

Genetics in Cardiomyopathies – Genetic Tests Decoded for the Clinical Cardiologist

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Abstract

The era of personalized medicine emphasizes the provision of health care guided by the cardiomyopathy phenotypes described, their interpretation based on genotype, and genetic counseling. The identification of high-risk cardiomyopathy subtypes and the diagnosis of rare etiologies with potential therapies cannot be neglected. Genetic sequencing of these patients, in addition to advances in cardiac imaging techniques, has indicated a new perspective for these concepts, and consequently possible new classifications of cardiomyopathies and new clinical practices. The interaction between multidisciplinary teams and cardiology genetic experts is fundamental for a more appropriate management of gene variants, especially variants of uncertain significance that may be relevant in the expression of cardiomyopathies. This article helps cardiologists in the ordering of genetic tests and their indications, provides information about pathogenicity of variants and emphasizes family screening, challenges that may be overcome in daily practice.

Introduction

Increased access to new generation sequencing (NGS) has led to the adoption of new routine clinical measures by the clinical cardiologist. Genetic testing in family screening, the definition of subtypes of dilated cardiomyopathy (CMP) of high arrhythmic risk, and the diagnosis of rare etiologies with potential treatments (e.g., cardiac amyloidosis) are some of the genetic applications in the management of CMP that cannot be neglected. If on the one hand, recommendations on molecular investigation in patients with heart diseases have been adopted, on the other hand, the complexity of genetics has raised questions about its use.

Keywords

Cardiomyopathies; Genetics; NGS; Familial Screening.

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The objective of this review article is to help cardiologists in the applicability of genetics in CMPs, including key concepts for genetic test ordering and indications, family screening, result interpretation and clinical decision making.

Genetic CMPs

Genetic CMPs are a heterogeneous group of diseases that affect cardiac muscle, mainly caused by changes in genes that encode sarcomeric, desmosomal, cytoskeletal proteins, among others.^{1,2} Table 1 describes different forms of genetic CMPs with respective prevalence. Although the diagnostic criteria of CMPs have been well established in the literature,³⁻⁷ genetic sequencing of these patients and advances in cardiac imaging techniques have pointed to a new perspective on these

Table 1 – Prevalence, genes and performance of genetic test in cardiomyopathies

Cardiomyopathy	Prevalence	Prioritized genes associated with the disease**	% of positive cases****
HCM	1/500	MYH7, MYBPC3, TNNT2, TNNC1, TNNI3, TPM1, MYL2, MYL3, ACTC1, FHOD3, CSRP3, JPH2, PLN, TTR, PRKAG2, LAMP2, GLA.	60%
MCD	1/250 to 1/2500	TTN, LMNA, BAG3, DES, DMD, TAZ, RBM20, SCN5A, FLNC. Include the genes associated with HCM and ACM	40%
MCA	1/2.000 to 1/5.000	DES, DSC2, DSG2, DSP, JUP, PKP2, PLN, RYR2, TMEM43. Include the genes associated with DCM	50%
MCNC	Unknown	Evaluate the genes associated with HCM and DCM	Unknown
MCR	Unknown	Evaluate the genes associated with HCM	60%

HCM: hypertrophic cardiomyopathy; DCM: dilated cardiomyopathy; ACM: arrhythmogenic cardiomyopathy, non-compaction cardiomyopathy; RCM: restrictive cardiomyopathy. **Prioritized genes associated with each cardiomyopathy. Adapted from guidelines.^{19,36} **** Maximum efficiency of genetic testing applied in cohorts of index-cases (probands).^{36,37}

concepts. Since the 1994 MOGE(S) classification (Figure 1), extracardiac manifestations, family heritage and genetic etiology have been highlighted in the definitions CMPs.⁸ Recent clinical trials with cohort of patients carriers of specific variants have shed light on CMP subtypes, which will probably allow new classifications and clinical practices.⁹ Examples include specific treatments, such as tafamidis in cardia amyloidosis and genome editing approaches with CRISPR/Cas9 for Duchenne muscular dystrophy. Similarly, arrhythmogenic CMP, which is classically described as right ventricular dysplasia, has been revealed to share common etiologies with dilated CMP, particularly arrhythmogenic right ventricular CMP.^{9,10}

The expression of genetic CMPs varies among individuals, even among family members affected by the same genetic variant, which makes risk stratification of these patients a challenge. Penetrance is related to the absence or presence of any clinical manifestation known to be determined by a gene and is given as percentage as a function of age. In CMPs, penetrance of most genes is incomplete, *i.e.*, less than 100% of carriers manifest the disease, and seems to increase with age. However, depending on the genotype, some etiologies may have complete penetrance at young ages.¹³⁻¹⁶ Current prevalence estimates of hypertrophic CMP and dilated CMP described in Table 1 are based on cohorts of patients with a

NOTATION	M MORPHO-FUNCTIONAL PHENOTYPE	O ORGAN/SYSTEM INVOLVEMENT	G GENETIC INHERITANCE PATTERN	E ETIOLOGY	S STAGE
CHARACTERISTICS	Proband's cardiomyopathy (CM) diagnosis (DCM, HCM, RCM, ARVC/D, LVNC)	Clinical history and evaluation Organ involvement: Extracardiac organs/tissues Multidisciplinary evaluation according per clinical needs or diagnostic hypothesis	Aconselhamento com árvore genealógica Clinical family screening Affected, asymptomatic relative unaware of the disease Relatives with ECG and/or Echo abnormalities Healthy family members with normal ECG and echo	Genetic testing in the proband Positive Negative New tests novel genes Regular monitoring in relatives	Functional status ACC/AHA, NYHA
SUBSCRIPT	D Dilated H Hypertrophic R Restrictive R EMF Endomyocardial fibrosis LV left ventricle RV right ventricle RLV biventricular A ARVC M = major m = minor c = category LV left ventricle RV right ventricle RLV biventricular NC LVNC E Early, with type in parentheses NS Nonspecific Phenotype Na Information non available O Unaffected*	H Heart LV : left ventricle RV : right ventricle RLV : biventricular M Muscle (skeletal) N Nervous C Cutaneous E Eye, Ocular A Auditory K Kidney G Gastrointestinal Li Liver Lu Pulmonar S Skeletal O Absence of organ/system involvement*, e.g. in family members who are healthy mutation carriers; the mutation is specified in E and inheritance in G	N Family history negative U Family history unknown AD Autosomal dominant AR Autosomal recessive XLD X-linked dominant XLR X-linked recessive M Matrilineal O Family history not investigated* Under Inheritance still undetermined S Phenotypically Sporadic (apparent or real)	G Genetic cause OC Obligate carrier ONC Obligate non-carrier DN De novo Neg Genetic test negative for the known familial mutation N Genetic defect not identified O No genetic test, any reason* G-A-TTR Genetic amyloidosis G-HFE Hemochromatosis Non-genetic etiologies: M Myocarditis V Viral infection (add the virus identified in affected heart) AI Autoimmune/immune-mediated; suspected (AI-S), proven (AI-P) A Amyloidosis (add type: A-K, A-L, A-SAA) I Infectious, non viral (add the infectious agent) T Toxicity (add cause/drug) EO Hypereosinophilic heart disease O Other	ACC-AHA stage represented as letter A, B, C, D NA Not applicable NU Not used followed by NYHA class represented as Roman numeral I, II, III, IV

Figure 1 – MOGES classification of cardiomyopathies. Arbustini et al., 20148 HCM: hypertrophic cardiomyopathy; DCM: dilated cardiomyopathy; RCM: restrictive cardiomyopathy; ARVC: arrhythmogenic right ventricular cardiomyopathy; LVNC: left ventricle non compaction cardiomyopathy; ECG: electrocardiogram; ECHO: echocardiogram.

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definite diagnosis of the disease and probably underestimate the actual prevalence of the disease. This is important information as many carriers of causal genetic variants, at risk of cardiovascular complications, have mild manifestations that do not establish the diagnosis and/or are of late onset.¹⁷

Ordering a gene panel testing

In cardiology, genetic investigation in a family starts with a gene panel (NGS panel), preferably of a patient with a clear diagnosis of CMP, who we call “index-case” (or proband).^{18,19} The NGS panel should include all prioritized genes, associated with the CMO observed in the index-case, recommended by the guidelines (Table 1).

Prioritized genes are genes with several variants, that cosegregate with the disease in different families and that have a causal relationship with the disease, as corroborated by functional studies (*in vitro* or animal models).²⁰⁻²² In these genes, most of the genetic variants classified as either pathogenic or probably pathogenic are identified, facilitating the diagnosis and the clinical decision making. Other genes that may be included in the panel are called secondary or candidate genes; these are either ultrarare causes or their association with the disease is still uncertain.^{23,24} Thus, the level of evidence of their pathogenic potential is lower, resulting in a more frequent identification of more genetic variants of uncertain significance, which precludes molecular diagnosis of the disease.^{24,25} It is also worth pointing out that most of the genetic variants described are missense, and major deletions or duplications correspond to a low number of cases (1-3%).^{24,26} Major deletions or duplications was initially analyzed by multiplex ligation-dependent probe amplification (MLPA); however, nowadays, these genetic variants have been assessed by NGS panels by analysis of the copy number variation.²⁶

In cases when the gene panel testing cannot be ordered for a patient with suspected CMP due to the clinical findings and family history, the cardiologist may opt for the clinical examination of first-degree relatives; if a family member with a well-established diagnosis is found, the gene panel may then be ordered.¹⁸ Specialized centers have used successful strategies of risk communications by letters, electronic applications, and telephone calls to raise families’ awareness about the importance of cardiological evaluation and genetic screening.²⁷⁻³⁰ It is recommended that risk communication be used in a context of genetic counseling.^{18,31-33}

So far, the availability of gene panels in the context of the Brazilian unified health system has been limited to specific research projects carried out in public university hospitals. In addition, there is no obligation for the private healthcare system to cover gene panel tests,^{3,4} which we believe to change in coming years with the emergence of sufficient scientific evidence and the clinical, family and social impact of sudden death and heart failure.

Indications of genetic studies

Although there are particularities in the indication of genetic tests among the different types of CMPs, a trend can be seen.¹⁹ Genetic CMPs have a key familial or hereditary character,

and hence the genetic examination is always recommended, especially when the benefit of familial screening is clear.^{19,35,36} The performance of the genetic test (percentage of cases in which a causal variant is identified) is variable among the CMPs (Table 1).^{37,38} It may be higher in individuals younger than 45 years old, in those with a more pronounced phenotype and in individuals with a positive family history of CMP or sudden cardiac death.³⁹

In Brazil, there has been a trend of cardiologists to order the genetic testing especially in borderline cases aiming at more accurate diagnosis and risk stratification. In these situations of uncertainty, although there is an indication for molecular analysis, its strength of recommendation is lower.³⁵ Since these are borderline cases, the number of negative results is, as expected, lower, with no identification of a causal genetic variant. On the other hand, in right ventricular arrhythmogenic CMP, genetics plays an important role as a diagnostic criterion since in some cases the clinical findings are not definite for the diagnosis.¹⁰

In hypertrophic CMP, the use of genetics as a prognostic marker has not been consolidated, except in the identification of rare genotypes associated with high risk.^{35,40,41} Maybe because of it, the European guidelines on hypertrophic CMP suggest that genetic tests should be conducted at laboratories with expertise in the interpretation of genetic variants.³⁵ On the other hand, risk stratification in dilated CMP has become a well-established indication in genetic studies. In dilated CMPs, the objective of genetic test is to identify etiologies with significant arrhythmia potential, in which variants in the lamin, filamin-C, or desmoplakin genes would be found.¹⁰ For patients affected by variants in these genes, an early implantation of a cardioverter defibrillator is recommended if specific clinical markers are present.^{10,36}

Special attention should be given to patients with genetic variants, likely to have syndromic presentations. Genetic testing may be applied in cases of extracardiac or even cardiac manifestations, known as red flags (Figure 2), with suggest a syndromic CMP.^{35,42} In hypertrophic CMP, in which syndromic presentations are also known as phenocopies, the molecular diagnosis may reveal the need for a multidisciplinary management due to possible involvement of other organs. Genes related to mitochondriopathies, malformation syndromes (e.g. RASopathies) and deposition diseases, among other inborn errors of metabolism have been associated with phenotypes that include hypertrophic forms of CMPs.³⁵ This is also true for different syndromes in dilated CMP, especially neuromuscular diseases.⁴² Cardiologists should be aware that syndromic phenotypes are not always evident, and many of these patients reach adult age without an appropriate diagnosis. In some cases, cardiac manifestations may be the initial presentation of the disease, with need for implementing a multidisciplinary follow-up.

Finally, the genetic test is indicated for patients who had sudden cardiac death (identified in the autopsy reports or resuscitated patients).³⁶ The definition of a genetic etiology allows to identify the cause, perform the family screening to identify or exclude family members at risk for the disease.^{10,35,36} In Brazil, an autopsy investigation of sudden cardiac death can be considered an exception, let alone

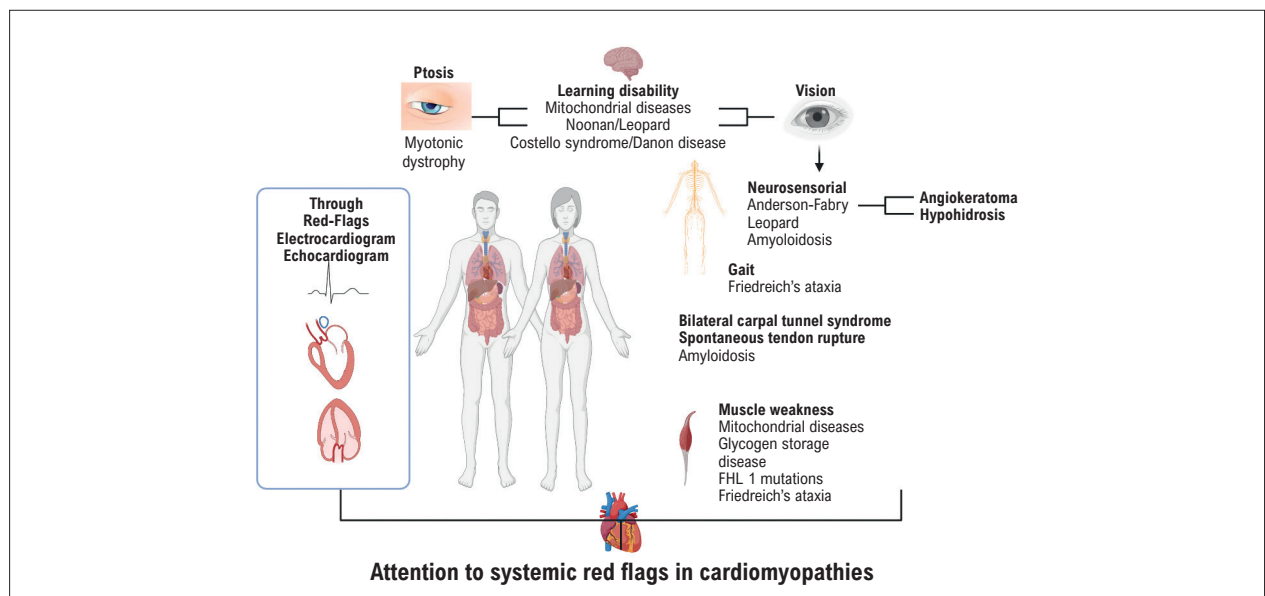


Figure 2 – Systemic red flags in cardiomyopathies.

a post-mortem molecular analysis. Thus, in case of deaths probably due to a cardiovascular event, the physician may perform the clinical assessment of the family and initiate the genetic investigation, preferably by a NGS of the affected relative. When there is no family member affected, the indication for the genetic test may be controversial and discussed by a group of experts.

Pathogenicity of variants and family screening

Genetic variants (a better term than “mutation”) can be classified as pathogenic, likely pathogenic, variant of uncertain significance (VUS) and benign. This classification is based on several criteria defined by international consensuses,⁴² although many genes in CMPs have nuances for the classification of their variants.^{43–48} The classification of genetic variants is basically determined by the existing level of evidence, considering the description of affected families (causal relationship) *versus* their prevalence in the generally healthy population (benign variant). Molecular aspects and functional studies can also suggest deleterious effects (or not) of specific variants, reinforcing their pathogenetic profile.⁴²

When a pathogenic or a likely pathogenic variant is identified in the index-case of a family, molecular diagnosis and family screening should be performed.^{18,19} While genetic analysis is conducted by NGS panels that simultaneously evaluates a series of genes associated with a certain type of CMP, in family screening, the family members are genotyped exclusively for the familial variant identified by the Sanger sequencing.¹⁹ If a family member carrying the respective variant is identified, periodic monitoring and risk stratification of this individual is recommended. Relatives identified as non-carriers should be discharged from the follow-up.^{19,35} All first-degree relatives of a carrier should be assessed, which would be called the cascade screening. In our routine, it is

not uncommon that the cardiologist ignores the hereditary aspect of genetic CMPs and does not even perform a clinical assessment of the family members when a genetic study is not available.

Clinicians should be careful in obtaining the family history, which may be unspecific. Patients’ reports of relatives who “died from infarction”, relatives using pacemakers or “with arrhythmias” should be valued, as well as cases of transplantation or reports of signs of heart failure (HF).¹⁸ Although ischemic heart disease is known as the main cause of sudden death and HF, one should bear in mind that probably past generations have not undergone detailed clinical examinations compared with today, and a proper diagnosis is hampered by inaccurate reports. In addition, other clinical information should be valued when syndromic forms of CMP may be suspected, including neurological signs and renal failure.¹⁸ The variable expressivity of syndromic CMPs could determine a predominantly non-cardiac presentation in a family member who would also have a high cardiovascular risk. The construction of a genogram of three or more generations would allow better visualization of the members at risk and implementation of a more appropriate management at long term. In fact, the construction of a genealogical tree is currently recommended and may increase the diagnosis of CMP.^{18,49}

Although most of genetic etiologies of CMP are autosomal dominant, X-linked or even *de novo* (not-inherited variants) may also be identified.¹⁸ This information may guide the familial screening, by selecting relatives that should or should not be genotyped or clinically assessed, which would optimize the clinical management and costs of genetic testing in the family members.

Questions have been raised regarding the use of VUSs in clinical practice.^{50–52} These variants are so classified when their level of evidence are insufficient to confirm or exclude a causal

relationship.⁴² In this case, familial screening with predictive purposes cannot be applied, neither can a molecular diagnosis be established.^{19,50} When a VUS is identified in a prioritized gene, a familial cosegregation analysis of the variant can be performed in the presence of an informative family (multiple individuals with the diagnosis of the disease).³⁵ Multidisciplinary teams, specialized in genetic cardiology, have provided better communication and management of VUSs as compared to cardiologists alone,⁵² and the clinical significance of these variants may be relevant in the expression of CMP.⁵³ The classification of genetic variants may change over time with the increase of knowledge and of sequenced patients. Thus, patients with VUS may be assessed periodically to update the classification of the variants.^{51,54} It is also worth pointing out that the presence of a VUS in a gene associated with syndromic presentation may guide the propedeutics towards an extracardiac evaluation to search for a genotype-phenotype correlation that may elucidate the causal role of the variant, as reported, for example, in Fabry disease.⁵⁵

In family management, it is recommended that only children older than 10 years be genotyped.¹⁹ An exception would be families including pediatric patients affected. In some cases, the possibility of early treatment, as the enzyme replacement therapy in Fabry disease, the benefits in identifying younger carriers outweigh eventual ethical precautions.⁵⁶

Family genetic testing should be conducted using a multidisciplinary counseling approach by a heart team including a geneticist.⁵⁷ In Brazil, the geneticist is the only professional able to perform this testing, while in other countries, there is an organized, extensive formation to obtain the title of genetic counselor. Genetic counseling would allow a better approach and communication to patients about risks, pre- and post-test genetic counseling, investigation of syndromic forms and other heritage-related issues.^{57,58} This would facilitate the application of genetics in cardiology, similarly to what observed with cancer genetic counseling in oncology in Brazil.

Large gene panels

A cardiologist may ask: why are there large gene panels including so many genes available in the market if the number of prioritized genes is relatively small? This could be explained by different reasons.

Prioritized genes are mostly associated with non-syndromic forms of CMP. However, in different types of CMP, many genes associated with ultra-rare syndromic forms are identified, and many of them are included in these large panels, as occurs with NGS in hypertrophic CMP for example. In case of a suspected syndromic form, a large panel could be considered.¹⁹ In our practice, there is no large gene panel, available in the market, that exhaustively includes all genes possibly associated with the syndromic forms of CMP. An example are the RASopathies, a group of multisystemic syndromes related to the Ras-MAPK signaling pathway, that may be present in hypertrophic CMP and/or congenital heart diseases, in which there are currently nearly 30 genes implicated. The inclusion of RASopathy-associated genes to hypertrophic CMP panels has been shown to increase clinical diagnoses.⁵⁹ However, none of the large gene panels available today includes all genes described in the different syndromes associated with Ras-MAPK signaling pathway.

In situations like this or in case of suspected ultra-rare etiologies, such as mitochondrial diseases or inborn metabolic disorders, the pathophysiology of CMP may be related to a large list of genes. In these cases, especially in pediatric cardiology, the whole-exome sequencing may be a viable option,^{60,61} with possible inclusion in the health care coverage established by the national health agency in Brazil. In addition, large gene panels can be used when the phenotype of the index-case is overlapped by different forms of CMP or when different types of the disease are manifested in the same family (e.g., hypertrophic CMP and non-compaction CMP). These are known as comprehensive CMP gene panels, that would be appropriately used in these situations. Also, there are comprehensive panels that, in addition to the CMP-associated genes, include those associated with channelopathies, or even aortopathies. Genetic studies may be ordered when there is no suspicion of the cause of sudden death in the family, or when cardiac arrhythmias or conduction disorder may be the first manifestation of a genetic CMP.⁶²

Conclusions

Genetic is a useful tool in the diagnosis, risk stratification and family management in CMPs. The guidelines provide established recommendations regarding its application, and recent studies have indicated a definition of the CMP subtypes that imply new treatment opportunities, greater assertiveness in risk stratification and will possibly lead to new classifications in this scenario. Despite its complexity, the challenge of the use of genetics may be overcome in daily practice, and multidisciplinary genetic counseling is recommended to optimize its use and the care provided.

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