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Using Genetic Testing to Guide Therapeutic Decisions in Cardiomyopathy

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Opinion statement

Genetic analysis of human cardiomyopathy has rapidly transitioned from a strictly research endeavor to a diagnostic tool readily available to clinicians across the globe. In contemporary practice, genetic testing improves the efficiency of family evaluations and clarifies the etiology of ambiguous clinical presentations. The great promise of genetic diagnosis is to enable preventative therapies for individuals at high risk of future disease development, a strategy that is under active clinical investigation. However, in the present and future, careful interpretation of DNA sequence variation is critical, and can be ensured by referral to a specialized cardiovascular genetics clinic.

Keywords

Genetics; Genetic testing; Hypertrophic cardiomyopathy; Dilated cardiomyopathy; Arrhythmogenic cardiomyopathy; Sarcomere

Introduction

Inherited cardiomyopathies are an important cause of heart failure and sudden death. By convention, they are categorized by ventricular morphology and associated arrhythmias into hypertrophic, dilated and arrhythmogenic cardiomyopathies. Each has distinct histopathology, natural history and clinical features. However, the clinical genetics of these disorders share much in common. Autosomal dominant inheritance, age dependent and incomplete penetrance, and variable expression are characteristic. Currently, genetic testing plays an important role in diagnosis. To a lesser extent in the present and perhaps to a greater extent in the future, genetic testing may inform therapeutic decisions made for these patients. This manuscript reviews the utility of genetic testing in the contemporary and future management of cardiomyopathy. Not included is a discussion of pharmacogenomics factors that can improve the management of most patients with heart failure and arrhythmia, including those with underlying genetic cardiomyopathy.

Genetic cardiomyopathy: core principals

Inherited cardiomyopathies are caused by rare genetic variants (aka mutations) that are generally private to individual families. Cardiomyopathy-causing mutations are typically

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inherited in an autosomal dominant fashion, implying a 50 % probability of transmission from parent to child, regardless of gender. Less common are X-linked, autosomal recessive and matrilinear transmission.

Collectively, thousands of mutations in many different genes have been associated with cardiomyopathy, indicating great allelic and locus heterogeneity. The clinical challenge presented by allelic and locus heterogeneity is that the entire coding sequence of multiple genes must be interrogated in the initial genetic evaluation of a proband (i.e. index case in a family). In hypertrophic cardiomyopathy (HCM), mutations in over nine sarcomeric genes have been identified, although the majority of patients with confirmed genetic disease harbor a mutation in either *MYH7* (beta myosin heavy chain) or *MYBPC3* (myosin binding protein C) [1]. This phenomenon is exaggerated in dilated cardiomyopathy (DCM), where over 40 genes have been implicated. However, truncation mutations in *TTN*, which encodes the giant sarcomeric protein titin, underlie ~ 25 % of DCM [2•]. Arrhythmogenic right ventricular cardiomyopathy (ARVC), perhaps a misnomer because a significant fraction may selectively involve the left ventricle, is a disease of desmosomal mutations, most commonly *PKP2* (plakophilin-2) [3]. Included in Table 1 are selected genes that commonly cause human cardiomyopathy. Many more genes have been implicated; however, data to convincingly prove a causative role are often lacking.

In general, cardiomyopathy mutations are incompletely penetrant, indicating that not all individuals who inherit a mutation will develop cardiomyopathy. Penetrance varies by gender, mutation and disease state, but most importantly by age. Few mutation carriers manifest cardiomyopathy in early childhood, and some may not develop overt disease until well into adulthood. For example, less than 40 % of individuals with an HCM causing *MYBPC3* mutations manifest overt HCM by 40 years of age [4].

Not all clinical variability is imposed by locus and allelic heterogeneity. Indeed, within families affected by the exact same disease mutation, clinical expression varies considerably. This can take the form of infantile and elderly cardiomyopathy onset within the same family [5]. Alternatively, associated clinical features, especially arrhythmias, may be absent or delayed in some family members. The factors that govern variable clinical expression are largely unknown, but implicate a significant role for genetic, epigenetic and environmental modifiers.

Interpretation of DNA sequence variation is the essence of genetic testing. Recognizing that some degree of genetic variation is expected, clinical pathologists must apply rigorous standards to determine if a DNA variant identified in a patient is pathogenic or benign [6••]. Historically, a DNA variant was deemed a pathogenic mutation if it were absent from a modestly sized control cohort and affected an evolutionarily conserved residue. These criteria incorrectly assigned pathogenicity to many variants, essentially providing an incorrect genetic diagnosis [7]. Although consensus criteria to assess the clinical relevance of a DNA variant are lacking, most Clinical Laboratory Improvement Amendments (CLIA)-approved labs judge pathogenicity based upon several different factors and now present results on a continuum from benign to pathogenic. Pathogenicity criteria are presented in Table 2. The most compelling data to support pathogenicity may be provided by the clinician through segregation analysis. Selective testing of family members, with and without disease, and the demonstration that a putative mutation is always present in an affected family member is supportive of DNA variant pathogenicity [8]. Alternatively, the absence of segregation strongly discredits the notion that a particular DNA variant causes disease. Segregation analysis is not always possible, usually due to small family size and unwillingness of affected family members to participate in genetic testing. Genetic test results should not be used in clinical practice if supportive criteria are lacking [6••].

Recently established cardiovascular genetics clinics bring together genetic counselors and cardiologists with expertise in both the management of genetic heart disease and the interpretation of genetic test results [9]. Beyond offering highly specialized care to patients with genetic cardiomyopathy, these clinics often serve as the entry point to ongoing clinical investigations that will usher in future therapeutic strategies. Referral to a cardiovascular genetics clinic should be considered when incorporating genetic data in the management of patients and families, as described below.

Current applications for genetic testing in the management of cardiomyopathy

Cascade screening

Cascade screening is the use of genetic testing to identify individuals who currently do not have cardiomyopathy, but are at future risk of disease due to harboring the family mutation (Fig. 1). Comprehensive testing of the index case (proband) is a prerequisite for cascade screening. If a mutation is identified, at-risk family members can be genotyped for the same mutation. Individuals who carry the mutation are screened on a longitudinal basis, typically with echocardiography and electrocardiography, while mutation non-carriers can be reassured and discharged from longitudinal screening. Without genotype, all first-degree family members are screened on a regular basis, which on average leads to twice the resource utilization. Cascade screening is cost effective, based upon the current cost of genetic testing, and is expected to be a cost-saving measure once probands testing falls below ~ \$200 [10]. Moreover, families assessed with genetic testing are more likely to follow up with screening recommendations [11]. The clinical rationale for clinical screening, with or without genotype, is that it enables the detection of heretofore unrecognized cardiomyopathy. These patients stand to benefit from early diagnosis through the application of evidence-based medical therapies and prevention of sudden death through selective implantation of a cardioverter-defibrillator. Both angiotensin converting enzyme inhibitors and beta blockers benefit patients with asymptomatic left ventricular systolic dysfunction, improving systolic function and delaying the development of heart failure. In a randomized trial conducted in 4,228 patients with asymptomatic left ventricular systolic dysfunction (mean LVEF 28 %), treatment with enalapril conferred a 20 % reduction in the combined endpoint of death and hospitalization for heart failure [12]. Similarly, metoprolol succinate improved indices of left ventricular function in a randomized comparison with placebo in patients with asymptomatic systolic dysfunction [13]. Sudden cardiac death risk stratification should be performed in all cardiomyopathy patients, regardless of symptomatic status [14].

An important pitfall of cascade screening is incorrect assignment of DNA variant pathogenicity. Therefore, we advise using only mutations with robust evidence to support a disease causing role to risk-stratify family members [6••]. An additional concern when genotyping asymptomatic family members is the potential to adversely impact their ability to obtain life insurance. Similar concerns have been assuaged in the health insurance and employment sectors, where federal legislation forbids genetic discrimination [15]. If performed in conjunction with a genetic counselor, cascade screening for cardiomyopathy does not have a negative impact on quality of life [16].

Diagnostic clarification

In several scenarios, genetic testing can be used to clarify ambiguous diagnosis. *Within HCM families*, the differentiation of primary HCM from other forms of hypertrophic remodeling has significant clinical consequence. For example, a patient with a family history of HCM, uncontrolled hypertension and concentric left ventricular hypertrophy

(LVH) may have either primary HCM or hypertensive heart disease [17•]. If genetic etiology was previously established in the proband, genotyping for the family mutation can help make this distinction. Athletic remodeling can create a similar dilemma that can be informed by genotyping. Genetic testing is less definitive when used to evaluate a *proband* with ambiguous diagnosis. A “positive” result, the identification of a potentially disease causing mutation, is informative; however, a negative result does not imply non-genetic disease. For example, the differential diagnosis of biventricular systolic dysfunction with heavy burden of ventricular arrhythmia includes ARVC (genetic disease) and cardiac sarcoidosis (non-genetic disease) [18]. The identification of a desmosomal mutation can be pivotal in this case; however, a negative result cannot rule out ARVC, as mutations are present in only ~ 50 % meeting task force criteria for ARVC [3].

Cardiac storage disorders, caused by mutations in the X-chromosome genes *GLA* (Fabry), *LAMP2* (Danon) and the autosomal gene *PRKAG2*, cause LVH, which may be misdiagnosed as HCM [19] or hypertensive heart disease [20]. These diseases are usually accompanied by ventricular preexcitation, and may have associated extra-cardiac features. Diagnosing storage cardiomyopathy can be accomplished with genetic testing; indeed, most CLIA-approved labs include these genes on their HCM panels. A diagnosis of Fabry is missed when associated clinical features (pre-excitation, renal failure, neuropathy, hypohidriasis, angiokeratomas) are absent or unrecognized. Diagnosis, which can also be made by identifying low alpha-galactosidase activity, is critical because enzyme replacement therapy is effective and available [21]. Cardiac Danon disease may present with associated clinical features and is characterized by a very poor prognosis [22]. Because patients are unlikely to survive beyond their third decade without advanced therapies, referral to a transplant center is a strong consideration.

Preimplantation genetic diagnosis

Propagation of genetic disease can be prevented through preimplantation genetic diagnosis (PGD). A requisite for performing PGD is the identification of a disease causing mutation in the prospective parent. The process of PGD includes in vitro fertilization, genotyping of fertilized embryos, and selective uterine implantation of only genotype-negative embryos to enable offspring free from disease [23]. PGD is clinically available, although is not universally effective and may not be reimbursed by health insurers. The general use of PGD for cardiovascular disorders has been low, and is probably best suited to families with universally malignant disease course. The use of PGD *to prevent disease* is not controversial; however, there are clear ethical concerns and legal obstacles when using PGD to select offspring gender and other traits (e.g. hair color).

Emerging applications for genetic testing in the management of cardiomyopathy

Identifying an individual patient's risk of sudden death and progression to heart failure is a major challenge in the management of cardiomyopathy. Early studies of sarcomeric HCM identified “malignant” and “benign” mutations, and suggested that risk stratification could be accomplished with genetic testing. Watkins et al. reported significantly reduced survival in patients with the Arg403Gln mutation in *MYH7* (mean age at death 33 years) compared with those with the Arg453Cys mutation (normal life expectancy) [24]. However, subsequent reports challenged the prognostic implications of these findings [25]. Moreover, allelic heterogeneity renders mutation specific prognostication unfeasible, as mutations are usually private to individual families [26]. Practically, information obtained from a careful review of family history, including arrhythmic events, progression to end-stage heart failure and thromboembolic events, is readily ascertained and will likely prove more prognostic

than information derived from a specific mutation. However, the family history should be repeatedly reviewed, as patients often have limited knowledge of the health of their relatives and repeated questioning may improve the accuracy of this data [15].

Where individual *genotype*-phenotype correlations have limited clinical utility, *gene*-phenotype correlations are present. Amongst patients with arrhythmogenic cardiomyopathy, the presence of a desmoplakin mutation may indicate a greater likelihood of left (versus right) ventricular involvement [27]. HCM patients who test positive for a sarcomere mutation are more likely to experience adverse events than patients without identifiable sarcomere mutations. In a cohort of 203 unrelated HCM patients managed at a referral center in Italy, sarcomere mutation carriers were four times more likely to experience the combined endpoint of death, stroke or progression of severe heart failure [28].

Mutation type (i.e. truncation versus missense) has emerged as a predictor of sudden death amongst patients with LMNA related dilated cardiomyopathy. In a study of 269 *LMNA* mutation carriers, the presence of a non-missense mutation (e.g. truncation) was an independent risk factor of malignant ventricular arrhythmia, along with male gender, systolic dysfunction and non-sustained VT [29]. Likewise, patients with two mutations, representing ~ 5 % of patients with genetic cardiomyopathy, appear to have a more malignant course [30].

Future applications of genetic testing for cardiomyopathy

Genetic testing has allowed the identification of a unique and intriguing patient population: individuals who have inherited a mutation known to cause cardiomyopathy, who have not yet developed overt disease [6••]. These individuals have been alternatively termed preclinical, or genotype-positive/phenotype-negative cardiomyopathy. Clinical events such as arrhythmia are extremely uncommon in preclinical disease [31]. However, recent study has revealed that preclinical mutation carriers do manifest subtle and early evidence of disease in the absence of the overt ventricular remodeling that characterizes the overt phenotype. In HCM, preclinical sarcomeric mutation carriers without LVH show evidence of impaired myocardial relaxation [32], subtle electrocardiographic abnormalities [33], myocardial fibrosis [34, 35] and abnormal energetics [36]. Similar findings in preclinical DCM have identified subtle systolic dysfunction in the absence of ventricular dilation or drop in ejection fraction [37]. These early phenotypes may represent targets for therapy, or inform the prognosis and identify which patients are at risk for developing overt disease.

Clinical trials to interrupt disease pathways in preclinical disease are ongoing, and have the potential to fundamentally change the management of genetic cardiomyopathy. If effective, overt cardiomyopathy and associated clinical outcomes could be attenuated or avoided all together. Ho and colleagues have recently conducted a trial comparing diltiazem to placebo in preclinical carriers of hypertrophic sarcomere mutation carriers (NCT00319982). This study follows a translational model where diltiazem was shown to attenuate the development of LVH when administered to HCM mice early in life, prior to the onset of hypertrophy [38]. Although results are forthcoming, changes in the intermediate phenotype of impaired relaxation was used as the outcome of interest in the human trial. It will be logistically challenging to study the effect of preventive therapies on “harder” outcomes, such as LVH development or clinical events, given the delayed penetrance and relatively good prognosis of sarcomeric HCM. In order to accrue sufficient events, large cohorts followed for long periods of time would be required.

RNA interference (RNAi) is an alternate strategy to pharmacologic prevention of genetic disease. Discovered recently as a fundamental pathway to regulate gene expression, investigators have begun leveraging RNAi to target human disease. In a mouse model of

cardiomyopathy, RNAi targeted to inhibit phospholamban restored contractile function without off-target effects on hepatic function [39]. Similar therapies to target inherited cardiomyopathy may allow for treatments targeted to an individual patient. These considerations may prove relevant to ongoing efforts to enable myocardial recovery in end-stage heart failure. Clinical trials conducted in this space have largely used endogenous stem cells to foster recovery [40]. However, the use of cells carrying a disease causing mutation may prove futile unless expression of disease alleles is managed.

Conclusion

Genetic evaluation of human cardiomyopathy has arrived. Multiple commercial labs offer testing for cardiomyopathy, and thousands of patients have been tested to date. It is anticipated that the cost of genetic testing will plummet in the coming years, enabling substantial increases in the numbers of patients tested in the future. Nevertheless, the clinical impact of genetic testing has been modest to-date, largely useful in diagnosis rather than therapy. However, ongoing research that leverages genetics to identify patients at high risk of developing disease in the future may offer effective preventative therapy. This would fundamentally change the management of these diseases, and establish genetic testing as an imperative in the evaluation of cardiomyopathy. Nevertheless, enthusiasm for genetic testing should be dampened by the realities of DNA sequence variation and the necessity to carefully review genetic data prior to determining that a patient's disease is caused by a mutation.

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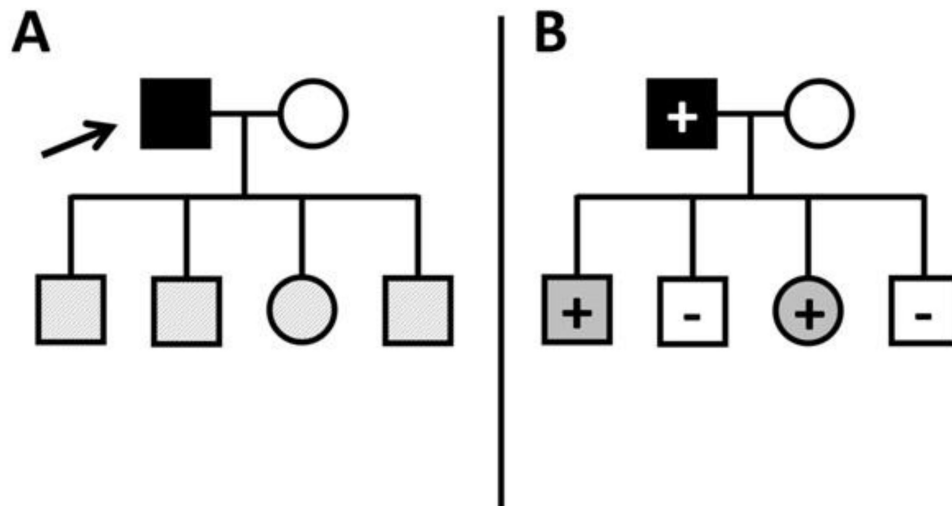


Figure 1. Genetic testing can improve the efficiency of clinical evaluations for familial cardiomyopathy

A. Without genotype, all first-degree family members (grey crosshatch) of the affected individual (arrow, black) are advised to undergo life-long serial clinical evaluations with echocardiography and electrocardiography.

B. If genotype is known, longitudinal clinical evaluations can be restricted to family members who carry the mutation (+ sign) and deferred in those without the mutation (–sign)

Table 1
Common cardiomyopathy genes*

Disease	Yield of Genetic Testing	Common Disease Genes (Class)
Hypertrophic Cardiomyopathy	~ 60 %	MYBPC3 (sarcomere) MYH7 (sarcomere) TNNT2 (sarcomere) TPM1 (sarcomere)
Dilated cardiomyopathy	~ 35 %	TTN (sarcomere) MYH7 (sarcomere) LMNA (nuclear lamina) TNNT2 (sarcomere) RBM20 (spliceosome)
Arrhythmogenic (right) ventricular cardiomyopathy	~ 50 %	PKP2 (desmosome) DSG2 (desmosome) DSP (desmosome)

* Genes selected based upon frequency and data supporting their role in disease pathogenesis. Not included are genetic causes of phenocopy (e.g. Fabry and left ventricular hypertrophy)

Table 2
Selected criteria to determine clinical impact of DNA variants*

Features of Pathogenic DNA Variants		
Criteria	Explanation	Comment
Segregation	DNA variant and clinical disease segregate together within a family. Measured by LOD score.	Greater number of segregation occurrences in family indicate greater likelihood of pathogenicity
Absence from control population		Control population should be large (> 5,000) and ethnically matched
<i>De novo</i>	DNA variant not present in either parent	Requires confirmation of paternity
Loss of function	DNA variant leads to truncated protein predicted to be nonfunctional	DNA variant may introduce premature stop codon or affect splicing
Conservation	DNA variant causes amino acid substitution at an evolutionarily conserved residue	
<i>In silico</i> analysis	Computational algorithms to predict functional affect of DNA variant	Different algorithms may provide conflicting interpretation
Features of Benign DNA Variants		
Non-segregation	DNA variant and clinical disease do not segregate together within a family	May be confounded by phenocopies (i.e. hypertensive heart disease masquerading as HCM)
Synonymous	DNA variant does not change amino acid sequence	Pathogenicity still possible via effects on splicing
Present in control population		Control population cardiac phenotype may not be available

* Criteria are applicable to novel DNA variants identified in genes known to be associated with cardiomyopathy