functional effects of mutations or phenotype-modifying effects of background genetic variation.

Over recent years, advances in sequencing technologies facilitated a major breakthrough in DCM genetics with the discovery that truncating variants in the *TTN* gene, that encodes the giant sarcomeric protein titin,

occur in up to 1 in 4 patients with DCM [16]. The high prevalence of truncating *TTN* variants has recently been confirmed in a multicentre study of >5000 subjects in which these variants were identified in 13% ambulatory, 22% end-stage and 27% familial cases of adult-onset non-ischaemic DCM, respectively [17]. Interestingly, truncating *TTN* variants are rarely the sole cause of disease in patients who present with DCM during childhood (<15 years) [18]. Since truncating *TTN* variants are present in 1-3% of population control subjects, it remains unclear whether they are sufficient alone to cause DCM or are common modifying factors that increase susceptibility to DCM. This is currently a topic of intense international research interest and better insights into the clinical impact of *TTN* variants should be gained within the coming years. In children with DCM, pathogenic sarcomeric mutations are relatively frequent causes.

2.2 Genetic testing

Who to test?: The most recent international guidelines for genetic testing in DCM have class I recommendations for (i) selective testing of the *LMNA* and *SCN5A* genes in patients with DCM and conduction-system disease and/or a family history of premature unexpected sudden death, and (ii) cascade testing of relatives in families in which a likely disease-causing variant is identified in the index case (proband). In general, genetic testing in DCM cases has a class IIa recommendation (can be useful) [19] and is gaining a growing acceptance as part of the work-up for children with otherwise unexplained DCM. These recommendations are based in part, on the low yield (~20%) of testing undertaken in the past, which has largely comprised of targeted re-sequencing of panels of subsets (<10) of DCM disease genes [20-24]. With the introduction of high throughput sequencing methodologies (see below), the numbers of genes that can be tested has increased, and this has resulted in a higher yield of potential mutations (up to 50%) [25,26]. It can be anticipated these trends will continue and that genetic testing will play an increasingly important role in DCM family management. Genetic testing is most likely to be informative and clinically useful in the setting of familial disease. The main value of genetic testing is to guide screening in unaffected family members if a mutation is identified in someone with familial DCM. An unaffected family member who carries the family mutation (genotype positive-phenotype negative) will require ongoing clinical surveillance. Non-carriers can be reassured and may be discharged from intensive longterm clinical surveillance. However, the possibility that there are >1 mutations in the family cannot be entirely excluded, and there needs to be a low threshold for investigating apparent non-carriers if any symptoms develop.

How to test?: For decades, Sanger sequencing was the gold-standard method for mutation detection. Sanger sequencing enables high-quality sequence data to be obtained, but the costs and time involved make it unsuitable for screening multiple genes, especially large genes such as *TTN*, that have hundreds of coding exons. Three options for genetic testing are currently available that utilise high throughput next-generation sequencing technologies [27-30]. The most commonly-used method offered by commercial laboratories is targeted re-sequencing of panels of genes that have been associated with cardiomyopathies.

Targeted re-sequencing has a very high reproducibility for variant detection, but is limited by the number of genes evaluated and panels need to be revised every time a new disease gene is discovered. Whole-exome sequencing (WES) evaluates the 1% of the human genome that is protein-coding (the “exome”). WES has the advantage that it provides information about all genes but the depth of sequence coverage is often highly variable, due to varying capture efficiency in the library preparation, and variants in some exons may be mis-called or missed. For clinical diagnostic use, this may necessitate extensive follow-up Sanger sequencing to fill in gaps, particularly in high-probability disease genes. Sequencing of the entire genome (whole-genome sequencing, WGS) offers the possibility of providing a single comprehensive test for detection of variants within known and novel genes or in intronic or intergenic regions. Significant potential advantages of WGS include: more consistent depth and breadth of coverage than other methods, the ability to detect copy number and noncoding regulatory variants, which are increasingly being shown to drive disease, and perhaps most importantly, the ability to reinterpret undiagnosed patients in light of new disease gene discoveries. The clinical utility of WGS over targeted re-sequencing and WES for genetic screening in DCM is currently under investigation.

Interpretation of genetic test results: New sequencing data are revealing that every person carries 20,000 or more single nucleotide polymorphisms [29] and the major challenge when assessing patient DNA samples is how to identify those variants that are likely to be disease-causing. The interpretation of DNA sequence variants is not straightforward and it is becoming increasingly apparent that many of the criteria relied upon in the past to define pathogenicity lack specificity. For example, variants that are novel or high impact (i.e. those that significantly alter the encoded protein such as nonsense mutations, splice site mutations, and frame-shift insertion/deletion mutations) have been thought to be potentially pathogenic. However, it is now appreciated that a majority of all rare variants are novel and that even healthy people carry numerous high-impact variants [29,31]. Moreover, many variants reported in the literature as causing inherited heart disease are now being recorded in population databases [32-34]. These issues highlight the need for careful interpretation of the significance of variants detected before giving “positive” results to patients with DCM and their families. 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. Rapid progress in this field can be anticipated in the next few years.

3. MANAGEMENT

3.1 Affected individuals

Clinically-affected family members with DCM should receive standard pharmacological, device, and surgical management (circulatory support and transplantation) as indicated by the severity of symptoms and signs of heart failure, the electrocardiographic findings and the degree of left ventricular dysfunction.

In families with DCM and conduction-system disease, young family members who present with conduction-system disturbances (sinus bradycardia, atrioventricular conduction block, \pm atrial fibrillation) should be followed for arrhythmias that might necessitate pacemaker implantation and for the onset of DCM in later life. Electrophysiological studies/review \pm ICD implantation should be considered in individuals with syncope episodes, and/or a strong family history of sudden death, particularly in those families with *LMNA* mutations [35]. In most families, however, treatment choices for affected individuals are not currently altered by the discovery of a causative gene mutation. In selected cases, elucidation of the molecular mechanisms underpinning disease may permit specific gene-targeted intervention [36]. The natural history of familial DCM varies widely. It is likely that family genotype will be a very important determinant of prognosis but genotype-phenotype correlations in large populations of family members have yet to be performed. Recent data suggest that patients with genetic causes of DCM have a worse long-term outcome if there are co-existent non-genetic environmental factors including viral infection, immune-mediated cardiac inflammation and toxic exposure [13].

3.2 Asymptomatic family members

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 [12]. 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 that may be indicative of early disease and may range from 6-12 months to 5 years. Familial DCM exhibits age-related penetrance, ie. family members who are born with a gene defect may not develop manifestations of disease until later in life. 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. In the case of an affected child, all first degree relatives, including parents, should be screened and siblings are offered ongoing screening into adult life.

Early disease: As part of clinical screening for molecular genetics studies, a subgroup of family members with asymptomatic echocardiographic changes (left ventricular dilation and/or mild impairment of contractile function) has been identified [9,37]. 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 [38-41]. 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 [42-44]. 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, including avoidance of alcohol excess, regular moderate exercise, healthy diet, and weight control. Female family members who are considering pregnancy should have initial cardiac review and regular follow-up during pregnancy, since familial DCM may be unmasked or accelerated in the peri-partum 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 molecular cardiologists, clinical geneticists and genetics counsellors in a multidisciplinary cardiac genetics clinic. The participation of families in genetics research studies will continue to play a vital role in ongoing advancements in this field.

Further Information

For further information about these guidelines, please contact Prof. Diane Fatkin, Molecular Cardiology Division, Victor Chang Cardiac Research Institute, PO Box 699, Darlinghurst NSW 2010; tel: +61 2 9295 8618; email: d.fatkin@victorchang.edu.au.

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