Canadian Journal of Cardiology 31 (2015) 1309–1312

Viewpoint

The Rationale and Timing of Molecular Genetic Testing for Dilated Cardiomyopathy

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ABSTRACT

The genetic evaluation of dilated cardiomyopathy (DCM) has been challenging, owing in large part to marked genetic heterogeneity. However, lower costs from next-generation sequencing have enabled gene discovery and the expansion of genetic testing panels. These advances have improved molecular diagnostics and predictive testing in DCM. We provide a rationale and recommendation for clinical genetic testing in all DCM cases.

RÉSUMÉ

L'évaluation génétique de la cardiomyopathie dilatée (CMD) s'est avérée difficile, en grande partie en raison de la très grande hétérogénéité génétique. Cependant, les coûts plus faibles du séquençage de nouvelle génération ont permis la découverte des gènes et le développement des panels de dépistage génétique. Ces avancées ont amélioré les diagnostics moléculaires et le dépistage présymptomatique de la CMD. Nous donnons les raisons et les recommandations qui justifient le dépistage génétique clinique dans tous les cas de CMD.

Molecular genetic sequencing, made cost-effective by next-generation sequencing, has provided an enormous opportunity to transform the practice of cardiovascular medicine. The most tractable genetic conditions in clinical practice are those known to be familial—the cardiomyopathies, channelopathies, and aortopathies. We focus on idiopathic dilated cardiomyopathy (DCM), a pan-ethnic condition, characterized by left ventricular enlargement and systolic dysfunction.

DCM is the most common heritable cardiomyopathy, with an estimated prevalence of 1 in 200-1 in 500 persons.[1] DCM is also the most common indication for heart transplantation in pediatric and adult populations.[2] Understanding DCM genetics and skillfully using genetic testing for all cases of DCM, both familial and nonfamilial (a recommendation that currently exceeds published guidelines,[3] although our preliminary data suggest that the frequency of relevant variants in familial and nonfamilial DCM is similar),[4] presents enormous opportunity to prevent the morbidity and mortality that eventually accompanies most cases. This is because DCM usually presents with heart failure, arrhythmia, stroke, or sudden cardiac death, which are very late-phase aspects of disease (Fig. 1).[5] However, an asymptomatic phase precedes symptomatic DCM, which can be divided into periods of risk. In the first period, an individual carries a predisposing rare variant, but clinical evidence of DCM is not present. During the second period, diagnostic structural or functional changes of DCM are present, but there are no symptoms. DCM may continue in this asymptomatic phase for years.

During the first phase, genetic risk can be identified only by molecular genetic testing (Fig. 1). If a pathogenic variant is identified, the individual should then undergo cardiovascular screening at intervals to identify early disease onset. With the earliest evidence of DCM, medical therapy can be started to prevent symptomatic advanced disease. All efforts to prevent or ameliorate heart failure, by definition a symptomatic condition, is a laudable goal.

In most cases, individuals with DCM come to clinical attention only when symptoms appear, usually between the ages of 30 and 60 years. Symptomatic presentation may also occur at younger or older ages—from neonates to the elderly. A subset of DCM, peripartum or pregnancy-associated cardiomyopathy (PPCM/PACM), presents during pregnancy or the postpartum period.

DCM may also occur in the fetal, neonatal, and pediatric population,[6] and although fetal, neonatal, and early pediatric DCM is phenotypically similar to the adult population reviewed earlier, including evidence of rare variant cause,[7,8] the DCM epidemiology already discussed is primarily applicable to adults.

Received for publication April 1, 2015. Accepted June 17, 2015.

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See page 1311 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2015.06.034

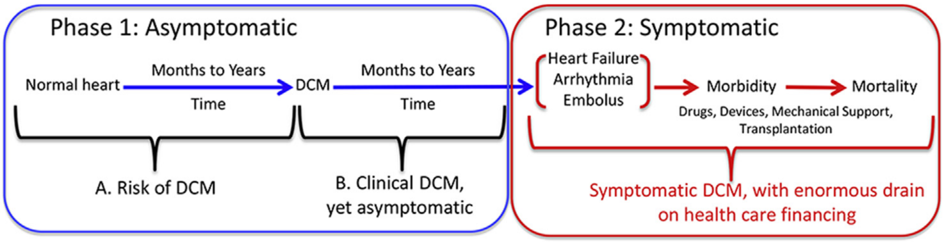

Figure 1. The asymptomatic and symptomatic phases of dilated cardiomyopathy (DCM). Phase 1 includes 2 periods, both asymptomatic. In the first period (1A), individuals who harbor 1 or more rare DCM variants have a risk of DCM developing over time. During this phase, genetic information identifies the individuals who would benefit from periodic clinical screening to detect early clinical disease. In phase 1B, DCM is present but asymptomatic, at times for years, thus evading detection without periodic efforts to detect it. With detection of asymptomatic clinical disease (phase 1B), medical therapy can be initiated in an effort to prevent progression to phase 2. In phase 2, late-stage disease becomes symptomatic with heart failure, arrhythmia, or embolus, the presenting features of DCM. As noted in the text, this construct is useful principally in the adult population.

Genetics of DCM

Clinical genetics

A study comparing family history and cardiovascular screening of relatives of DCM probands found that family history information can reveal familial dilated cardiomyopathy (FDC) in only 5% of cases, whereas cardiovascular screening can detect FDC in 20% of cases.[9] Subsequent studies found an FDC prevalence of 25%-35%.[10-12] Considering that isolated left ventricular enlargement may precede DCM, and thus may be taken as early evidence of disease, FDC was estimated to be present in 48% of family members.[11] Most families show an autosomal dominant pattern of inheritance, in which first-degree relatives have a 50% probability of having the condition. However, not all affected family members have the same degree of severity (variable expressivity).[1] Further complicating the assessment of FDC is the observation of some family members who carry the DCM-causing mutation but escape the condition (reduced penetrance).[1]

Molecular genetics

Research studies have shown that mutations in approximately 40 genes (locus heterogeneity) of diverse ontology segregate in approximately 40% of these families.[1] When a genetic cause is known, the 2 most frequently implicated genes in DCM are *TTN* (truncating variants, 20%) and *LMNA* (6%). Preliminary studies have shown a similar yield of genetic variants among individuals with FDC and those with a negative family history,[4] suggesting that most idiopathic DCM may have a genetic basis. A complicating factor is that almost all mutations are unique to individual families and thus require unique sets of molecular data and functional validation to be proved pathogenic.

Clinical Impact

Genetic testing panels can identify a pathogenic variant in about 20% of cases. A pathogenic variant is one that—based on previous cases, family studies, or functional data (or a combination of these factors), among others—is unequivocally expected to cause DCM (Table 1). If a pathogenic variant is identified in an affected individual, a genetic diagnosis of DCM is confirmed. Moreover, finding a pathogenic variant in *LMNA* or *DES* may have prognostic significance when identified in an affected individual because of the increased risk of sudden cardiac death.[3,13] In addition, for patients with DCM and conduction system disease (often caused by *LMNA* mutations), early insertion of an implantable cardioverter defibrillator may be recommended to avoid syncope or sudden cardiac death.[3,13]

Testing for the variant in unaffected at-risk family members helps to realize the enormous potential of cardiovascular genetic medicine. If an at-risk family member is found to carry the pathogenic variant, this individual is expected to have an increased lifetime risk for the development of DCM. Such individuals have been recommended to pursue cardiovascular clinical screening every 1-3 years, consisting of echocardiography, electrocardiography (ECG), and cardiovascular-directed examination.[3] At-risk family members in whom the variant is not identified are no longer considered to be at increased risk and thus may be discharged from cardiac surveillance.

If, in contrast, an affected individual undergoes panel testing and a variant is not identified, a genetic cause cannot be ruled out, because the detection rate of genetic testing for DCM is not 100%. These individuals may benefit from follow-up genetic testing in the future as more genes are discovered and added to panels. Importantly, first-degree relatives of these individuals remain at risk for DCM. Therefore, screening ECG and some measure of ventricular size and function, usually by echocardiography, is recommended every 3-5 years.[3] The same guidelines apply for

Table 1. Variant terminology

Pathogenic	The variant causes the patient's phenotype
Likely pathogenic	There is a > 90% probability that the variant is pathogenic
Variant of uncertain significance	The variant cannot be classified
Likely benign	There is a > 90% probability that the variant is benign
Benign	The variant is not the cause of the patient's phenotype

This follows terminology recommended by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[14]