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MINIREVIEWS

Role of genetic testing in cardiomyopathies: A primer for cardiologists

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Abstract

Recent advances in cardiovascular genetics have transformed genetic testing into a valuable part of management of families with inherited cardiomyopathies. As novel mutations have been identified, understanding when to consider genetic testing has emerged as an important consideration in the management of these cases. Specific genetic testing has a paramount importance in the risk stratification of family members, in the prognosis of probands at higher risk of a serious phenotype expression, and finally in the identification of new mutations, all of which are discussed in this review. The indications for each type of cardiomyopathy are described, along with the limitations of genetic testing. Finally, the importance of public sharing of variants in large data sets is emphasized. The ultimate aim of this review is to present key messages about the genetic testing process in order to minimize potential harms and provide suggestions to specialized clinicians who act as a part of a multidisciplinary team in order to offer the best care to families with inherited cardiomyopathies.

Key Words: Cardiomyopathy; Genetic counselling; Genetic testing; Variant; Hereditary

Core Tip: In a considerable percentage of patients with cardiomyopathies, there is a

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genetic component. If the presence or severity of the cardiomyopathy cannot be explained by acquired causes, the genetic component should be investigated in order to reveal potential inherited forms of cardiomyopathies. The genetic testing process is also helpful to minimize potential harms and provide suggestions to specialized clinicians who act as a part of a multidisciplinary team, with the objective of offering the best care to families with inherited cardiomyopathies.

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INTRODUCTION

Cardiomyopathies represent a group of disorders of the myocardium associated with cardiac dysfunction, aggravated by arrhythmias, heart failure, and sudden cardiac death (SCD). They can be classified according to their morphological and functional phenotypes, specifically as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), and arrhythmogenic right ventricular (ARVC)/arrhythmogenic cardiomyopathy (ACM), and as unclassified forms[1]. In a considerable percentage of patients with cardiomyopathies, there is a genetic component, even for cases in which interaction with environmental factors cannot be excluded[2-5]. If the presence or severity of the cardiomyopathy cannot be explained by acquired causes, the genetic component should be investigated in order to reveal potential inherited forms of cardiomyopathies.

The continual rapid progress of molecular techniques over the past 2 decades and the related increased choices of different genetic testing options have led to a dramatic increase in our understanding of the genetic architecture of these diseases[6,7]. For better understanding of the terms used in the genetic testing process, relevant definitions are provided in Table 1. The aim of this review is to discuss the benefits of genetic testing in cardiomyopathies and the current indications in diagnosis and prognostication of probands and risk stratification for family members, in order to promote provision of optimal care for patients and their families.

GENETIC TESTING TECHNIQUES

The type and the available technologies for gene-based sequencing have been in constant evolution; turnaround times are shorter, while their cost has been dramatically decreasing. Whole blood, dried blood spots, or tissue specimens regarding post-mortem examination could serve as acceptable specimens for genetic testing. Conventionally, genetic testing by Sanger sequencing, for individual genes has been performed[8]. Due to the genetically heterogeneous nature of cardiomyopathies and the development and availability of next-generation sequencing (NGS) technique in the clinical setting, a multi-gene panel instead of individual gene-testing is now desirable practice for these diseases. Therefore, Sanger sequencing and targeted analysis is only preferable for cascade testing, when a pathogenic or likely variant has been identified in the proband. The composition of gene panels varies and some laboratories propose larger gene panels. However, increasing the number of genes in the panel also possibly increases the likelihood of identifying variants of uncertain significance. It is therefore evident that the ordering cardiologist should be aware of the benefits and limitations of specific test types in order to select the most appropriate technique[9]. Currently, testing a small specific panel of genes is usually recom-mended for each well-defined phenotype. Together, these techniques provide excellent precision and accuracy to detect single nucleotide substitutions that produce missense, nonsense, and splice site mutations and small insertion/deletions. A subset of cases with large insertion or deletion variants or other structural DNA changes, whereas the above analyses turn out negative, might benefit from copy number assays using microarray or multiplex ligation-dependent probe amplification[8,9].

Table 1 Terminology of commonly used genetics vocabulary

Term	Definition
Allele	One of several alternative versions of a particular gene
Heterozygote	An individual who has different alleles at a particular gene locus on homologous chromosomes (carrier of a single copy of the mutation)
Mutation	Any alteration in the inherited nucleic acid sequence of the genotype of an organism; a mutation considered in the context of a genetic disease usually refers to an alteration that causes a Mendelian disease
Penetrance	Proportion of individuals carrying a mutation who also express a cardiomyopathy phenotype
Genome sequencing	Sequencing of entire genome (coding and non-coding regions)
Exome sequencing	Sequencing of the coding regions (exons)
Proband or index case	Index case in the family, usually the one with the most severe phonotype
Variant	A change in the DNA sequence which may or may not be disease-causing
Pathogenicity	Process of determining whether a variant is causative or not

CURRENT RECOMMENDATIONS FOR EACH CARDIOMYOPATHY

The prevalence, inheritance pattern, genes and indications for genetic testing involved in specific cardiomyopathies are summarized in Table 2.

HCM

HCM, a disease of the sarcomere, is the most common inherited cardiomyopathy, with an autosomal-dominant type of transmission, leading to left ventricular (LV) hypertrophy and diastolic dysfunction. It is most often caused by variants in genes encoding cardiac sarcomere proteins[10]. The phenotype ranges from asymptomatic forms to SCD as the first and only manifestation, as seen especially in young athletes, all depending on the penetrance of the disease-causing mutations. Genetic testing should include not only the most common sarcomere genes [β-myosin heavy chain (MYH7); myosin-binding protein C3 (MYBPC3); troponin T2; troponin I3; tropo-myosin; actin alpha cardiac muscle 1; myosin light chain 2; myosin light protein] but also genes causing rare syndromic diseases with a HCM-phenotype [α-galactosidase (Fabry disease); protein kinase AMP-activated non-catalytic subunit gamma 2 (PRKAG2) (PRKAG2-glycogen storage disease); lysosomal-associated membrane protein 2 (Danon disease)][11,12]. In some of these diseases, such as Fabry or Danon disease, the positive genetic test result may change the clinical care of the proband, such as to involve enzyme replacement therapy or a more aggressive clinical management, respectively[12]. The diagnostic yield for the proband with a definite clinical diagnosis of HCM is approximately 30%-60%, and even higher in individuals who have severe LV hypertrophy, a known family history of HCM, or who were diagnosed at a younger age. MYBPC3 and MYH7 account for approximately 80% of all cases with positive genetic test.

DCM

About 30% of DCM cases appear to be familial in origin, isolated, or as a part of a syndrome[13-15]. The mode of inheritance is mostly autosomal dominant (AD). However, sporadic forms of DCM could be caused by non-genetic factors (*i.e.*, drugs, alcohol, viruses). Similar to HCM, the clinical severity of DCM is heterogeneous, so genetic testing is important for the surveillance of the asymptomatic genotype-positive carriers. Clinical screening combined with a three-generation pedigree of the proband are warranted in order to establish the need for genetic testing in DCM[5].

Over 100 genes have been implicated in DCM, all encoding sarcomeric and cytoskeleton proteins[16]. After the addition of titin (TTN) variants in genetic testing, the diagnoses of familial DCM increased by about 10%[17]. However, interpretation of the TTN mutations is challenging, due to the large size of the gene and the high frequency of benign variants in healthy populations. Mutations in the lamin A/C (LMNA) gene are also detected in approximately 4%-6% of familial DCM cases, causing a distinct phenotype characterized by systolic impairment together with progressive conduction disturbances and malignant arrhythmias[15]. DCM may also

Table 2 Prevalence, inheritance pattern, genes and indications for genetic testing involved in specific cardiomyopathies

Inherited CMP	Prevalence	Pattern of inheritance	Key genes	Diagnostic yield of genetic testing	Recommendation for genetic testing
HCM	1 in 500	AD	MYH7, MYBPC3, TNNT2, TNNI3, TPM1, ACTC1, MYL2, MYL3, GLA, PRKAG2, LAMP2	30%-60%	For any patient with clinical diagnosis of HCM; Familial screening with a mutation after identified in the index case
DCM	1 in 2500	AD, X-linked	DES, DMD, DSP, FLNC, LMNA, MYH7, PLN, RBM20, TNNI3, TNNT2, TTN, TPM1	20%-30%	For patients with DCM and conduction disease and/or family history of SCD; Familial screening with a mutation after identified in the index case
ARVC	1 in 2000-5000	AD, AR	DSC2, DSG2, DSP, JUP, PLN, TMEM43	50%	Familial screening with a mutation after identified in the index case
RCM	Rare	AD, AR X-linked or mitochondrial	Troponin; MYBPC3, MYL3	Unknown	Familial screening with a mutation after identified in the index case

ARVC: Arrhythmogenic right ventricular cardiomyopathy; DCM: Dilative cardiomyopathy; HCM: Hypertrophic cardiomyopathy; RCM: Restrictive cardiomyopathy; AD: Autosomal dominant; AR: Autosomal recessive; MYH7: β-myosin heavy chain; MYBPC3: Myosin-binding protein C3; TNNI3: Troponin I3; TNNT2: Troponin T2; TPM1: Tropomyosin; ACTC1: Actin alpha cardiac muscle 1; MYL2: Myosin light chain 2; MYL3: Myosin light protein; GLA: Alpha-galactosidase; PRKAG2: Protein kinase AMP-activated non-catalytic subunit gamma 2; LAMP2: Lysosomal-associated membrane protein; DES: Desmin; DMD: Dystrophin; DSP: Desmoplakin; FLNC: Filamin C; LMNA: Lamin A/C; PLN: Phospholamban; DSC2: Desmocollin 2; DSG2: Desmoglein 2; JUP: Junction plakoglobin; RBM20: RNA-binding protein 20; SCD: Sudden cardiac death; TMEM43: Transmembrane protein 43; 2; TTN: Titin.

appear as a complication of neuromuscular diseases (*e.g.*, Duchenne and Becker muscular dystrophy). As the mode of inheritance is X-linked recessive, genetic testing should be provided in mothers of probands with Duchenne or Becker, because carrier females may develop later on[18]. At this point, we should also emphasize that due to phenotype overlapping among cardiomyopathies, HCM and ACM genes are included in DCM panels.

ACM, including right ventricular

ARVC is currently considered as a subtype of the broader group of ACM, with fibro-fatty replacement of the ventricular myocytes[19]. Clinical manifestations may vary with age and stage of disease, from asymptomatic but at-risk for SCD to end-stage heart failure with symptomatic arrhythmias. It is considered familial, with AD inheritance; although, there are recessive forms (*e.g.*, Naxos disease, Carvajal syndrome)[20]. Initially, it was identified as a disease caused by mutations in genes encoding desmosomal proteins. A pathogenic variant has been detected in up to 50% of cases referred for genetic testing who meet the 2010 Task Force criteria[3]. Mutations in the plakophilin-2 gene account for 20%-30% of cases, while variants in four other desmosomal genes (desmocollin 2; desmoglein 2; desmoplakin; junction plakoglobin) have also been detected. Changes in DNA sequence of the abovementioned genes should be cautiously approached, since different benign variants may present frequently in unaffected control populations[20].

Further genetic subtypes have been described recently; so, under the broad term of arrhythmogenic cardiomyopathies, additional genes should be included in the genetic testing, such as transmembrane protein 43, LMNA, filamin C, desmin, RNA-binding protein 20, phospholamban (PLN) and TTN genes. According to the revised Task Force criteria for the diagnosis of ARVC/ACM, for a definite diagnosis, two major criteria or one major and two minor criteria, or four minor criteria from different categories are needed. The presence of a disease-causing mutation is considered as a major criterion. However, in order to avoid confusing results, if the patient shows only one minor criterion from the revised Task Force Criteria, then genetic testing should not be recommended[3]. It is noteworthy that desmosome gene mutations have also been identified in patients diagnosed with DCM.

RCM

RCM is a rare form of cardiomyopathy, with a heterogeneous phenotype. Multiple causes have been identified, including infiltrative storage, non-infiltrative and endomyocardial diseases, many of which are associated with specific genes[21]. The

most frequent variants that have been found in RCM cases are in genes known to cause HCM. Therefore, genetic testing for RCM should include HCM genes[22].

IMPORTANCE OF FAMILY HISTORY IN THE PROCESS OF GENETIC TESTING

Irrespective of the type of cardiomyopathy, thorough comprehension of the proband's family history with an at least three-generation family pedigree and counselling should precede genetic testing[23]. Therefore, the family history is of paramount importance and should not be overlooked in clinical practice. Specifically, it reveals the phenotype of each member, the pattern of inheritance (AD, autosomal recessive, X-linked and maternal mitochondrial conditions) and enables the clinicians to provide preliminary recommendations for clinical surveillance[6,24]. Importantly, it also helps genetic counsellors to discuss the process of genetic testing with the proband and the family members, including providing realistic expectations of the findings and to develop a relationship of trust. Effective communication and psychological support are key points. Pre-genetic counselling constitutes an important clinical part of the medical management of such cases[4,25].

VARIANT INTERPRETATION AND RECLASSIFICATION

The most challenging aspect of the genetic testing process is the interpretation of results. According to the Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology, each variant should be classified according to specific criteria in one of the following categories: Benign, likely benign, variant of uncertain significance (VUS), likely pathogenic, or pathogenic (Table 3)[26]. Causality is based on various criteria, such as population frequency and type of identified variant (*i.e.*, missense, nonsense, *de novo*, truncating splice site); information of segregation in a pedigree and *in silico* tools are also used. It is important to bear in mind that in order to avoid the vast amount of uncertainty, rather than choosing a binary 'yes' or 'no' outcome, it is preferable to gather and weigh-up sufficient lines of evidence. A key step in this direction is the public sharing of important variant information among laboratories, such as through scientific repositories (*e.g.*, ClinVar) and the creation of large reference datasets[27]. Another important issue is the periodic reclassification of variants; although, guidelines on how this can be performed feasibly are lacking[28]. Certainly, the latest technologic advancements of NGS, together with bioinformatics software, allow accurate and rapid high-output sequencing of the human genome[29]. And, in the real world, the ability to efficiently sequence coding and non-coding regions has led to the production of multigene panels used in clinical practice currently.

At this point, we should also note that the complexity of cardiomyopathies and the difficulties in defining a specific phenotype according to genetic causes present new challenges for cardiologists who manage these patients singlehandedly. Therefore, a multidisciplinary team is required for genetic counselling and testing, as well as psychological support. This can be achieved through trained healthcare providers, in order to help individuals deal with the psychological, social, professional, ethical and legal implications of a genetic disease[30].

SPECIFIC BENEFITS OF GENETIC TESTING

Identification of undiagnosed family members

The principal advantage of the process of genetic testing is the detection of family members of the proband who have inherited the causal variant of the gene and are at-risk of developing the clinical phenotype of each cardiomyopathy. The importance of this procedure is huge, considering that life-threatening arrhythmias or SCD can be the first manifestation of a cardiomyopathy. Thereafter, only genotype-positive individuals need periodic monitoring instead of all first-degree relatives[5]. The importance of familial screening is better established in HCM and ARVC, where the yield of genetic testing is higher, and gives the opportunity for better planning to assess and address the need for implantable cardioverter-defibrillator (ICD) devices in genotype-

Table 3 Definitions of the variant classifications

Variant	Definition
Pathogenic	Variant is disease-causing with > 99% confidence; Cascade genetic testing should be offered to family members
Likely pathogenic	Variant is disease-causing with > 90%-95% confidence; Cascade genetic testing should be offered to family members
VUS	Variant is considered uncertain with an unknown effect on clinical phenotype, as there is insufficient or conflicting evidence for pathogenicity; Cascade genetic testing cannot be offered to family members
Likely benign	Variant is probably not disease-causing; Cascade genetic testing should not be offered to family members
Benign	Variant is not disease-causing; Cascade genetic testing should be offered to family members

VUS: Variant of uncertain significance.

positive carriers.

Regarding SCD in young people, almost 30% of cases are caused by a non-diagnosed type of cardiomyopathy[31]. Genetic testing in post-mortem samples could enhance the likelihood of finding a disease-causing variant and performing subsequent genetic screening of family members. Indeed, in a clinical screening in 198 cases of unexplained SCD in people below 35 years of age, five families suffering from inherited cardiomyopathies were detected; whereas, 27% of the cases had a definite or likely disease-causing mutation[32]. Therefore, according to European Society of Cardiology (ESC) guidelines, targeted post-mortem genetic analysis of potentially disease-causing genes should be considered for victims in whom a specific inheritable or cardiomyopathy is suspected[33].

Prognostic role

Several studies have proven that genotype status itself is associated with worse outcomes in HCM[34,35]. Sarcomere protein mutations in HCM have been found to be associated with increased rates of cardiovascular and SCD-related mortality[34]. In 628 HCM patients with a 12-year follow-up, positive genetic test result was identified as an independent prognostic factor for mortality in SCD and heart failure as well as all-cause mortality for the carrier, after adjustment for established risk factors[36]. In DCM, the approximately 5%-10% of probands with mutations in the LMNA gene are the best characterized, as LMNA variants manifest early-onset atrial arrhythmias and early development of conduction disturbances, coupled with a higher risk of SCD, often with only LV systolic impairment[37]. According to ESC guidelines, an ICD implantation should be considered in patients with DCM along with a confirmed disease-causing LMNA mutation and clinical risk factors, such as a non-sustained ventricular tachycardia, LV ejection fraction below 45% at first evaluation, male sex, and non-missense mutations[33].

Regarding ARVC, the prognostic role of genetic testing is not fully realized. Although probands with ARVC and known causal variants have been reported to develop ventricular arrhythmias approximately 4 years earlier than patients without a known mutation, no difference in mortality was detected in that study[38]. In another study of 105 probands with known ARVC-causal variants, the identification of a variant was found to be less important for predicting risk of life-threating arrhythmia or SCD than other factors, like sex and repolarization abnormalities in electrocardiogram or LV dysfunction[39]. Mutations in the PLN gene are also related to a poorer prognosis[40].

NGS analysis has allowed widespread identification of novel disease-causing genetic mutations[41]. Open availability of the ClinVar and ExAC databases in recent years has helped laboratories and clinicians to determine the possible pathogenicity of new detected variants. As a result, previously characterized genetic variants have been reclassified[42]. Genetic testing may identify predisposition for cardiomyopathies with unclear pathophysiological mechanisms; for example, risk of peripartum cardiomyopathy or anthracycline-induced cardiomyopathy may be identifiable by genetic testing. In patients with peripartum cardiomyopathy, in particular, and carrying mutations in the TTN gene, LV ejection fraction remains significantly lower compared to patients without this mutation[43]. Similarly, there is emerging evidence that a genetic predisposition may also be involved in anthracycline-induced cardiomyopathy [44,45]. Unfortunately, the current evidence is not sufficient to alter management decisions about the use of anthracycline but could lead to a personalized medicine

approach in patients carrying specific mutations[46].

Prenatal genetic counselling

Prenatal genetic counselling is helpful in couples at risk of transmitting a genetic condition to their offspring. Through this process, a certified genetic counsellor explains the risk of transmission of disease, the impact of the disease on an affected child, as well as the benefits and limitations of all the available reproductive options. These options include *in vitro* fertilization with preimplantation genetic diagnosis, prenatal genetic screening, and postnatal genetic testing. The benefits and potential harms can be discussed for each of these options, such that the individual or couple can make a fully informed decision[12].

BARRIERS IN GENETIC TESTING

Despite the novelties in genetic techniques, there are still limitations in performing genetic testing for every diagnosed cardiomyopathy. Genetic testing seems to be of little to no value in low-yield cases with unclear inheritance pattern[36-38,47]; for this reason, the guidelines discourage genetic testing in isolated cases of idiopathic DCM where no evidence of inheritance exists[4,5]. In a study of 102 patients with idiopathic DCM, a disease-causing mutation was identified in only 10, whereas the clinical management was changed for only 1 patient, who received an ICD[47]. Unfortunately, even in disease where the yield of genetic testing is high, such as in HCM, when more possible genes were added, few additional causal variants were identified[48]. Another limitation in performing genetic testing when there is no clear clinical indication is the finding of a VUS. VUS may mislead clinicians, as it can neither confirm a genetic diagnosis nor exclude the need for familial surveillance[12]. The best practice in order to avoid an uncertain result is the performance of genetic testing after a thorough evaluation of the clinical case and a multidisciplinary management in pre-genetic counselling. Hence, any result from a genetic test can be further investigated at the research level[6,12].

CONCLUSION

At present, the mainstay of genetic testing in inherited cardiomyopathies is the identification of family members who have inherited the same causal mutation with the proband, which is important in terms of clinical decision-making. On the other hand, when the mutation is not detected in family members, anxiety and unnecessary clinical screening are avoided. This procedure is more helpful in cardiomyopathies where the yield of a positive genetic result is higher, such as HCM and ARVC. However, recent studies have provided more evidence on the genetic predisposition in specific cardiomyopathies and suggested a prognostic component when pathogenic variants are found.

Despite the progress in genetic techniques, there are currently well-documented limitations of cardiac genetic testing. Therefore, the role of family history should not be downgraded when the utility of genetic testing is questioned. A specialized multidisciplinary clinic incorporating cardiologists and genetic counsellors along with a move to a more precision-based approach seems to be the ideal model of management. Last but not least, focus should be given to teamwork of worldwide research groups in order to develop large databases that may elucidate the complexity of underlying genetics in inherited cardiomyopathies.

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