

State of the Art Review



Genetics of Cardiomyopathy: Clinical and Mechanistic Implications for Heart Failure

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Conflict of Interest

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The data generated in this study is available from the corresponding author(s) upon reasonable request.

AUTHOR'S SUMMARY

Genetic cardiomyopathies are an important cause of sudden cardiac death across all age groups. Genetic testing in heart failure clinics is useful for family screening and providing individual prognostic insight. Obtaining a family history of at least three generations, including the creation of a pedigree, is recommended for all patients with primary cardiomyopathy. Additionally, when appropriate, consultation with a genetic counsellor can aid in the success of a genetic evaluation. Clinical screening should be performed on all first-degree relatives of patients with genetic cardiomyopathy.

ABSTRACT

Genetics has played an important role in the understanding of different cardiomyopathies, and the field of heart failure (HF) genetics is progressing rapidly. Much research has also focused on distinguishing markers of risk in patients with cardiomyopathy using genetic testing. While these efforts currently remain incomplete, new genomic technologies and analytical strategies provide promising opportunities to further explore the genetic architecture of cardiomyopathies, afford insight into the early manifestations of cardiomyopathy, and help define the molecular pathophysiological basis for cardiac remodeling. Cardiovascular physicians should be fully aware of the utility and potential pitfalls of incorporating genetic test results into pre-emptive treatment strategies for patients in the preliminary stages of HF. Future work will need to be directed towards elucidating the biological mechanisms of both rare and common gene variants and environmental determinants of plasticity in the genotype-phenotype relationship. This future research should aim to further our ability to identify, diagnose, and treat disorders that cause HF and sudden cardiac death in young patients, as well as prioritize improving our ability to stratify the risk for these patients prior to the onset of the more severe consequences of their disease.

Keywords: Cardiomyopathy; Hypertrophic cardiomyopathy; Dilated cardiomyopathy; Genetics; Heart failure

Author Contributions

Conceptualization: Kim KH, Pereira NL; Writing - original draft: Kim KH; Writing - review & editing: Pereira NL.

INTRODUCTION

Cardiomyopathies constitute a diverse group of diseases that are the leading cause of heart failure (HF) and are defined by structural or functional disorders of myocardium in the absence of secondary causes of HF such as hypertension, valvular heart disease, ischemic heart disease, or congenital heart disease that are sufficient to explain the observed myocardial abnormality.¹⁻³⁾ Over the last quarter-century, an incredible amount of progress has been made in elucidating the genetic components of cardiomyopathy. The clinical translation of this research through genetic testing makes it possible to more precisely classify affected patients according to molecular etiology and identify individuals with no symptoms of disease who maybe at increased risk of developing cardiomyopathy. This progress allows insights into the early manifestations of cardiomyopathy and could help define the molecular pathophysiological basis for cardiac remodeling. New genomic tools and analytic methodologies provide unprecedented opportunities to thoroughly examine the genetic architecture of cardiomyopathies, even though these efforts are yet incomplete. Such data suggest that gaining a better understanding of variant gene-specific pathophysiology may result in the identification of novel therapeutic targets and herald the dawn of precision medicine. Cardiomyopathies may present late in their course with advanced disease, including HF, arrhythmias and sudden cardiac death. Therefore, the rationale for identifying genetic risk is compelling, as it allows those who are at risk to undergo interval screening to detect the phenotype's earliest manifestations. The early detection of a phenotype allows for earlier interventions,⁴⁾ such as lifestyle modifications; medication to slow or stop the progression of the disease or to prevent thromboembolism; and procedures, drugs, or devices to reduce the risk of sudden cardiac death. Individuals at-risk, whether affected but asymptomatic or clinically unaffected, may benefit from genetic counseling and reproductive decision-making if they are identified. Genetic testing is recommended for patients with hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), cardiomyopathy with other extra cardiac manifestations, and left ventricular noncompaction (LVNC).⁵⁾ Substantial genetic overlap has become evident between these cardiomyopathies; both genetic and phenotypic overlap among them has been observed. Careful evaluation of family history, phenotypic screening, and genetic counseling are recommended for relatives of patients with genetically confirmed inherited cardiomyopathies. We intend to provide clinicians with a focused, evidence-based guide to the use of genetic testing to aid the management of inherited cardiomyopathies in this review.

THE NECESSARY TERMINOLOGY FOR CLINICIANS

The terms “mutation” and “polymorphism,” which are widely misused interchangeably, frequently cause confusion due to inaccurate assumptions regarding their pathogenic and benign effects, respectively. Thus, it is recommended that both terms be replaced by the term “variant.” The following modifiers have been described by the American College of Medical Genetics (ACMG) and Genomics and the Association for Molecular Pathology⁶⁾:

- Pathogenic variant (PV): A genetic alteration with sufficient evidence to contribute to the development of disease based on population frequency, computational and predictive data, functional data, segregation data, de novo data, allelic data, and reputable database. Some PVs may show reduced penetrance.

- Likely pathogenic variant (LPV): A genetic alteration with high likelihood (greater than 90% certainty) to classify as pathogenic or disease-causing.
- Variant of uncertain significance (VUS): A genetic alteration with limited and/or conflicting evidence regarding pathogenicity.
- Likely benign variant (LBV): A genetic alteration with high likelihood (greater than 90% certainty) to classify as benign.
- Benign variant (BV): A genetic alteration with sufficient evidence against pathogenicity.

HYPERTROPHIC CARDIOMYOPATHY

HCM is a genetic disease of the cardiac muscle with substantial variation in morphology, clinical manifestation, genetic etiology, and cardiac outcome.⁷ HCM has been an important model disease for studying many inherited cardiac diseases because it is also relatively common, with an estimated 1 in 500 people affected.⁸⁾⁹ HCM can be diagnosed clinically in adult patients by imaging, specifically with 2D echocardiography or cardiovascular magnetic resonance (CMR) that demonstrates a maximal end-diastolic wall thickness of ≥ 15 mm anywhere in the left ventricle, in the absence of a confounding cause of hypertrophy.¹⁰ A patient with more limited hypertrophy, only a wall thickness of 13–14 mm, can also be diagnosed with HCM when present in conjunction with a family history of HCM or a positive genetic test. HCM is typically inherited in an autosomal dominant pattern, but there is considerable variation in its expression and penetrance.¹¹⁻¹³ The offspring of each affected family member has a 50% chance of inheriting the genetic variant. In the case of HCM, the chance of developing the disease is significantly increased among family members who carry a pathogenic variant, but the age at which the disease manifests in an individual is variably distributed. The mechanisms are not clear, but these genetic alterations result in the characteristic pathological (myocyte disarray and fibrosis) and morphological (hypertrophied, nondilated left ventricle) features of HCM. The phenotypic variability is due, in part, to the causal PVs that interact with a variety of other genetic and nongenetic effects. Around 60% of patients with HCM have clearly identifiable familial disease.¹⁴ Although autosomal recessive and X-linked inheritance modes have been described, they are uncommon.¹⁵ A genetic basis for HCM was first described in 1990, when a PV in a gene encoding a sarcomeric protein was identified in a large family with HCM, sudden death, and HF.¹⁶⁾¹⁷ Since then, reports of multiple other PVs in genes encoding distinct sarcomere proteins,¹⁸⁾¹⁹ which act as effectors and regulators of contraction and relaxation of the heart, established HCM as a genetically heterogeneous disease.

Hypertrophic cardiomyopathy caused by pathogenic variants in genes encoding sarcomeric proteins

PVs in genes encoding sarcomeric proteins have been implicated in the majority of HCM cases (**Figure 1** and **Table 1**). Among the known causal genes, the β -myosin heavy chain (*MYH7*) and myosin binding protein C (*MYBPC3*) are the two most common,²⁰⁻²² followed by PVs in the genes encoding cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), and α -tropomyosin (*TPMI*).¹¹⁾²³ PVs in the genes encoding cardiac α -actin 1 (*ACTC1*), myosin light chain 2 (*MYL2*), myosin light chain 3 (*MYL3*), and cysteine and glycine rich protein 3 (*CSRP3*) have also been identified as less frequent causes of HCM.²³⁾²⁴ Combined, *MYH7* and *MYBPC3* account for up to 50% of all clinically recognized cases of HCM, and constitute at least 75% of probands when a PV is identified, whereas other HCM genes account for <10% of cases.²⁵⁻²⁷ These PVs generally cause single-residue substitutions in proteins that become

Table 1. Genes associated with sarcomere hypertrophic cardiomyopathy

Gene	Protein	Estimated prevalence in HCM (%)	Notes*
Sarcomere			
Thick myofilament			
<i>MYH7</i>	β-Myosin heavy chain	25–40%	- Prognosis variable depending on site of genetic variant; homogeneity within families - Sometimes restrictive cardiomyopathy phenotype
<i>MYBPC3</i>	Myosin-binding protein C	25–40%	- Prognosis variable depending on site of genetic variant; homogeneity within families
<i>MYL2</i>	Myosin light chain 2, regulatory	<5%	
<i>MYL3</i>	Myosin light chain 3, essential	<5%	
Thin myofilament			
<i>TNNT2</i>	Cardiac troponin T	5–10%	- Left ventricular hypertrophy is rare in children with <i>TNNT2</i> mutations. Particularly among males, SCD-predisposition and minimal hypertrophy (some reports)
<i>TNNI3</i>	Cardiac troponin I	5%	- This mutation is associated with sudden death at any age and dilated cardiomyopathy-like features in those aged >40 years - Sometimes restrictive cardiomyopathy phenotype
<i>TNNC1</i>	Cardiac troponin C	<1%	
<i>ACTC1</i>	Cardiac α-actine	<1%	- Benign prognosis and apical LV hypertrophy morphology
<i>TPM1</i>	α-Tropomyosin	1–5%	

HCM = hypertrophic cardiomyopathy; LV = left ventricular; SCD = sudden cardiac death.

*As the field of prognostically relevant mutations expanded, a series of studies directly contradicted, or at least failed to replicate, many of these initial observations.

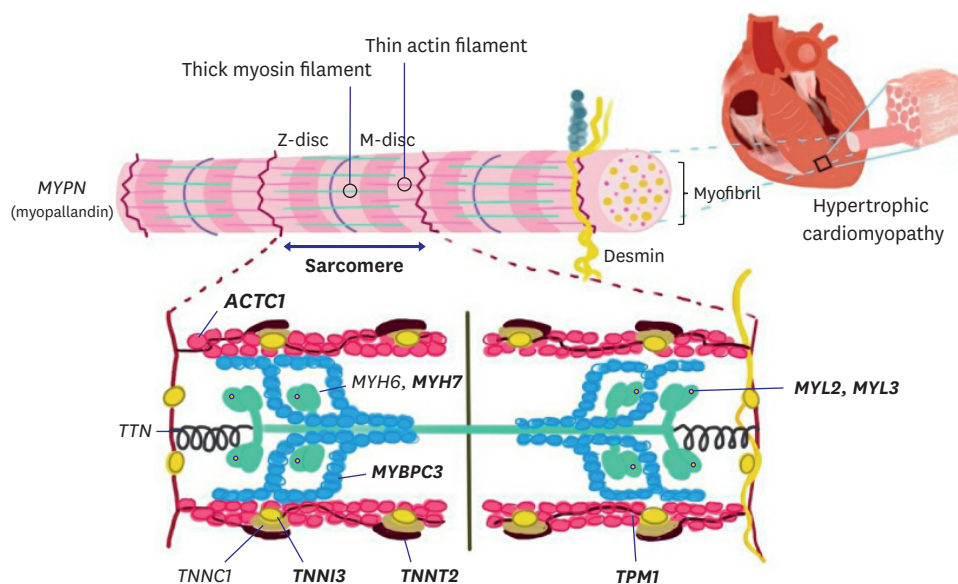


Figure 1. Main structural elements of the cardiac sarcomere and their respective genes involved in the pathogenesis of hypertrophic cardiomyopathy. A schematic of definitive (bold) hypertrophic cardiomyopathy genes in sarcomere.

ACTC1 = cardiac α-actin 1; *MYBPC3* = myosin binding protein C; *MYH6* = α-myosin heavy chain; *MYH7* = β-myosin heavy chain; *MYL2*, *MYL3* = myosin light chain; *TNNI3* = cardiac troponin I; *TNNT2* = cardiac troponin T; *TPM1* = α-tropomyosin; *TTN* = titin.

incorporated into the sarcomere; however, approximately half of the reported PVs in *MYBPC3* variant are truncations, and some *MYBPC3* missense variants can result in haploinsufficiency, a condition in which the gene product of the wild-type allele is not sufficient to compensate for the decreased or absent protein from the variant allele.²⁸⁾²⁹⁾

Pathogenic variants in genes encoding nonsarcomeric proteins

Additionally, the spectrum of HCM-associated genes has expanded to include nonsarcomeric genes, such as those encoding proteins found in the Z-disk, sarcoplasmic reticulum, and plasma membrane. However, these variants are uncommon, and our understanding of their role in disease is limited. Several of these nonsarcomeric genes are strongly associated with genetic evidence, such as disease segregation or in vivo functional data (e.g., *CSRP3*)³⁰; however, many of these genes' involvement with HCM (e.g., *MYH6*, *MYLK2*, and *TCAP*) is supported only by the presence of variants in affected individuals, absence from controls, and computational assessments. Other genes' clinical significance has not been fully elucidated due to a lack of evidence. Titin (*TTN*), α -actinin (*ACTN1*), α -myosin heavy chain (*MYH6*), *CSRP3*, telethonin (*TCAP*), and vinculin (*VCL*) are among these genes.³¹⁻³⁴ Despite their rarity in isolated cases and small families, variants in myozenin 2 (*MYOZ2*), ubiquitin E3 ligase tripartite motif protein 63 (*TRIM63*), and four-and-a-half LIM domains 1 (*FHL1*) have been described as causes of HCM.^{35,36}

Coexistence of a restrictive cardiomyopathy phenotype with the genetic basis of hypertrophic cardiomyopathy

In the gray zone (minimal or no left ventricular hypertrophy [LVH, maximum LV wall thickness ≤ 13 mm] and severe diastolic dysfunction) between HCM and RCM, diagnosis may be problematic. HCM may share many hallmarks with other cardiomyopathies and progress to a compensatory phase.^{37,38} Kubo et al.³⁹ showed that typical RCM phenotypes were found in 1.5% of the over 1,200 patients with familial HCM. PVs in either *MYH7* or *TNNI3* were found in half of the RCM probands.³⁹ On biopsy, all RCM patients with a PV showed either marked myofibrillar disarray, indicating a mixed phenotype with HCM, or had relatives with a clear HCM diagnosis.³⁹ The restrictive phenotype comprised of increased dyspnea, decreased exercise capacity, and a significantly higher composite rate (56%) of mortality, cardiac transplantation, or implantable cardioverter defibrillator (ICD) discharges.³⁹ The study's limitation is that it focused exclusively on known HCM-causing genes; it is uncertain whether additional genetic modifiers contributed to the RCM phenotype. Mogensen et al.^{40,41} identified a c.569A>G (p.Asp190Gly) variant of *TNNI3* that was associated with marked restrictive physiology and a history of sudden cardiac death (SCD). Variants in *TNNI3* now appear to be responsible for the development of RCM in a large proportion of young patients.⁴⁰ Although the majority of PVs in *TNNI3* that have been reported are generally missense, frame shift or splice variants.⁴¹ *TNNI3*-related variant phenotypes manifest with significant myofibrillar disarray even in the absence of typically LVH. A recent report described a genetic investigation of nine unrelated HCM patients with a marked restrictive filling pattern, significant atrial dilation, and normal wall thickness.⁴² Myocardial histology revealed the distinctive myofibrillar disarray associated with HCM. The majority of these patients had a *TNNI3* variant. Hwang et al.⁴³ described a large family in which a single *TNNI3* PV resulted in variable phenotypic expression ranging from restrictive cardiomyopathy to HCM to a near-normal phenotype. It has been proposed that different variants exhibit varying degree of Ca²⁺ sensitivity; strong sensitivity leads to HCM or RCM, whereas low sensitivity results in DCM.⁴⁴ These discoveries may have an effect on the evolution of the so called "restrictive phenotype." However, not all patients from the same family develop the restrictive phenotype, suggesting the involvement of additional genetic and/or environmental variables and highlighting the genetic/phenotypic variability of HCM (**Figure 2**).

Implications of genetic testing in hypertrophic cardiomyopathy

Guidelines

2020 American College of Cardiology/American Heart Association (ACC/AHA),¹⁰⁾ Heart Rhythm Society/European Heart Rhythm Association (HRS/EHRA)*, and 2014 European Society of Cardiology (ESC) guidelines⁵¹⁾

- (1) Genetic testing recommended in patients fulfilling diagnostic criteria for or with signs or symptoms suggestive of HCM (class I).
- (2) In patients with suspected HCM, comprehensive physical examination and complete medical and three-generation family history are recommended as part of the initial diagnostic assessment (class I).
- (3) Pathogenic variant-specific cascade screening is recommended (class I).
- (4) In first-degree relatives of patients with HCM, both clinical screening (electrocardiogram [ECG] and echocardiography) and cascade genetic testing should be offered (class I).
- (5) Genetic testing should be considered in deceased patients with pathologically confirmed HCM to facilitate cascade screening (class I).
- (6) In families affected by HCM, preconception and prenatal reproductive and genetic counseling should be offered (class I).

*Updated in 2018 in a joint publication with the ACMG.⁵²⁾

Diagnostic value

There are a number of clinical benefits to having genetic testing in HCM, including but not limited to, confirmation of diagnosis, detect the presence of preclinical disease, enable cascade genetic testing in the family and informed reproductive decisions.⁵³⁾⁵⁴⁾ The “genetic substrate” is typically present in approximately 60–70% of patients with HCM whose family history includes HCM, and it is present in 10–50% of those without a family history of the disease.¹⁰⁾⁵⁵⁾⁵⁶⁾ However, as the genetic architecture of HCM is still being mapped, it would be premature to rule out its genetic nature in patients with negative tests. Because HCM is primarily a sarcomere disease, first-line genetic testing focuses on panel testing for genes with strong evidence for being disease-causing in HCM.⁵⁷⁾ Numerous technological platforms are available for genetic testing, including gene panels, exome sequencing, and whole genome sequencing.⁵⁴⁾ *MYH7*, *MYBPC3*, *TNNI3*, *TNNT2*, *TPM1*, *MYL2*, *MYL3*, and *ACTC1* are the eight sarcomere genes that are typically included in the gene panels. Typically, the index case (proband) undergoes initial genetic testing.⁵³⁾ When the targeted gene panel testing does not find a PV, the choice may be to perform exome sequencing on a clinical or research basis, which can provide additional support when used alongside genetic counseling to explain the low yield of the test and the likelihood of finding susceptibility variants associated with disease other than the disorder being studied. About 40% of patients with HCM have no sarcomere disease-causing variant and no family history of the disease.⁵⁶⁾ Although the discovery of a VUS is not a clinically actionable result, it can be useful for clarifying the pathogenicity of variants by conducting further investigations that include cosegregation analysis in family members, parental DNA testing to see whether the VUS is de novo, and functional studies (**Figure 3**).

It can help elucidate the diagnosis and provide the opportunity for cascade (predictive) testing of at-risk family members if a clinically actionable result (i.e., likely pathogenic or pathogenic) from genetic testing is identified in the proband.¹⁰⁾⁵⁸⁾ A higher yield of genetic testing and

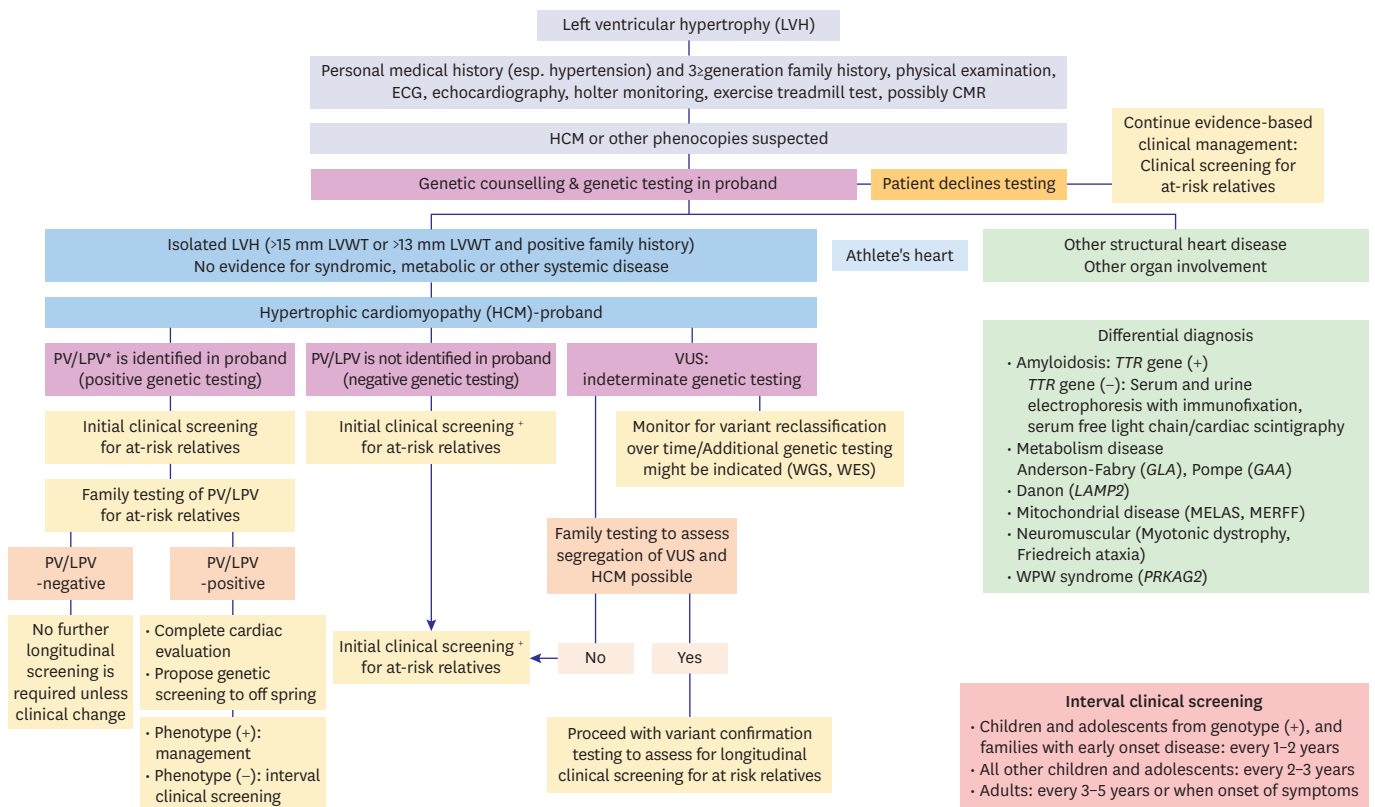
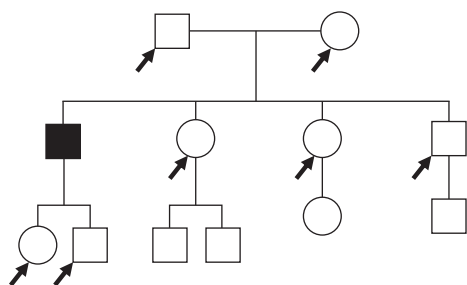


Figure 3. Schematic for employing hypertrophic cardiomyopathy genetic testing in the proband (index patient) and family members.

CMR = cardiovascular magnetic resonance; ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; LPV = likely pathogenic variant; LVH = left ventricular hypertrophy; LVWT = left ventricular wall thickness; PV = pathogenic variant; VUS = variant of uncertain significance; WES = whole exome sequencing; WGS = whole genome sequencing.

a more severe phenotype are associated with diagnosis of HCM during early childhood to adolescence.⁵⁹⁾ The construction and analysis of family pedigrees enables the identification of specific features, such as familial history of SCD, unexplained HF, cardiac transplantation, pacemaker and ICD implants, and evidence for systemic disease, which may aid in diagnosis and help to determine the mode of inheritance in the family. Because PVs in HCM variant are highly penetrant, carriers have a substantial lifetime risk (>95%) of developing the phenotype.¹⁰⁾ In general, the penetrance (proportion of variant carriers with clinically detectable disease) of HCM increases with age. However, in 2 large pediatric studies, approximately 9.9% of children screened for HCM were already phenotype-positive at first evaluation. The median age at HCM onset was 8.9–10 (4–13) years with earlier onset in males, those with a family history of SCD, and PVs in *MYH7/MYBPC3*.⁶⁰⁾⁶¹⁾ Similarly, the median time interval between the onset of HCM and major cardiac events, such as death, SCD, or cardiac intervention (myectomy, ICD), was 1.5 years. These studies suggest that the prevalence of HCM in children and preadolescents is comparable to that in adolescents owing to the fact that the phenotype of familial HCM in childhood varies and includes severe disease. This finding implies the importance of initiating clinical screening at a younger age. Taken together, these findings support the concept of initiating family screening in childhood and repeating it periodically. Therefore, regular follow-up in genotype-positive/phenotype-negative individuals with serial ECG, transthoracic echocardiography (TTE), and clinical assessment at periodic intervals (every 1–2 years in children and adolescents and every 3–5 years in adults) is recommended for early detection of clinical disease expression and timely initiation of therapy (Figure 4).¹⁰⁾



■ Proband: The solid square indicates a male with a diagnosis of HCM

Clinical evaluation is recommended for 1st degree relatives, indicated by the arrows

Although most HCM is adolescent or adult onset, it occur in neonates and young children

Recommended clinical screening of family members* in HCM

Physical examination, echocardiography and ECG

Children and adolescents from genotype (+), and families with early onset disease[†]

- At the time HCM is diagnosed in another family member
- Repeat evaluation every 1–2 years

All other children and adolescents

- At any time after HCM is diagnosed in a family member but no later than puberty
- Repeat evaluation every 2–3 years

Adults

- Repeat evaluation every 3–5 years, or in response to symptoms

If genetic results available:

- Genotype (+) family members: serial clinical evaluation, as above
- Genotype (–) family members: reassurance: no need for further testing

Figure 4. Recommended clinical screening of family members* in HCM. The screening interval may be modified (e.g., at the onset of new symptoms or in families with a malignant clinical course or late-onset HCM). These screening intervals apply to at-risk family members when genetic testing has not been performed or is uninformative in the proband, or when it has identified a likely pathogenic or pathogenic variant in the at-risk family member. HCM = hypertrophic cardiomyopathy; ECG = electrocardiogram; LVH = left ventricular hypertrophy.

*Includes all asymptomatic, phenotype-negative, first-degree relatives deemed to be at risk for developing HCM based on family history or genotype status, and may sometimes include more distant relatives based on clinical judgment. [†]Severe family history of early HCM-related death, sudden cardiac death, early development of LVH, or other adverse complications.

Factors that influence the hypertrophic cardiomyopathy phenotypes

The morphological, histological, and clinical phenotypes of HCM result from complex interactions among a large number of contributing factors, ranging from the effects of causal gene variants to environmental factors. Penetrance of variants increase with age but remains less than 100%. In the majority of patients with HCM, hypertrophy begins throughout adolescence. According to Lafreniere-Roula et al.,⁶⁰ 9.9% of children evaluated for HCM were already phenotype-positive at initial evaluation and experienced major adverse cardiac events (MACEs) at a median follow-up of 1.5 (0.5–4.1) years from HCM beginning. This indicates that many children by the time of diagnosis have already developed a well-defined phenotype, which also supports the notion that disease prevalence and penetrance in children are comparable to those in adolescents.⁶⁰ Clinical presentation may differ from asymptomatic to SCD, the latter of which targets younger adults. According to genotype-phenotype correlation studies, certain causal genes are strongly correlated with the phenotypic expression of HCM, such as *MYH7*, *TNNT2*, and *MYBPC3*. These genes appear to influence the severity of cardiac hypertrophy and the likelihood of SCD.^{62–66} The PVs in *MYH7* are generally found in younger patients, and they have more significant hypertrophy, along with a higher risk of SCD.^{67–69} On the other hand, PVs in *MYBPC3* are linked to relatively mild hypertrophy and late-onset clinical manifestations.⁶⁴⁾⁷⁰⁾⁷¹ PVs in the *MYBPC3* are often associated with low penetrance, mild hypertrophy, and a low incidence of SCD. The phenotype frequently manifests late, and may coincide with the concomitant presence of hypertension. Despite the overall benign nature of PVs in *MYBPC3*, significant variability exists in the phenotypic expression of HCM; so-called malignant PVs have also been reported in *MYBPC3* genes.⁶⁰⁾⁷⁰ *TNNT2* PVs may cause premature sudden cardiac death in patients with only mild or no LVH.⁷² PVs in *TPM1* are generally benign and associated with mild LVH. Despite a mild degree of hypertrophy, a high rate of SCD has also been reported.⁷³ Certain studies have suggested that PVs in essential and regulatory myosin light chains (*MYL1*, *MYL2*) can lead to mid-cavity obstruction in HCM

and skeletal myopathy in some patients,⁷⁴⁾ while other studies have found no correlation.⁷⁵⁾ Although PVs are quite rare in *TTN*⁶⁾ and *ACTC1*,⁷⁷⁾ they have been detected in a small number of HCM phenotype families.

Although the exact mechanisms by which sarcomere variants cause clinically relevant phenotypes have not been thoroughly elucidated, it can be presumed that these mechanisms may involve contractile elements. In vitro and in vivo research reveal that PVs exhibit a diverse array of functional defects, such as reduced actin-myosin interaction, reduced cross-bridging kinetics, myocyte contractility, ATPase activity of myosin, and altered Ca²⁺ sensitivity.⁷⁸⁾⁷⁹⁾ Hypertrophy, along with other clinical and pathological phenotypes, is considered compensatory phenotypes that occur as a result of functional defects. Various disease features, including abnormal intramural coronary arteries causing small vessel ischemia, elongated mitral valve leaflets, and congenital anomalies of the sub-mitral valve apparatus, are widely recognized components of the HCM phenotype which appear to have no known direct connection with sarcomere variants.

Is genotype-phenotype correlation in hypertrophic cardiomyopathy really clinically useful in predicting prognosis?

Some studies have noted that although *MYH7*-p.Val606Met is known “benign” variant, it appears to be associated with increased risk of SCD in a family with HCM.⁸⁰⁾ A previous study observed that three individuals, including a son of the index case, experienced SCD at a young age with marked septal hypertrophy. Among the surviving four HCM phenotype-positive individuals with the p. Val606Met variant, all were diagnosed before 18 years of age, and three demonstrated either nonsustained ventricular tachycardia (VT) or atrial fibrillation (AF).

After Menon et al.⁸¹⁾ identified its association with SCD in 4/9 variant-positive individuals, the “malignant,” the *TNNT2*-p.Ile89Asn variant also suffers from similar contradictions variant.⁸¹⁾ The variant was identified in each of the nine affected family members who were diagnosed with RCM (n=2), DCM (n=2), HCM (n=4), and mixed cardiomyopathy (n=1). Furthermore, although there was a high incidence of atrial tachyarrhythmia, there was no incidence of SCD. The results of these studies question the association between individual genetic variants and patient survival. There are also contradictory reports regarding the role of specific variants influencing other aspects of HCM, such as septal hypertrophy morphology.

Recent advances in the prognostic role of genotyping in hypertrophic cardiomyopathy

There are several ongoing controversies regarding the relative value of variant-specific and genotype-specific risk stratification, but recent evidence suggests that unrelated patients with a positive HCM genetic test have a greater likelihood of developing a more severe phenotype (diastolic and systolic dysfunction and symptoms) than those without genetic variants. According to a Mayo Clinic study, patients who were genotype positive were found to be younger at diagnosis, demonstrated greater hypertrophy, were more likely to have a positive family history of HCM, and were more likely to receive an ICD than negative genotype counterparts.⁸²⁾ Furthermore, a positive genetic test conferred a hazard ratio of 4.3 (95% confidence interval, 1.5–12.5%), which was greater than that of age, degree of outflow tract obstruction, and presence of AF. These differences were also observed in patients with HCM from Italy between those who tested positive and negative for HCM variants. In this study, Olivotto et al.⁸³⁾ found that patients with a positive myofilament genetic test had drastically different outcomes. Of the cases in this cohort of 203 index cases, 62% (126 of 203) of those who had a positive HCM genetic test had an increased combined risk of cardiovascular death,

nonfatal stroke, or progression to New York Heart Association class III or IV symptoms, whereas the rest (38%) with a negative genetic test result had lower risk. Additionally, myofibrillar-positive patients were more likely to have severe LV systolic (EF <50%) and diastolic (restrictive filling pattern) dysfunction. These studies indicate for the first time that a “positive genetic test” may be associated with adverse outcomes in patients with HCM. These observations remain to be translated in a clinically meaningful way. Perhaps clinicians can consider that patients with a negative result for HCM ultimately exhibit milder disease phenotypes and are far less likely to progress. HCM is a complex disease that presents itself with variable hypertrophy and outflow tract obstruction at any age. While knowledge of genetic variants are becoming increasingly understood, HCM susceptibility variant and their roles in disease pathogenesis still present a difficult challenge. This is particularly due to the multiple factors including that the same genetic variant can lead to dramatically different phenotypic variations of HCM in different individuals. Until these factors and the relationship between specific HCM variants and its impact on phenotypes are fully understood, specific isolated variants currently do not have feasible prognostic clinical utility.

DILATED CARDIOMYOPATHY GENETICS

DCM is defined by the presence of LV or biventricular dilatation (>112% of LV end-diastolic dimension predicted for age and body surface area) and systolic dysfunction (LVEF <45%) in the absence of abnormal loading conditions (hypertension, valve disease) or coronary artery disease sufficient to cause global systolic impairment.⁸⁴⁾ Familial DCM is diagnosed when 2 or more family members meet the criteria for DCM or when the patient of interest (proband) meets the criteria for DCM, and a first-degree relative has experienced sudden cardiac death aged <35 years.⁸⁵⁾ However, the definitions of these terms are merely arbitrary and, in many cases, can only be documented partially. In general, if family members of the proband have been reported to have HF or premature sudden cardiac death with no identified cause, it is reasonable to consider familial DCM.⁸⁶⁾

DCM has a highly diverse genetic basis. Approximately up to 40% of DCM may have a genetic basis, and over 50 distinct genes have been implicated, many of which influence the functionality of diverse protein assemblies.⁸⁷⁻⁸⁹⁾ Despite the fact that these genes are implicated in various genetic pathways, the end result is the same: a specific DCM phenotype. The sheer numbers of genes and diversity of variants identified (allelic and locus heterogeneity) with DCM are more extensive than with the other cardiomyopathies.³⁾⁹⁰⁾⁹¹⁾ The range of diversity among these individuals is extremely relevant to the practice of clinical medicine because DCM, more so than any other etiology, underlies a large proportion of HF cases and their resulting morbidity and mortality. The majority of genetic DCM is inherited in an autosomal dominant pattern with variable expressivity and penetrance, although specific forms of autosomal recessive, X-linked recessive, and mitochondrial inheritance do infrequently occur.⁹²⁻⁹⁴⁾ De novo variant can also lead to genetic cardiomyopathy and is defined as the absence of the offspring's variant in parents. Variants that are considered de novo have been described in many different genes, and the existence of a de novo variant can be used to infer the pathogenic status of genetic variants. This is because it is quite rare for de novo variants to appear in the coding exons of each genome. So, these newly developed pathogenic variants, which introduce changes that alter the protein in the cardiomyopathy gene, may be considered pathogenic.⁹⁵⁾ Although many of these variants may be potential pathogenic variants, a new pattern of oligogenic inheritance is emerging (for example,

diseases caused by a small number of variants in more than one gene), which requires genetic counseling and results in predictive testing becoming an important challenge. This may provide one explanation for the variation in disease penetrance seen in some individual families. From a clinical standpoint, it is critical to conduct a thorough phenotypic evaluation of patients and their families in order to correctly interpret genetic findings.⁸⁷⁾

Table 2 summarizes the most frequently implicated genes in DCM and their estimated prevalence in non-syndromic DCM.⁹⁶⁻⁹⁸⁾ The location of the proteins encoded by these genes in cardiomyocytes is depicted in **Figure 5**. While some ethnic differences in the proportion of causative genes exist, *TTN* truncating variants and lamin A/C (*LMNA*) variants are considered major genetic factors for the development of DCM.

Table 2. Major genes associated with dilated cardiomyopathy

Gene	Protein	Estimated prevalence in DCM (%)	Age of onset of DCM (years)	Notes
<i>TTN</i>	Titin	12–25%	DCM: Usually 40–59	- Usually, isolated DCM - More common in women than in men; variable prognosis but family clustering
<i>LMNA</i>	Lamin A/C Nuclear membrane	5–10% (up to 30 if conduction disease also present)	30–49 and penetrance is almost complete at the age of 70; conduction disease usually prominent	- Subset of Emery–Dreifuss muscular dystrophy - Phenotypic expression is characterized by a relatively high incidence of sudden cardiac death or major ventricular arrhythmias, even before the development of systolic left ventricular dysfunction - Class IIa for ICD implantation: NSVT during monitoring, EF <45% at first evaluation, male and non-missense mutations ⁹⁶⁾⁹⁷⁾
<i>MYH7</i>	β-Myosin heavy chain Sarcomere	4–10%	Variable: adolescence to 49	- Primarily HCM; also, LVNC and RCM - Prognosis variable depending on site of genetic variant; homogeneity within families
<i>MYH6</i>	α-Myosin heavy chain Sarcomere	4%	Variable: adolescence to 49	- Primarily HCM - Prognosis variable depending on site of genetic variant; homogeneity within families
<i>MYPN</i>	Myopalladin Sarcomere, Z-disc	3–4%	Variable: adolescence to 59	- Usually, isolated DCM - Variable presentation with some early deaths due to heart failure
<i>DSP</i>	Desmoplakin Desmosome	3–4%	Variable: mostly 40–49	- ARVC - Identified in multiple patients with advanced DCM although natural history uncertain; arrhythmic burden seems to be much lower than in ARVC
<i>RBM20</i>	RNA-binding protein 20 Spliceosome	1–5%	Adolescence to 50; can present with SCD or advanced heart failure	- Usually, isolated DCM - Rapid progression: SCD and end-stage heart failure are common, with a high incidence of ventricular arrhythmias - Severe disease expression in male patients ⁹⁸⁾
<i>TNNT2</i>	Cardiac muscle troponin T Sarcomere	2–3%	Variable: adolescence to 49	- HCM, LVNC, and RCM - Prognosis variable depending on site of genetic variant; homogeneity within families
<i>SCN5A</i>	<i>SCN5A</i> (sodium channel protein type 5, α subunit) Ion channel	2–3%	Adolescence	- Brugada syndrome and LQTS - Early onset, commonly with atrial fibrillation; not associated with risk of ventricular arrhythmias
<i>TPM1</i>	α-Tropomyosin Sarcomere	0.5–1.0%	Variable: adolescence to 49	- Other cardiomyopathy: HCM, LVNC, and RCM - Prognosis variable depending on site of genetic variant; homogeneity within families

ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; ICD = implantable cardioverter defibrillator; LQTS = long QT syndrome; LVNC = left ventricular noncompaction; NSVT = nonsustained ventricular tachycardia; RCM = restrictive cardiomyopathy; SCD = sudden cardiac death.

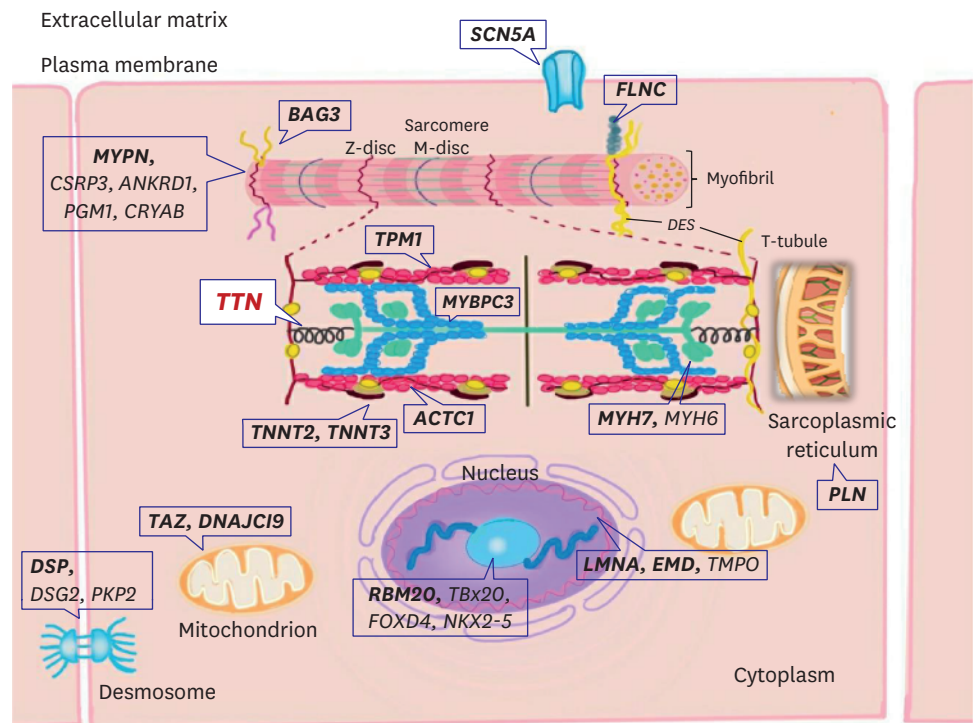


Figure 5. A schematic of definitive (bold) and posited dilated cardiomyopathy genes with the subcellular localization of the encoded proteins. Pathogenic genes encode proteins that participate in many diverse biological processes of cardiomyocytes. *TTN* truncating mutations are the most frequent cause of dilated cardiomyopathy. *ACTC1* = cardiac α -actin 1; *BAG3* = BAG cochaperone 3; *DES* = desmin; *DSG2* = desmoglein-2; *DSP* = desmoplakin; *EMD* = emerin; *FLNC* = filamin C; *LMNA* = lamin A/C; *MYBPC3* = myosin binding protein C; *MYH6* = α -myosin heavy chain; *MYH7* = β -myosin heavy chain; *MYPN* = myopalladin; *PKP2* = plakophilin-2; *PLN* = phospholamban; *RBM20* = RNA-binding protein 20; *SCN5A* = sodium voltage-gated channel alpha subunit 5; *TMPO* = trimethylphosphate; *TNNT* = cardiac troponin T; *TPM1* = α -tropomyosin; *TTN* = titin.

Genetic variants causing dilated cardiomyopathy

TTN

TTN truncating variants are the most common cause of DCM,⁹⁹⁾ accounting for about 15–25% of DCM cases.⁸⁸⁾¹⁰⁰⁾ Titin is the giant protein that encodes the *TTN* gene, the largest known protein expressed in the heart. Titin has 4 major protein domains (the Z-disk, the I-band, the A-band, and the M-band) that are located on either side of the length of the sarcomere. Titin serves as a spring providing both an inner and outer force. Additionally, it regulates sarcomere contraction and signaling.¹⁰¹⁾ The clinical phenotypes of *TTN* truncating variants include low penetrance, low association with abnormalities in the conduction system, relatively good prognosis, sex differences in prognosis (males have a worse prognosis than females), and a tendency for LV reverse remodeling.⁸⁸⁾⁸⁹⁾¹⁰²⁾ Despite the low penetrance of *TTN* truncating variants, additional cardiac insults such as pregnancy and alcohol abuse may cause cardiac dysfunction.¹⁰³⁾¹⁰⁴⁾ Patients who have a *TTN* truncating variant tend to develop severe LV dysfunction at diagnosis, but with optimal medical therapy they tend to have a good outcome, and the patients' cardiac function may often improve significantly (**Figure 6**).⁸⁸⁾

LMNA

LMNA variants are the second most common cause of DCM,¹⁰⁵⁾ accounting for 5–10% of DCM cases.⁸⁸⁾⁸⁹⁾ The single *LMNA* gene encodes lamins A and C, and differential splicing at the 3' end results in two proteins that are identical across their first 566 amino acids. PVs in *LMNA* lead to a constellation of diseases, from premature aging to myopathies and DCM.¹⁰⁶⁾ There is

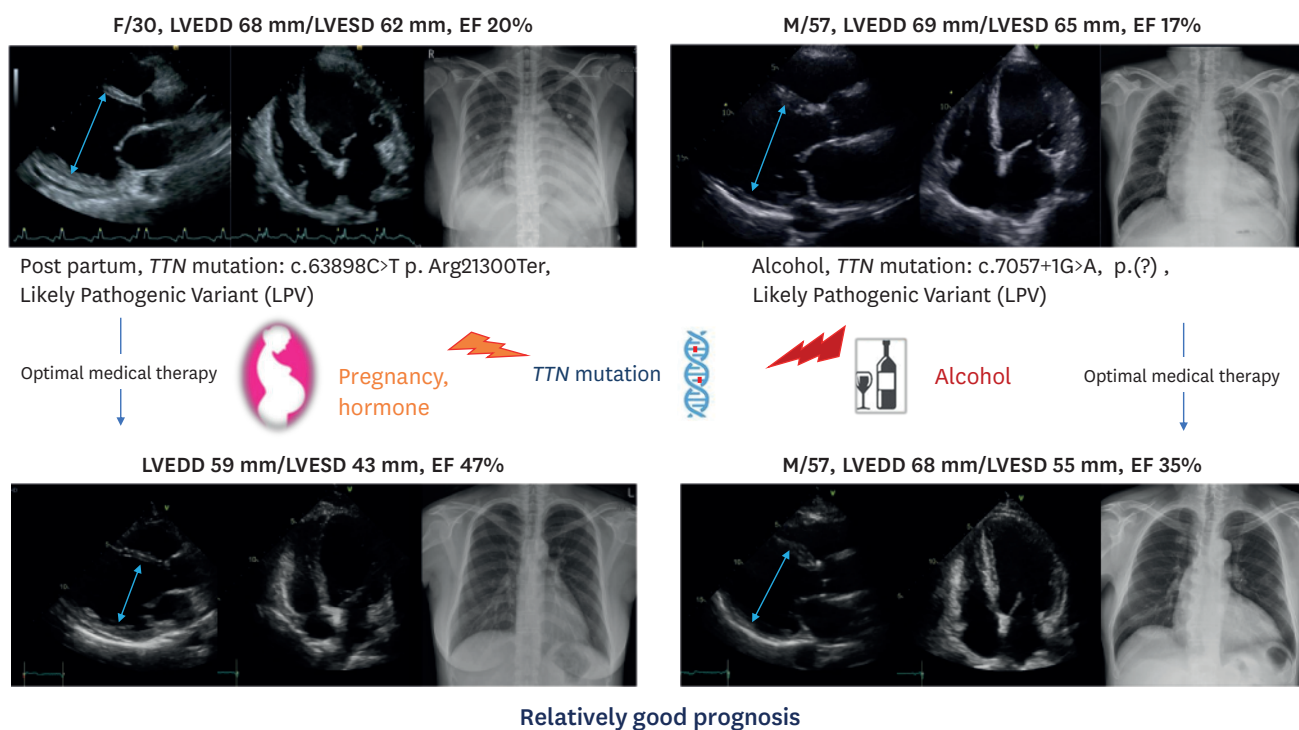


Figure 6. Two cases of *TTN*-related dilated cardiomyopathy. Although cardiomyopathy patients with *TTN* truncating variants show severe left ventricular dysfunction at diagnosis, they tend to present with a good response to appropriate medical therapy and their cardiac function improves drastically. EF = ejection fraction; LPV = likely pathogenic variant; LVEDD = left ventricular end diastolic dimension; LVESD = left ventricular end systolic dimension; *TTN* = titin.

compelling evidence for the clinical significance of *LMNA* variants. *LMNA* variants have high penetrance, a young -onset, coexistence with an abnormalities in the conduction system, high occurrence of ventricular arrhythmias and SCD, a poor response to medical therapy, and a frequent need for heart transplantation.⁸⁹⁾¹⁰²⁾¹⁰⁷⁾¹⁰⁸⁾ Due to the frequent coexistence of *LMNA* variants with ventricular arrhythmias, the European Society of Cardiology guidelines recommends the use of an ICD in patients with DCM and a confirmed disease-causing *LMNA* variant to prevent sudden cardiac death despite not meeting left ventricular ejection fraction criteria.⁹⁷⁾¹⁰⁹⁾ It is suggested that pathogenic *LMNA* variants result in a failure in mechano-transduction and the development of laminopathy, which can lead to various clinical symptoms, including skeletal and/or cardiac muscular dystrophy, lipodystrophy, dysplasia, neuropathy, leukodystrophy, and premature aging.¹⁰⁹⁾ Overall, out of a selected tertiary referral population of patients with familial DCM, 30% had the *LMNA* variant while 88% had the DCM/muscular dystrophy syndrome combination, and 25% had the isolated conduction system disease without DCM.¹¹⁰⁾

Sarcomeric (motor) genes

PVs in genes encoding proteins that form thick and thin sarcomeric filaments have been implicated in DCM. These proteins (myosin-heavy chain alpha and beta [*MYH6* and *MYH7*, respectively], *MYBPC3*, troponins [*TNNT2*, *TNNI3*, *TNNC1*], tropomyosin 1 [*TPM1*], cardiac actin 1 [*ACTC1*], and myopalladin [*MYPN*]) share catalytic activity and are involved in sarcomeric contraction. Structural properties found in Z-disk genes are also shared by *MYPN*. Variants that have been discovered to contribute to DCM, have phenotypic heterogeneity, often each variant resulting in a different DCM manifestation. Up to 10% of familial DCM result from genetic variants that encode contractile proteins, with substantial phenotypic variability.¹¹¹⁾

RBM20

RBM20 encodes the RNA binding motif 20 protein, a chaperone protein that interacts with mRNA and regulates exon splicing to generate distinct gene isoforms. *RBM20* regulates the splicing of *TTN*, which is one of several cardiac targets.¹¹²⁾ In rats, an *RBM20* deletion alters *TTN* splicing and results in a DCM phenotype. With respect to prevalence in DCM families, *RBM20* represents a rare genotype, accounting for 1–5% of cases.¹¹³⁻¹¹⁵⁾ For this reason, evidence-based genotype-phenotype correlations remain unproven. However, it has been shown that *RBM20* variants can be found in those who have a higher risk of developing DCM phenotype characterized by rapid progression of HF, high risk for arrhythmias, and the need for cardiac transplantation, especially in males.⁹⁸⁾¹¹⁶⁾ These findings underscore the importance of conducting clinical and genetic investigations to identify patients at risk of developing disease complications to initiate proper and timely treatment.

FLNC (structural cytoskeleton-Z-disk gene)

More recently, PVs in *FLNC* encoding filamin C, have been described in DCM.¹¹⁷⁾¹¹⁸⁾ Deletion of *FLNC* in mice causes skeletal muscle weakness, which suggests a positive interaction between filamin C and the dystrophin complex.¹¹⁹⁾ In humans, truncating variants lead to cardiomyopathy, which is associated with a high rate of ventricular arrhythmias and SCD; these findings suggest that filamin C plays a role in the cardiac conduction system in addition to cardiomyocyte function.¹²⁰⁾

SCN5A (ion channel gene)

The major sodium channel expressed in the heart is encoded by *SCN5A*. In both long QT syndrome and Brugada syndrome, heterozygous autosomal dominant PVs are found in *SCN5A*. Missense variants in *SCN5A* have been described in familial DCM, and these PVs carry a higher risk for arrhythmias.¹²¹⁾¹²²⁾ There is significant amount of genetic heterogeneity in the *SCN5A* gene in the general population, which makes it challenging to accurately interpret pathogenicity of variation in *SCN5A*.

DSP, PKP2 (Desmosomal genes)

The desmosome is a symmetric myocyte structure in which each part resides in the cytoplasm of one of a pair of adjacent cells, anchoring the intermediate filaments in the cytoskeleton to the cell surface. It is essential that the desmosome serves as a coupling agent between cardiac myocytes and cell gap junctions to ensure both the mechanical and electrical integrity of the heart. There is a traditional correlation between ARVC and variants in genes encoding desmosomal proteins. However, a number of desmosomal genes, usually inherited from an autosomal dominant heritage, have been identified in patients with DCM patterns independent of right ventricular involvement. Elliott et al. discovered a prevalence of 5% of desmosomal protein-coding gene variants among 100 unrelated patients with DCM patients.¹²³⁾ Therefore, the true pathogenesis of ARVC or DCM caused by variants in desmosomal gene products has not been fully characterized.

Implications of the genetic test in dilated cardiomyopathy

Guidelines

Similar to HCM, the identification of the genetic cause of DCM provides significant clinical insight into family screening, management, and prognosis, but the yield of genetic testing is lower as compared to HCM.⁸⁶⁾ The prevalence of underlying PVs is estimated to be between 15% and 25% in unselected DCM patients and between 20% and 40% in familial DCM patients.⁵²⁾¹²⁴⁻¹²⁶⁾ While modern genetic testing methods enable the evaluation of a

greater number of genes, the detection rate has remained relatively constant over the last decade.¹²⁵⁾¹²⁶⁾ The guidelines vary slightly for sporadic DCM (without a family history of the disease), primarily due to the unknown diagnostic yield and clinical utility of genetic screening in this population.

ACC/AHA^{*},¹²⁷⁾¹²⁸⁾ HRS/EHRA[†], and 2010 ESC guidelines¹²⁹⁾

- (1) Obtaining a family history of at least three generations, including the creation of a pedigree, is recommended for all patients with primary cardiomyopathy (class I).
- (2) Clinical (phenotypic) screening for cardiomyopathy in at-risk 1st-degree relatives is recommended (class I).
- (3) Variant-specific cascade screening is recommended (class I).
- (4) Comprehensive or LMNA/SCN5A-targeted genetic testing is recommended for all patients with DCM and severe cardiac conduction disease or a family history of SCD (class I).

^{*}2013 ACC/AHA Heart Failure Guideline, 2016 AHA Scientific Statement on DCM.

[†]Updated in 2018 in a joint publication with the ACMG.⁵²⁾

Diagnostic value

Genetic testing is not utilized to make a diagnosis in patients with DCM but rather to search for an underlying cause. The identification of a PV does not significantly alter clinical care in many patients with overt DCM. However, DCM genetic testing allows the identification of populations at risk of developing DCM and facilitates the close monitoring of DCM cases associated with a high risk of SCD.⁵⁵⁾ Because these aggressive forms of DCM are often difficult to recognize at early stages, genetic testing appears to be beneficial in young individuals with early symptoms of DCM. The results of genetic testing should be interpreted in conjunction with comprehensive cardiac and systemic evaluations.

In contrast, genetic test results (PV or LPV) in a DCM susceptibility gene are useful for assessing asymptomatic family members, allowing identification of those at risk of future disease and rationalizing follow-up. Echocardiographic screening is recommended for asymptomatic family members. Testing of asymptomatic family members highlights the necessity for echocardiographic screening and is a cost-effective approach. Family members who are both genotype-positive and phenotype-negative require routine echocardiographic evaluation to detect early signs of contractile dysfunction that may manifest even before symptoms develop.⁵⁾¹³⁰⁾ In the past, it was thought that no further cardiac evaluation was necessary if an at-risk family member tested negative for a previously identified pathogenic or likely pathogenic variant in the context of a negative baseline cardiac evaluation, depending on the strength of the association between the variant and the disease.⁵⁾ However, with growing awareness of the molecular complexity of DCM in many groups, there may be a way to identify DCM-susceptible individuals as being at lower risk of developing the disease rather than no risk, and these individuals could have their periodic clinical visits tailored accordingly. A comprehensive evaluation of index patients with DCM should ideally include family pedigree for at least 3–4 generations to identify the potential familial occurrence of the disease (**Figure 7**).

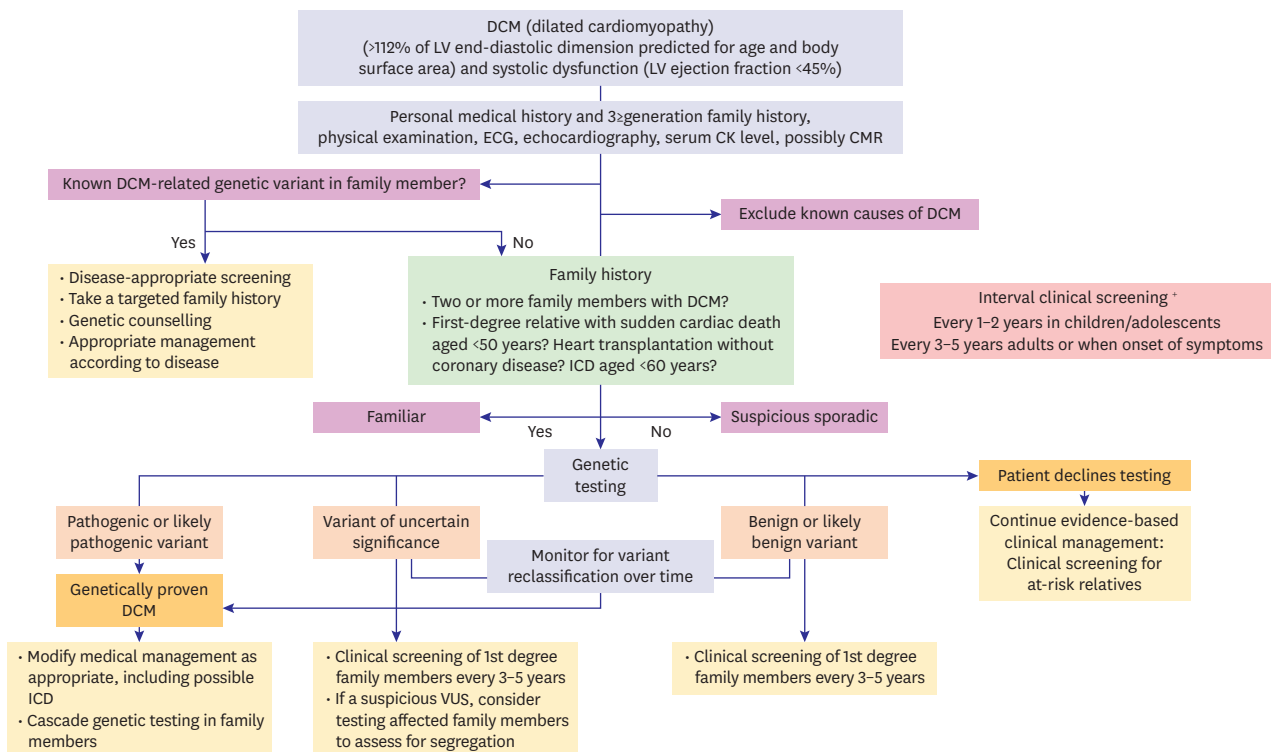


Figure 7. Schematic for employing dilated cardiomyopathy genetic testing in the proband (index patient) and family.

CK = creatine kinase; CMR = cardiovascular magnetic resonance; DCM = dilated cardiomyopathy; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; LV = left ventricular; VUS = variant of uncertain significance.

Complexity and phenotype correlates with definitive and putative dilated cardiomyopathy genes

The treatment of genetic DCM depends on the following factors: 1) the penetrance of the gene variant; 2) the phenotypic presentation; 3) the underlying molecular mechanisms leading to cardiac involvement; and 4) the gene–environmental interactions determining the DCM phenotype.⁹⁰⁾

The clinical phenotype of DCM is much more complex than commonly observed. Genetic and nongenetic interactions may influence the severity and outcome of DCM cases, including HF, arrhythmia, stroke, and the need for cardiac transplantation.⁹⁵⁾ The complicated underlying architecture of the phenotype emerges from many complex and dynamic interactions that arise from multiple genetic and nongenetic factors. This unknown, mysterious influence of epigenetic regulation of gene expression on the clinical phenotype is another example of something we need to study further.¹³¹⁾ Additionally, it is estimated that 94% of human genes undergo extensive alternative splicing, but the alternative splicing's effect on the expression of the clinical phenotype remains yet to be determined.¹³²⁾ A variety of posttranslational modifications, including phosphorylation, acylation, glycosylation, ubiquitinylation, and disulfide bridges, modify protein function, and thus they can also affect the phenotype. Additional acquired conditions such as toxic exposure, diabetes, arrhythmia, myocarditis, hormonal imbalance, and pregnancy also contribute to the phenotype and outcome.¹³³⁾ Often, genetic determinants increase susceptibility to DCM or alter risk factors in the presence of an external cause. Thus, the line between a genetic disorder and acquired disease becomes increasingly blurred, complicating patients' assessment but also opening new avenues for understanding and treating this etiologically heterogeneous disease (**Figures 8 and 9**).⁹⁰⁾

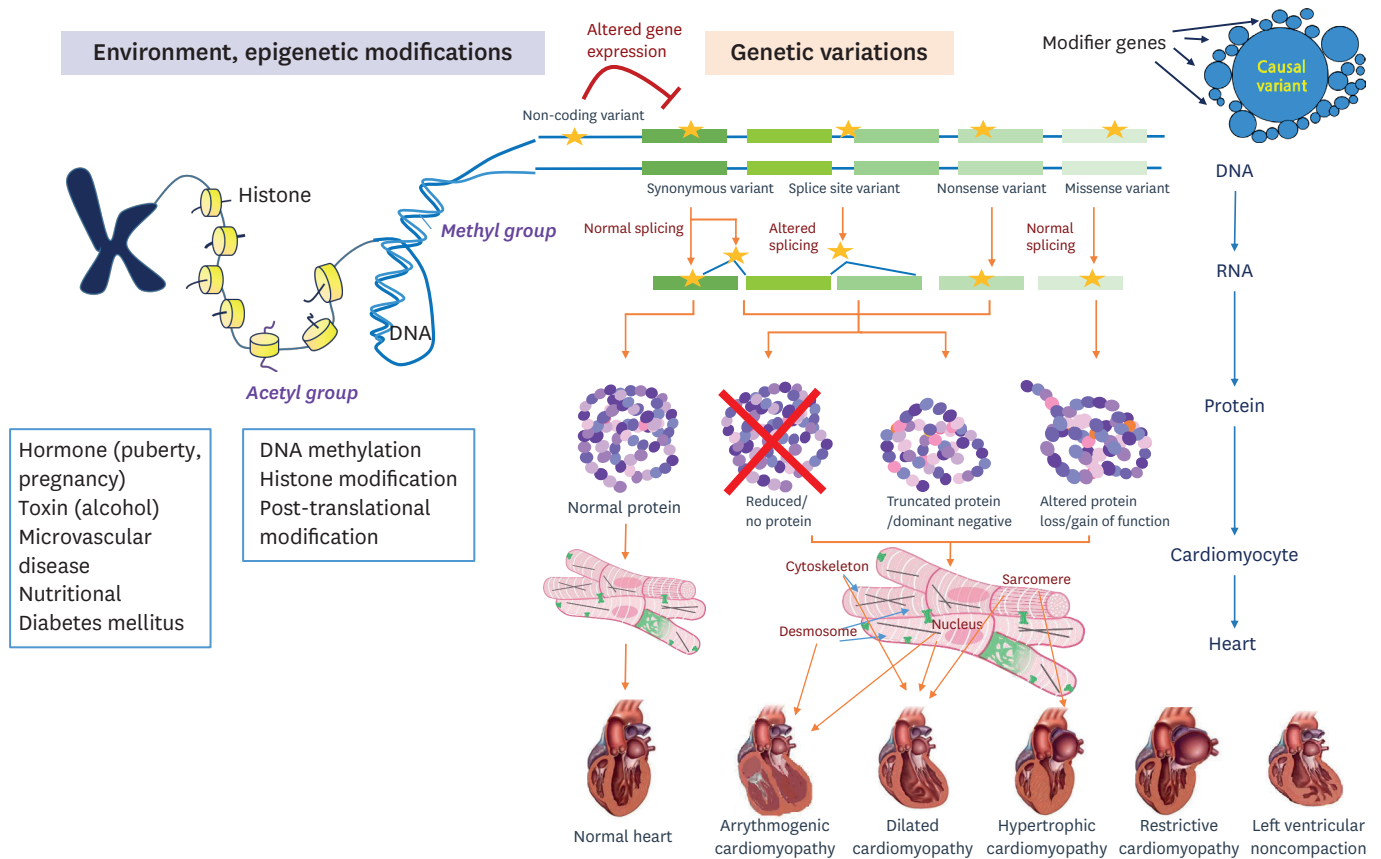


Figure 8. The diversity of the cardiomyopathies results from genetic, allelic, epigenetic, and environmental heterogeneity, all of which contribute to the phenotype. Hypertrophic cardiomyopathy caused by mutations in genes encoding sarcomeric proteins. *TTN* truncating variants and *LMNA* variants are considered to be major factors for the development of dilated cardiomyopathy. Desmosome is major cause of arrhythmic cardiomyopathy. The treatment of a genetic cardiomyopathy will depend on the 1) penetrance of the pathogenic variant, 2) the phenotypic presentation, 3) the underlying molecular mechanisms leading cardiac involvement, and 4) the gene-environmental interactions determining the DCM phenotype. *LMNA* = lamin A/C; *TTN* = titin.

DCM phenotype: gene-environmental interaction

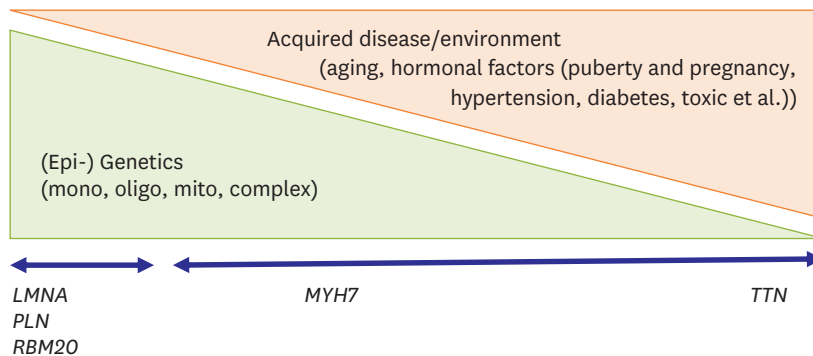


Figure 9. Gene-environmental interaction in dilated cardiomyopathies. DCM is a complex multi-factorial disease related to genetic determinants interfering with environmental factors. DCM = dilated cardiomyopathy; *LMNA* = lamin A/C; *MYH7* = β -myosin heavy chain; *PLN* = phospholamban; *RBM20* = RNA-binding protein 20; *TTN* = titin.

Prognostic value

According to emerging evidence, variants in *LMMA* or *SCN5A* could put individuals at a high risk of developing HF and cardiac arrhythmias. As a result *LMNA*-related cardiac disease patients

are at risk of experiencing SCD, receiving ICD therapy, or suffering from end-stage HF that necessitates heart transplantation.¹³⁴⁾ Eventhough not all variants in these genes are necessarily arrhythmogenic or cause advanced HF, each variant should be evaluated independently for its potential pathogenicity. Also, guidelines do recommend as Class II to consider ICD implantation in mildly reduced LVEF patients with *LMNA* variant under certain conditions.

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY/ARRHYTHMOGENIC CARDIOMYOPATHY GENETICS

The prevalence of ARVC in the general population is approximately 1 in 5,000¹³⁵⁾; however, due to the difficulty of its diagnosis, the disease is not widely recognized.¹³⁶⁾ In order to standardize the clinical diagnosis of ARVC, the working group revised the guidelines in 2010 to improve diagnostic sensitivity, mainly for the clinical screening of family members; this goal was achieved by providing quantitative criteria for diagnosing right ventricular abnormalities and adding molecular genetic criteria.¹³⁶⁾ However, due to the low specificity of electrocardiographic abnormalities, the various causes of right ventricular arrhythmias, and the difficulty of using imaging to assess the structure of the right ventricle, challenges in phenotypic diagnosis increases the difficulty in interpreting genetic testing results.¹³⁷⁾¹³⁸⁾ International expert documents highlight the potential limitations of current criteria to propose solutions for better clinical use and identifying potential areas of improvement, such as the identification of early disease in the pediatric population.¹³⁸⁾

ARVC is a progressive myocardial disease, which is defined as the replacement of myocardial cells with fat and fibrosis. The disease is related to abnormalities in the structure and function of the right ventricle (RV).¹³⁷⁾ The classical form of ARVC is an autosomal dominant genetic disease, which accounts for 30–50% of ARVC cases with a variable penetrance. ARVC also includes Naxos disease (a cardiocutaneous syndrome characterized by palmoplantar keratosis, wooly hair, and heart muscle disease)¹³⁹⁾ and Carvajal syndrome, which are two specific autosomal recessive inherited diseases. While RV disease defines the condition, there are a number of features that may overlap with DCM, as defined in this statement. In particular, the degree of LV involvement ranges from cardiac magnetic resonance imaging (MRI) scarring to severe LV dilation and systolic deterioration. There is also an overlap in causation; for example, PVs in the desmosomal genes in ARVC are also relatively common in patients with a clinical diagnosis of DCM.¹⁴⁰⁾ Although the degree of family coexistence of both DCM and ARVC has not been well described, the presence of RV abnormalities, such as ventricular dilatation and ventricular ectopy of RV origin in relatives of patients with DCM, may be a diagnostic red flag (**Table 3**) for the presence of familial disease.¹⁴¹⁾ Similarly, it is important to keep in mind that the presence of LV dysfunction in a patient with clearly defined ARVC does not imply another disease. Myocarditis with or without a DCM phenotype may resemble ARVC, and this sometimes requires endomyocardial biopsy for proper differential diagnosis.¹⁴¹⁾

Arrhythmogenic right ventricular cardiomyopathy is often caused by pathogenic variants in the desmosome genes

Patients with ARVC usually have genetic abnormalities in the genes encoding desmosomal proteins. Desmosomes are mechanical bridges that link cardiomyocytes. When these

Table 3. Family history of red flags

Any of the following findings in the family history should prompt further investigation:
Sudden cardiac death (aged <50 years)
Sudden infant death syndrome
Unexplained syncope, particularly if it occurs during physical activity
Seizures without objective ictal activity
Heart transplantation in the absence of coronary artery disease
Presence of a pacemaker and/or implantable cardioverter-defibrillator in a young person (aged <50 years)
Muscle weakness or myopathy
Individual who died of a supposed heart attack at a young age, in the absence of known coronary risk factors and with no autopsy performed.

proteins are dysfunctional, the mechanical bonds that hold cardiomyocytes together stop functioning. This defect plays a key role in the pathogenesis of fibrofatty replacement of the myocardium and the development of the disease phenotype.¹³⁷⁾¹⁴²⁾ This separation triggers the process of scarring and fat replacement, which can be increased by high physical activity, which explains why it is common in young athletes.¹⁴³⁾ Pooled data from major studies on molecular genetic screening for desmosomal gene variants have shown that the overall success rate of genetic testing for patients who meet the diagnostic criteria was about 50%.¹⁴⁴⁾ A small number of affected patients may have defective nondesmosomal genes, such as *TMEM43* and *PLN*, in certain groups due to the influence of the founder.¹⁴⁵⁾¹⁴⁶⁾ The most common causative variants occur in *PKP2* (encoding plakophilin-2, 10–45%), followed by *DSP* (encoding desmoplakin, 10–15%), *DSG2* (encoding desmoglein-2, 7–10%), and *DSC2* (encoding desmocollin-2, 2%).¹⁴⁷⁾¹⁴⁹⁾ PVs in these genes have also been associated with ARVC, RCM, DCM, and SCD.¹⁵⁰⁾¹⁵¹⁾ Affected patients usually suffer from HF, advanced atrioventricular and VT that require pacemaker implantation and/or ICD.

Implications of the genetic test in arrhythmogenic right ventricular cardiomyopathy

Guidelines

HRS/EHRA*

- (1) Variant-specific cascade screening is recommended. (class I).
- (2) Clinical (phenotypic) screening in at-risk 1st degree relatives is recommended (level of evidence A).
- (3) Comprehensive or targeted (*DSC2*, *DSG2*, *DSP*, *JUP*, *PKP2*, and *TMEM43*) arrhythmogenic cardiomyopathy (ACM)/ARVC genetic testing can be useful for patients satisfying task force diagnostic criteria for ACM/ARVC (class IIa).
- (4) Genetic testing may be considered for patients with possible ACM/ARVC (1 major or 2 minor criteria) according to the 2010 Task Force Criteria (class IIb).

*Updated in 2018 in a joint publication with the ACMG.⁵²⁾

†Clinical phenotype screening includes the following:

- Medical history, with special attention to HF symptoms, arrhythmias, presyncope or syncope, and thromboembolism.
- Electrocardiography, holter, and echocardiography.
- Cardiac magnetic resonance is recommended if echocardiography is insufficient to define the phenotype.

Diagnostic value

Unlike all other forms of cardiomyopathy, the diagnostic criteria for ARVC include the

presence of a pathogenic variant in genes associated with ARVC as the major diagnostic criteria.¹⁵²⁾ However, it has not been determined which variants have sufficient evidence to be considered as disease-causing; therefore, it may be challenging to define the pathogenicity to a variant. In addition, a negative genetic test does not rule out the possibility that the phenotype is due to a variant in an unknown gene or that the molecular genetic screening technique cannot detect all disease-causing variants, including large deletions or duplications. According to the general recommendations for molecular genetic testing in inherited cardiomyopathies,¹⁵³⁾ genetic tests will be performed to detect a PV or LPV in a proband who have already fulfills the diagnostic criteria for ARVC phenotype. When the test is positive in an ARVC proband, cascade screening is recommended for family members. Early detection of asymptomatic at-risk individuals can suggest lifestyle changes (restrict vigorous physical exercise) to delay development of the phenotype.

Genotype-phenotype correlation

Based on the current classifications of other cardiomyopathies such as HCM and DCM and according to the 2019 HRS Expert Consensus Statement on arrhythmogenic cardiomyopathy,¹⁵⁴⁾ it is appropriate to propose a disease classification that covers various conditions of different etiologies, including: the RV, the LV, or both and either genetic or non-genetic causes, are collectively referred to as “arrhythmogenic cardiomyopathy (ACM).” The common denominator is obvious nonischemic ventricular myocardial scarring and scar-related ventricular arrhythmias. Since myocardial fibrosis acts as a substrate for malignant ventricular arrhythmias, all disease conditions manifesting with the ACM phenotype are associated with a distinctively significantly increased risk of SCD. Therefore, the existence of significant arrhythmogenic ventricular scarring necessitates ICD implantation for patients affected by either genetic or nongenetic ACM, as their primary prevention regardless of the patient’s systolic ventricular function.

Prognostic value (risk stratification)

Patients with multiple PVs in major desmosomal genes (compound or digenic heterozygosity), ranging from 6%¹⁵⁵⁾ to 20%,¹⁵⁶⁾¹⁵⁷⁾ has been associated with earlier manifestation of disease, a higher prevalence of arrhythmic events, and more frequent LV dysfunction and risk of HF¹⁵⁸⁾ than those with a single mutation. It is noteworthy that multiple desmosomal gene mutations and male gender resulted in independent predictors of life threatening arrhythmic events with hazard ratio of 2.3 and 2.9, respectively.¹⁵⁹⁾ Women with desmosomal genetic variants have a lower risk of expressing the disease than men and are therefore more likely to be healthy carriers. It is not fully understood why there are differences in the prevalence of sexual penetrance, but there could be differences due to varying levels of participation in competitive and intensive sports among men, or due to the influence of hormones.¹⁶⁰⁾

Nearly 86% of variant-carrying relatives of ARVC patients were asymptomatic at the time of diagnosis. The presence of phenotypic expression has been shown to be a prerequisite for malignant ventricular arrhythmias and SCD. In a cohort of ARVC desmosomal genetic variant carriers who were prospectively investigated during a long-term follow-up (8.5 years), Merner et al.¹⁴⁵⁾ found that major arrhythmic events generally occurred in desmosomal gene mutation carriers who fulfilled morpho-functional criteria and had major risk factors. Patients with desmosomal gene mutation and no apparent ARVC phenotype have a relatively benign prognosis. The electrical and structural abnormalities found on CMR in ARVC genetic variant carriers identified those who are at risk for arrhythmic events and may benefit from ICD implantation.¹⁵²⁾¹⁶¹⁾

RESTRICTIVE CARDIOMYOPATHY GENETICS

Although rare, RCM in part shares a genetic basis with HCM. RCM is usually diagnosed by TTE, that demonstrates the characteristic (yet nonspecific) morphological constellation of a nonhypertrophied, nondilated ventricle with preserved ejection function and dilated atria.¹⁶²⁾ Doppler techniques reveal restrictive filling dynamics of the LV and RV and an abnormally high E/A ratio, indicating accentuated early filling with diminished late filling.

*Guidelines*⁵²⁾⁵⁵⁾

- (1) Obtaining a family history of at least three generations, including the creation of a pedigree, is recommended for all patients with RCM (level of evidence A).
- (2) Clinical (phenotypic) screening for cardiomyopathy in at-risk 1st-degree relatives is recommended (level of evidence A).

The frequency of RCM is extremely low, which has limited understanding its genetic characteristics to assessing a small number of genes in small patient groups. Familial RCM is usually passed on in an autosomal dominant manner, but other possible modes of inheritance include autosomal recessive and compound heterozygous forms. Hereditary forms of RCM may not typically be a distinct genetic cardiomyopathy; but may be part of the broad phenotypic spectrum of HCM that is manifested by limited (or absent) hypertrophy and restrictive physiology. A main observation was that the RCM phenotype coexists with HCM-related gene variants as discussed above. Variants have also been described in other sarcomeric genes, including *TTNT2*, *MYBPC3*, *MYL2* and *MYL3*, and *ACTC1*.¹⁶³⁾¹⁶⁴⁾ Menon et al.⁸¹⁾ have reported a PV in *TTNT2* that is inherited in an autosomal dominant manner and may present with three distinct clinical phenotypes: RCM, HCM, or DCM. Linkage analysis followed by sequencing identified a missense variant resulting in p.Ile89Asn substitution in *TTNT2*. De novo sarcomeric variants appear to be associated with severe disease expression and premature death or heart transplantation in childhood.¹⁶⁵⁾ Nonsarcomeric variants have also recently been identified in RCM. PVs in *MYPN* and *TTN* may cause myofibrillar disarray and restrictive physiology.¹⁶⁶⁾ The mechanism proposed for the progress of RCM is altered myofibrillogenesis. PVs in *FLNC* have also been recognized in several families and demonstrate autosomal dominant inheritance.¹⁶⁷⁾

In addition, various systemic diseases that distress the heart can mimic the RCM phenotype, including hereditary amyloidosis (mainly caused by PVs in *TTR* gene, but also in *CST3*, *FGA*, *LYZ*, *GSN*, *APOA2*, and *APOA1*), metabolic disorders such as glycogen storage diseases, Fabry disease (*GLA*), hemochromatosis (*HFE*), cystinosis, sarcoidosis, lymphoma, Danon's disease (*LAMP2*), and PRKAG2-mediated heart disease.¹⁶⁸⁾

It is also important that clinicians be aware that there are forms of familial RCM for which a recognized genetic basis does not exist, and some RCM patients with an identified variant will not have an affected family member due to variable penetrance.

Implications of the genetic test in restrictive cardiomyopathy

The yield of genetic tests in RCM remains undetermined. It is presently unclear whether genetic testing has any value in classifying the risk stratification for patients with isolated RCM, but it can be important when evaluating patients with secondary causes of RCM, such as infiltrative diseases (amyloidosis, sarcoidosis) or storage disorders (Gaucher disease,

glycogen storage disease, and Fabry disease).¹⁶²⁾ In addition, it is crucial to ascertain the genetic status of asymptomatic members to determine their potential risk of developing RCM or other cardiomyopathy phenotypes later in life.

LEFT VENTRICULAR NONCOMPACTION CARDIOMYOPATHY GENETICS

LVNC is cardiomyopathy characterized by prominent trabeculations of the LV with deep intertrabecular recesses and thinning of the compact epicardium.¹⁶⁹⁾ Current imaging diagnostic criteria, including the most commonly used echocardiographic Jenni criteria, are based on the ratio between a severely thickened myocardium. This myocardium has a noncompacted layer that is at least twice as thick as the compacted layer, as measured in systole in the short-axis view.¹⁷⁰⁾ LVNC is thought to occur in approximately 1 in 7,000 live births and occurs in newborns, young children, and adults. Major adverse events include life-threatening arrhythmias, thromboembolism, and HF. Infants who have conditions such as systemic disease and metabolic derangement have reportedly experienced the worst outcomes. It is estimated that 30–50% of cases of LVNC are genetic, as each year differently sized cohorts of pediatric and adult cases are studied. Autosomal dominant transmission is the most common mode of inheritance, followed by X-linked and maternal modes.¹⁷¹⁻¹⁷⁴⁾ In addition, sporadic cases are common and are thought to be involved in 60–70% of cases. Although several known LVNC susceptibility genes have been identified, no single susceptibility gene predominates, and systematic evaluations of large populations have not been conducted to date. Variants in more than 15 genes encoding sarcomeric proteins (*MYH7*, *MYBPC3*, *ACTC1*, *TNNT2*, and *TPM1*),¹⁷⁵⁻¹⁷⁷⁾ ion channel proteins (*HCN4*, *SCN5A*),¹⁷⁸⁾¹⁷⁹⁾ and other proteins have been linked to LVNC. Previous studies have identified that sarcomere-encoding genes are most common in approximately 32–41% of the adult cohorts with LVNC.¹⁷³⁾¹⁸⁰⁾ These studies, however, used various definitions for LVNC, and many did not account for the co-occurrence of hypertrophic or DCM. Among the LVNC genes, *MYH7*, *MYBPC3*, and *TTN* are the most prevalent and are also frequent causes of HCM and DCM. Previous family studies of LVNC occasionally reported relatives with HCM or DCM, apparently without noncompaction, in familial LVNC. Waning et al. showed that cardiac features and genetic defects in index cases may help to predict the cardiomyopathy phenotype and associated risk for relatives. Familial segregation of isolated LVNC, LVNC with DCM, or LVNC with HCM have been observed, and families in which a range of different LVNC phenotypes occurred have been studied. When the index case had isolated LVNC, relatives were more likely to have similarly isolated LVNC, which was linked to a better prognosis with less RV and LV systolic dysfunction and a low risk for MACEs.¹⁷³⁾ Almost half of the patients with isolated LVNC had a variant, mainly in the head domain of *MYH7*. LVNC with DCM was the most common LVNC phenotype and variants in the tail domain of *MYH7* and in *TTN*, which are associated with increased risk for LV systolic dysfunction and MACEs.¹⁷³⁾ Chances of cardiac symptoms, LV systolic dysfunction, and MACEs increased in the first year of life for children with a variant. In contrast, risk of MACEs was low in children with sporadic LVNC. LV systolic dysfunction is a high risk for MACEs in adults with a variant. Additionally, nuclear proteins *LMNA* and *RBM20* pathogenic variants were associated with worse outcomes.¹⁷¹⁾¹⁷²⁾ *HCN4* variants may also cause ventricular fibrillation (VF) in patients with LVNC. It is important to keep in mind that while the age of manifestation and the phenotype displayed by those affected by a LVNC-associated variant may differ in families.¹⁸¹⁾ As well, genetic testing is necessary to make an early diagnosis of syndromic forms of LVNC (i.e. Danon disease), allowing for early

medical interventions and family planning. Interestingly, some patients in the same family can exhibit different phenotypes with the same variant (variable expression of the disease), varying from LVNC to HCM or DCM.

Implications of the genetic test in left ventricular non-compaction

Diagnostic value

The diagnostic yield of genetic testing in adult proband patients with LVNC is low. In patient with LVNC accompanied by cardiac and syndromic features, genetic testing is most helpful for accurate diagnosis.¹⁸²⁾ In addition, identification of a definite PV in clinically affected probands should lead to screening of all at-risk individuals (siblings, parents, children), including those with a negative phenotype. One of the important aspects of genetic testing is the ability to confirm PV-positive or PV-negative status in family members of clinically affected, genotype-positive subjects. Due to possible X-linked inheritance in some patients, affected male family members may have a noticeable disease expression, while females may have milder signs of LVNC (or none at all); thus, these females may have a role as transmitters for subsequent generations.¹⁸²⁾

Prognostic role of genetic testing for left ventricular non-compaction

Thus far, genotype-phenotype correlations has not been well characterized in LVNC; therefore, prognostic value of genetic testing is unclear.

IMPORTANT INHERITED SYNDROMES ASSOCIATED WITH CARDIAC DISEASE

Table 4 summarizes the most frequently implicated genes and clinical features in inherited syndromes associated with cardiac disease.¹⁸³⁻¹⁸⁶⁾

Neuromuscular disease

Neuromuscular diseases may accompany cardiomyopathies; in some forms of neuromuscular disease, irregular heart rhythm may be the critical feature symptom. Patients with PVs in the *LMNA* gene may or may not have muscle disease, and it ranges from limb-girdle muscular dystrophy to Emery–Dreifuss muscular dystrophy, which is usually associated with contractures of the elbows and Achilles tendon.¹⁸⁷⁾¹⁸⁸⁾ Cardiac involvement includes progressive arrhythmias (brady/tachyarrhythmias, SCD) and often progresses to DCM. The genetic variants in DMD that encode dystrophin, are present in individuals who have an X-linked recessive pattern of inheritance. Dystrophin connects sarcomeric proteins to the plasma membrane via the dystroglycan complex. Duchenne muscular dystrophy is caused by muscle contraction, which results in the loss of cell membrane integrity, ultimately resulting in cell death and the replacement of the affected muscle tissue with fibro-fatty tissue.¹⁸⁹⁾ Duchenne muscular dystrophy cardiomyopathy usually manifests in the second decade of life, and screening for cardiomyopathy is crucial and is performed yearly in adult patients.¹⁹⁰⁾ Friedreich ataxia is an autosomal recessive inheritance caused by the loss of function variants in the *FXN* gene. The key clinical manifestations are neurologic dysfunction (e.g., progressive ataxia of limbs), HF and diabetes mellitus. Echocardiographic and electrocardiographic abnormalities are those of morphologically mild asymmetric septal hypertrophy with gradually systolic dysfunction.¹⁹¹⁾¹⁹²⁾

Table 4. Inherited syndromes associated with cardiac disease

Gene	Protein	Disease	Clinical features	Note
DMD	Large sarcolemmal protein dystrophin.	Duchenne muscular dystrophy	Early-onset DCM with history of muscular dystrophy	X-linked, recessive Duchenne: 1:4,000 to 1:6,000 live male births ¹⁸²⁾
		Becker muscular dystrophy	Milder and later onset age of onset of DCM tends to be later	Becker: 1:18,000 live male births ¹⁸³⁾
Mitochondria	Supply and regulation of energy metabolism	MERRF syndrome	Myoclonic epilepsy, septal hypertrophy and DCM	Maternal transmission or autosomal dominant
		MELAS syndrome	Mitochondrial encephalopathy Lactic acidosis Stroke like episodes Heart failure Symmetrical LVH	Maternal transmission or autosomal dominant
		Kearns-Sayre syndrome	Ophthalmoplegia, conduction defects and DCM, heart block	Maternal transmission or autosomal dominant
FRDA/FXN	Frataxin: a mitochondrial protein of iron homeostasis	Friedreich ataxia	Cerebellar ataxia, dysarthria, HCM, diabetes, neurosensory hearing loss, and visual impairment supraventricular tachycardia	Spinocerebellar ataxia
PRKAG2	5'-AMP-activated protein kinase subunit gamma-2	PRKAG2-related cardiomyopathy	Symmetrical nonobstructive hypertrophy, diastolic dysfunction ¹⁸⁴⁾ ¹⁸⁵⁾	Skeletal myopathy
TTR	Transthyretin	Amyloidosis	ECG: pseudo-infarct pattern, low-voltage QRS, conduction abnormalities Echo: LVH+right ventricular hypertrophy MRI: global subendocardial or transmural late enhancement, suboptimal myocardial nulling	Neuropathy, autonomic dysfunction, Carpal tunnel syndrome, renal failure and proteinuria
LAMP2	Lysosome-associated membrane glycoprotein 2	Danon disease	ECG: high-voltage QRS, preexcitation pattern, short PR interval Echo: LVH	Skeletal myopathy, intellectual disability
PTPN11/RAF1		Noonan syndrome	ECG: left or extreme right axis deviation Echo: congenital heart defects (mainly pulmonary stenosis and hypertrophic cardiomyopathy)	Typical facies, short stature, webbed neck, pectus excavatum/carinatum, developmental delay, bleeding disorders
GLA	Galactosidase Alpha	Fabry disease	ECG: LVH, high-voltage QRS, short PR interval, preexcitation, sinus node dysfunction, conduction abnormalities, atrioventricular block, supraventricular tachyarrhythmia ⁸ Echo: LVH	Angiokeratoma, cornea verticillata, neuropathic pain, stroke/transient ischemic attack, vertigo, tinnitus, hearing impairment, renal failure and proteinuria, GI symptoms

DCM = dilated cardiomyopathy; ECG = electrocardiography; GI = gastrointestinal; LVH = left ventricular hypertrophy; MELAS = mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes; MERRF = myoclonic epilepsy with ragged red fibers; MRI = magnetic resonance imaging.

Mitochondrial myopathies

Mitochondrial myopathies have 2 inheritance forms: maternal inheritance and autosomal dominant transmission.¹⁹³⁾ The final diagnosis is only made after pathological confirmation, including mitochondrial quantity and function or genetic testing.¹⁹⁴⁾ Mitochondrial DNA-related diseases constitute approximately 3% of DCM cases. MELAS is the syndrome of mitochondrial encephalo-myopathy with lactic acidosis and stroke-like episodes, and it is a maternally inherited multisystemic disorder caused by PVs in mitochondrial DNA. MELAS frequently manifests in childhood after normal early development.¹⁹⁵⁾ Cardiac involvement is occurred in over 1/3 of patients with MELAS syndrome and exhibits a bimodal age-related distribution with different final outcomes. Adult-onset cardiomyopathy appears to be a mild and nonprogressive mid-term manifestation.¹⁹⁶⁾

Amyloid cardiomyopathy

Cardiac disease due to the deposition of amyloid fibrils is seen in familial amyloid cardiomyopathy and hereditary TTR amyloidosis, as well as in nongenetic diseases (e.g., senile TTR amyloidosis). The cardiac manifestations of these diseases have been reviewed in prior articles.¹⁹⁷⁾¹⁹⁸⁾

Fabry disease

Fabry disease is an X-linked genetic multisystem disorder that results in a deficiency of the enzyme alpha galactosidase. Cardiac manifestations may be the predominant clinical features, usually with a phenotype of HCM and may also present in females.¹⁹⁹⁻²⁰¹⁾

IMPORTANT CONSIDERATIONS IN GENETIC CARDIOMYOPATHIES

The diversity of cardiomyopathies results from the multifactorial involvement of genetic, allelic, epigenetic, and environmental variables, all of which play a role in determining the cardiomyopathy phenotype.

Incomplete and age-related penetrance

Inherited cardiomyopathies typically exhibit significant phenotypic variability, and families can show greater diversity in their manifestations. Penetrance—the percentage of PV carriers with clinically detectable disease—increases with age but remains below 100%. Hypertrophy occurs in the majority of patients with HCM during adolescence, whereas sarcomeric DCM has a bimodal age of onset (with peaks during childhood and mid-adulthood).²⁰²⁾ It is infrequent to find multiple family members with clinically apparent ARVC in a single pedigree, suggesting a reduced penetrance. Therefore, it is difficult to identify family members with subtle phenotypes, because it may take decades to develop a reliable and robust phenotype. In addition, there is increasing evidence that, regardless of the phenotype, certain cardiomyopathy-related variants have a high arrhythmia prevalence, which make cascade genetic screening a key tool for identifying high-risk individuals in affected families.²⁰³⁾ The risk of developing inherited cardiac disease is affected by multiple genetic and environmental factors, and every case/family must be individually evaluated by a multidisciplinary expert team.

Missing causal genes

It is difficult to identify the remaining causal genes, usually called missing causal genes, which are usually related to cardiomyopathy manifesting as sporadic cases or in small families. The missing causal gene in cardiomyopathy might partly be due to the difficulty in determining the causality of the genetic variants in sporadic cases and small families.²⁰⁴⁾

Generally, the effect size gradient of genetic variants ranges from a large causal relationship to an insignificant scale.²⁰⁵⁻²⁰⁷⁾ Genetic variants that have influential large effect sizes are considered to be PVs accountable for autosomal dominant single-gene disorders in large families including cardiomyopathy. Through robust genetic techniques, such as cosegregation and linkage analyses, such PVs have been mapped and identified. The *MYH7* and *MYBPC3* genetic variants are good examples. Clinically small or subtle effects on the genetic level can be categorized as ‘effect sizes’ on the other end of the spectrum. When it is in the functional state, such variants have a moderate effect on the disorders in phenotype, but do not cause monogenic disorders. The center of the spectrum represents a subset of genetic variants with intermediate to large effect sizes and incomplete penetrance; their effects are influenced by other genetic and nongenetic factors. Although it is believed that these variants cause cardiomyopathy, the penetrance of these variants is insufficient or low. There is no clear cosegregation of the genetic variant and the phenotype in this case; thus, it is impossible to establish a strong linkage, even more so when the family size is small

and the disease is sporadic. This difficulty is partly due to the large number of variants in each genome. One strategy for identifying missing causal genes is to conduct large-scale association studies followed by rare variant analysis. The evidence for an association between a candidate gene and cardiomyopathy in a discovery population is considered tentative (i.e., hypothesis-generating) and requires replication in a separate population.

Modifier genes

The variability in the phenotype of cardiomyopathy is partly attributed to the influence of modifier genetic variants and environmental factors. Each human nuclear genome contains, on average, approximately 11,000 nonsynonymous variants, 160 premature protein truncation variants, and 500,000 variants in known regulatory regions.²⁰⁸⁾²⁰⁹⁾ PVs in genes and pathways implicated in regulating cardiac hypertrophy and fibrosis could influence the expression of the cardiomyopathy phenotype and function as modifier genetic variants. Modifier genes are genes other than the causal genes that affect the phenotypic expression of genetic disorders. Modifier genes are the genetic background of affected individuals, which differs because of DNA polymorphisms. Modifier genes are neither sufficient nor necessary to cause cardiomyopathy, but rather affect the severity of cardiomyopathy phenotypes, such as the degree of hypertrophy and the risk of SCD.

Epidemiological and family studies in humans²¹⁰⁾²¹¹⁾ and experimental data in animals²¹²⁾ have shown that the genetic background has an impact on the degree of cardiac hypertrophy observed in response to the hypertrophic stimulus. Clinical observations show a significant degree of variability in the phenotypic expression of hypertrophy, sudden death, and cardiac failure in patients with cardiomyopathy, a genetic model of the cardiac hypertrophic response; this variability underscores the influence of modifier genes on cardiac phenotypes. A large degree of heterogeneity in the phenotypic expression of the disease is readily apparent when individuals who have the same causative variants or family members who share the same variations all have varied outcomes. The final phenotype is the product of causal variants, modifier genes, and environmental factors. Thus, given the significance of the modifier genes in modulating cardiac phenotypes in cardiomyopathy, their identification and characterization of their role will complement the primary (causal) variant in predicting prognosis and could be essential for designing specific and more comprehensive therapies.

COUNSELING BEFORE GENETIC TESTING

Genetic counseling is recommended for all patients with cardiomyopathy and their family members. It is essential to take a multigenerational (preferably at least three generations) family history of cardiomyopathy and suspected SCD events. All patients with cardiomyopathy should receive counseling before a genetic test, ideally by an experienced physician with knowledge of cardiomyopathy genetics, such as a genetic counselor. Through use of this strategy, patients will understand the rationale for testing, gain empowerment. They will also be better equipped to communicate and deal with the dynamics within their families. Given that patients often communicate the results and implications of genetic testing to at-risk family members, their understanding of this information is imperative. Pretest genetic counseling is informed by the benefits and potential harm (including psychosocial, ethical, and insurability) of finding a genetic cause of the disease. Many patients may face financial stress because of the high cost of optional genetic tests that do not directly affect healthcare. Ensuring that patients have a full understanding of financial

and insurance implications of genetic testing is thus of critical importance, as private insurance coverage is not consistent. Theoretically, a genetic counselor is qualified to give financial advice about genetic testing, but most genetic counselors are not trained to provide financial advice on genetic testing, and they are not certified in this area.

CHOICE OF GENETIC TEST

Genetic testing, if positive, will assist the diagnosis in a proband; however, if the test is negative, it will not be ruled out. If a proband with a positive test is identified, cascade screening, or testing for the presence of the variant in family members should be undertaken. A positive screen, that is an identification of a relative carrying the same PV as detected in the proband with cardiomyopathy, should lead to a detailed examination for the presence of the cardiomyopathy phenotype. If the phenotype is manifested, the relative may be diagnosed with cardiomyopathy and treated appropriately. Relatives who are PV carriers but do not have the phenotype should undergo periodic clinical evaluations (history, physical examination, electrocardiogram, and echocardiogram), or more frequently if symptoms develop. Improved genome sequencing approaches have resulted in a remarkable increase in the speed and efficiency of testing and reduced costs, which has transformed our insights into cardiomyopathy variant genomic disease.²¹³⁻²¹⁵⁾

Next-generation sequencing (NGS) of cardiomyopathy genes for standard panels has emerged as a rapid testing alternative to Sanger sequencing, providing analytical characteristics for the comprehensive exploration of genetic causes.²¹⁵⁾ Various commercially available gene panels are routinely used to identify genetic variants in cardiomyopathies. On the other hand, NGS has some shortcomings, including a lack of representation and coverage of certain exons; this raises the risk of reduced sensitivity and the potential for false negatives with clinically relevant PV detection. As a result, the procedure that first required target enrichment and then NGS for high-throughput genetic testing of disease genes for DCM, HCM, and other cardiomyopathies has now become possible and has technically been validated by the nearly complete coverage and high accuracy of the approach.

Inherent to more extended genetic screening using whole exome sequencing (WES) and whole genome sequencing (WGS) is the detection of more variants of unknown significance and variants in genes that are unlikely to be associated with the phenotype. It is not recommended to report these results back to the patients on a routine basis. Careful variant classification according to the ACMG guidelines⁹⁾ is mandatory, and genetic counseling plays a central role in validating variants through familial segregation analysis, as well as in discussing the limits of risk stratification for relatives. Genetic counseling should include discussions on potential reanalysis and even retesting after predefined intervals in gene- elusive patients with a high suspicion of genetic disease.

Guided but systematic implementation of genetic testing in clinical practice is expected to allow us to precisely distinguish cardiomyopathies within broad phenotypes, improve the effectiveness of counseling for patients and their relatives, and better inform important clinical decisions, such as defibrillator implantation.

CONCLUSIONS

Although it is now easy to obtain human genome sequence data, the approach is far from perfect; this has encouraged the notion of incorporating genomic data into routine health care in order to advance precision medicine. Increasing numbers of rare genetic variants have been validated, and new common genetic markers for the risk of cardiomyopathy have been identified. The usefulness of the research depends on answering those questions, which in turn are contingent on whether and when other patients and relatives who have detrimental genetic variants should be treated, and how to investigate therapeutic efficacy. Despite these difficulties, a new clinical framework for future evidence-based and personalized HF care in cardiomyopathy is already emerging from the integration of comprehensive sequence analyses with detailed phenotyping. Genotype-phenotype correlations may seem inconsistent because traditional phenotypes (LVH, HF, and SCD) are late manifestations of the disease. Studying the earlier manifestations of a disease allows researchers to establish stronger correlations, discover more mechanistic pathways, and potentially find disease-modifying treatments. It is our hope that future research will allow the use of genetic testing to identify variants and subsequently improve treatment outcomes.

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