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Evolving Approaches to Genetic Evaluation of Specific Cardiomyopathies

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Abstract The understanding of the genetic basis of cardiomyopathy has expanded significantly over the past 2 decades. The increasing availability, shortening diagnostic time, and lowering costs of genetic testing have provided researchers and physicians with the opportunity to identify the underlying genetic determinants for thousands of genetic disorders, including inherited cardiomyopathies, in effort to improve patient morbidities and mortality. As such, genetic testing has advanced from basic scientific research to clinical application and has been incorporated as part of patient evaluations for suspected inherited cardiomyopathies. Genetic evaluation framework of inherited cardiomyopathies typically encompasses careful evaluation of family history, genetic counseling, clinical screening of family members, and if appropriate, molecular genetic testing. This review summarizes the genetics, current guideline recommendations, and evidence supporting the genetic evaluation framework of five hereditary forms of cardiomyopathy: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), restrictive cardiomyopathy (RCM), and left ventricular noncompaction (LVNC).

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Introduction

In the contemporary definitions and classification of cardiomyopathies by the American Heart Association in 2006, cardiomyopathies represent a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction, and can be divided into primary cardiomyopathies which predominantly involve the heart muscle, or secondary cardiomyopathies which are a result of generalized systemic (multiorgan) disorders [1]. With the rapid evolution of molecular genetics in cardiology, the knowledge and literature of the complex interplay between genetics and cardiomyopathies have expanded significantly over the past few decades. Inherited cardiomyopathies (or "primary cardiomyopathies of genetic origin") encompass a wide spectrum of clinical phenotypes which classically include dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), left ventricular noncompaction (LVNC), and others (glycogen storage, mitochondrial, conduction system, and ion channel disorders) [1–4].

As genetic evaluation of cardiomyopathies is inherently complex and rapidly advancing, various consensus statements and guidelines have been published to assist medical practitioners with the genetic evaluation of cardiomyopathies [5••, 6••, 7]. Genetic evaluation framework of inherited cardiomyopathies typically encompasses family history collection, genetic counseling, clinical screening of family members, and if appropriate, molecular genetic testing. In this review, we summarize the underlying genetics, practical considerations,

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guidelines' recommendations, and evidence supporting the genetic evaluation framework of these various hereditary forms of primary cardiomyopathy.

DCM

Genetics

The diagnosis of familial DCM is made when at least two closely related family members are affected by DCM, or in the presence of a first-degree relative of a DCM patient, with well-documented unexplained sudden death at ages 35 years or younger [8, 9]. Clearly, these criteria have been arbitrarily defined, and complete family history may not be readily available in those with unexplained DCM. In clinical practice, DCM is more commonly encountered than other inherited cardiomyopathies, but the familial component is less prevalent. Phenotype studies of DCM estimated that 20 to 48 % of idiopathic DCM had a familial component [10–12], with autosomal dominant inheritance being the predominant pattern of transmission, while X-linked, autosomal recessive, and mitochondrial inheritance being less common [13]. More than 40 genetic mutations associated with DCM have been identified in familial DCM genetic studies (Table 1) [9]. These genes encode components of a wide variety of cellular compartments and pathways, including the nuclear envelope, contractile apparatus, the force transduction apparatus (e.g., Z-disk and costamere), gene transcription and splicing machinery, and calcium handling [4, 16]. The variable phenotypic spectrum of familial DCM is possibly attributed to incomplete penetrance, the presence of modifier genes, age-related penetrance, and/or variable expressivity of the genetic mutations [9]. The recently discovered titin gene (*TTN*) is a good example of the clinical variability of the various mutations, whereby location and type of mutation in the gene can result in different degrees of functional alterations.

Family History

Family history remains an essential component in the evaluation of DCM, with the goals of ascertaining if the DCM may be familial, determining the inheritance pattern, and to identify family members who may be at risk [6••, 7]. A careful family history for three or more generations, including history of heart failure, DCM, cardiac transplantation, unexplained sudden death, unexplained cardiac conduction system disease and/or arrhythmia, or unexplained stroke or other thromboembolic disease should be obtained to assess the possibility of familial DCM. With a suggestive family history for familial DCM, medical records or death certificates of the affected family members should be requested to verify the diagnosis. If family history is negative, family members should be reminded that family history is insensitive to detect DCM and they should still undergo clinical screening [9]. It is also important to emphasize that a complete family history may demand repeated evaluation, occasionally requiring verification of primary sources of medical documentation from various family members to confirm their accuracies.

Molecular Genetic Testing

Genetic testing can be used to facilitate the establishment or confirmation of a diagnosis of familial DCM, especially in cases with inconclusive family history. The recent development of next-generation sequencing (NGS) methods has led to dramatic improvement in efficiency and speed of gene sequencing, as well as markedly reduced costs for clinical genetic testing [17, 18]. As a result, genetic testing for DCM is becoming more widely available in the laboratories and more commonly used in clinical practice. The lists of genes that can lead to inherited cardiomyopathies and the testing laboratories in the USA and worldwide are catalogued at the GeneTests website funded by National Institutes of Health and the Genetic Testing Registry of the National Center for Biotechnology Information website respectively [19, 20]. Due to significant locus and allelic heterogeneity, the variant spectrum and detection rates of genetic testing for DCM are less well-defined than those for HCM. The identification of variants of unknown clinical significance (VUS), wherein a genetic sequence variation is reported but the pathogenicity is unknown, limits its clinical utility particularly in the setting of predictive testing as asymptomatic at-risk family members should not be tested for these types of variants. It is estimated that the DCM genetic testing sensitivity now ranges from 15 to 25 % [9].

Genetic Counseling

Genetic counseling is an integral part of the DCM genetic testing process and has been recommended in major guidelines [6••, 7]. Genetic counseling sessions, commonly conducted by genetic counselors or medical geneticists, is of paramount importance in providing an explanation of the benefits, risks, and limitations of clinical and/or genetic testing for patients with familial DCM and their at-risk relatives. It also includes a review of the characteristics and genetics of familial DCM, a thorough pedigree analysis to ascertain the likely pattern of inheritance, and advice to assist families in making psychosocial adjustments to the recognition of a potentially heritable disorder in the family [21]. In fact, many insurance companies require pretest genetic counseling in order for the testing to be covered.

Table 1 Genetic mutations associated with cardiomyopathies

Gene symbol	Gene name	DCM	HCM	ARVC	RCM	LVNC	Inheritance pattern
ABCC9	ATP-binding cassette, subfamily C, member 9	X					AD
ACTC	α-Cardiac actin	X	X		X	X	AD
ACTN2	α-Actinin2	X	X				AD
ANKRD1	Cardiac ankyrin repeat, domain 1	X	X				Unknown
BAG3	BCL2-associated athanogene 3	X			X		AD
CASQ2	Cardiac calsequestrin 2					X	AR
CAV3	Caveolin 3		X				AD, AR
COX15	COX 15 homolog, cytochrome C oxidase assembly protein		X				AR
CRYAB	Crystallin αB		X				AD, AR
CSRP3	Cysteine and glycine-rich protein 3	X	X				AD
CTF1	Cardiotrophin 1	X					Unknown
CTNNA3	αT-catenin			X			Unknown
DES	Desmin	X		X	X		AD, AR
DNAJC19	DnaJ (Hsp40) homolog, subfamily C, member 19	X		X			AR
DSC2	Desmocollin 2	X		X			AD
DSG2	Desmoglin 2	X		X			AD
DSP	Desmoplakin	X		X			AD, AR
DTNA	α-Dystrobrevin					X	AD
DYS	Dystrophin	X				X	XL
EMD	Emerin	X					XL
EYA4	Eyes absent homolog 4	X					AD
FHL2	Four and a half LIM domains 2	X					Unknown
FKTN	Fukutin	X					AR
FOXD4	Forkhead box D4	X					Unknown
GLA	α-Galactosidase		X		X	X	XL
JUP	Junctional plakoglobin			X			AD, AR
LAMA4	α4-Laminin	X					Unknown
LAMP2	Lysosomal-associated membrane protein 3	X	X				XL
LDB3	LIM-domain binding 3	X				X	AD
LMNA	Lamin A/C	X		X		X	AD
MYBPC3	Myosin binding protein C	X	X			X	AD
MYH6	β-Myosin heavy chain 6	X	X				AD
MYH7	β-Myosin heavy chain 7	X	X		X	X	AD
MYL2	Myosin regulatory light chain 2, slow		X		X		AD
MYL3	Myosin light chain 3, slow		X		X		AD
MYLK2	Myosin light chain kinase 2		X				Unknown
MYO6	Unconventional myosin VI		X				AD
MYOZ2	Myozenin 2		X				AD
MYPN	Myopalladin	X	X		X		AD
NEBL	Nebulette	X					Unknown
NEXN	Nexilin (F actin-binding protein)	X	X				AD
PKP2	Plakophilin 2			X			AD
PKP4	Plakophilin 4			X			Unknown
PLN	Phospholamban	X	X				AD
PRKAG2	AMP=activated protein kinase, γ2, noncatalytic		X				AD
PSEN1	Presenilin 1	X					AD
PSEN2	Presenilin 2	X					AD
RBM20	RNA binding motif protein 20	X					AD
RYR2	Ryanodine receptor 2			X			AD

Table 1 (continued)

Gene symbol	Gene name	DCM	HCM	ARVC	RCM	LVNC	Inheritance pattern
SCN5A	Voltage-gated sodium channel, α subunit	X					AD
SDHA	Succinate dehydrogenase complex, subunit A, flavoprotein	X					AR
SGCD	δ-Sarcoglycan	X					AD, AR
STRN	Striatin			X			Unknown
SYNE1	Spectrin repeat containing nuclear protein 1	X					AR
SYNE2	Spectrin repeat containing nuclear protein 2	X					AR
TAZ	Tafazzin	X	X			X	XL
TCAP	Titin-cap (Telethonin)	X	X				AD, AR
TGFβ3	Transforming growth factor-β3			X			AD
TMEM43	Transmembrane 43			X			AD
TMPO	Thymopoeitin	X					UI
TNNC1	Cardiac troponin C, type 1	X	X				AD
TNNI3	Cardiac troponin I, type 3	X	X		X		AD
TNNT2	Cardiac troponin T, type 2	X	X		X	X	AD
TPM1	α-Tropomyosin 1	X	X		X		AD
TTN	Titin	X	X	X	X		AD
TTR	Transthyretin	X	X				AD
VCL	Vinculin	X	X				AD

From Teekakirikul et al. and Towbin [14, 15]

AD autosomal dominant, *AR* autosomal recessive, *XL* x-linked

Clinical Cardiovascular Screening for Family Members

Family members of patients with familial DCM are encouraged to undergo clinical screening with history, physical examination, electrocardiogram, and echocardiography [6••, 7]. The rationale for this recommendation is that majority of DCM patients present late with heart failure or sudden cardiac death, but early detection of asymptomatic DCM through screening allows presymptomatic intervention that may ameliorate disease progression [22]. As familial DCM is age-dependent, it is recommended that family members undergo rescreening every 2–5 years, even though the natural history of DCM may vary between patients as well as reimbursements of their testing [6••, 7]. Periodic clinical screening to detect emerging disease is especially important for family members with positive genetic testing for DCM, especially for atypical or subtle symptoms since patients may be less aware of their own symptomatic progression. For family members with negative genetic testing, their risk for DCM is substantially reduced (assuming the pathogenic mutation has been identified for the proband), and that clinical surveillance screening can be reduced or discontinued based upon the strength of evidence that the identified variant is causative of disease [9].

Practical Considerations for DCM Genetic Testing

Targeted gene or multi-gene panel testing is recommended in DCM patients with conduction system disease or with a family history of DCM or premature unexpected sudden death. Clear genotype-phenotype correlations remain a big challenge as nongenetic causes of DCM are also prevalent, with the exceptions of *LMNA*, *SCN5A*, and *DES* genes, which are typically associated with familial DCM with underlying or preexisting conduction system disease [23–25]. For patients with familial DCM, information from genetic testing can be useful to confirm the diagnosis, to identify those with highest risk of arrhythmia and syndromic features. This is particularly important in aggressive gene mutations such as *LMNA* (often accompanied by heart block and/or atrial fibrillation) and *DES* (sometimes associated with skeletal myopathy) which carry high risk of sudden arrhythmic sudden death due to malignant and recurrent ventricular tachyarrhythmia [25, 26]. As heart block and supraventricular arrhythmia commonly precede life-threatening ventricular arrhythmias, early prophylactic or preemptive defibrillator implantation prior to the occurrence of life-threatening syncope or sudden cardiac death has been advocated to improve the patient's prognosis, even though guideline recommendations are still evolving and has yet to endorse such approach routinely [6••, 27]. However, negative genetic testing in patients with familial DCM does not exclude genetic cause, as only 15–25 % of familial DCM genetic cause is known [9]. As genetic testing panels for DCM are continually updated with further genetic causes being discovered, repeat testing with an expanded multi-gene panel may be indicated in an individual who has prior negative testing with a smaller panel of genes. In selective syndromic DCM cases, a

broader whole exome sequencing approach may be appropriate, even though challenges in uniformly interpreting pathogenic mutations remain. This challenge is particularly relevant since the recent discovery of titin mutations, which are implicated in approximately 25 % of familial DCM, yet with substantial phenotypic heterogeneity [28]. What we have also learned from mutations from the titin gene is that a reasonable subset of mutations may not be clinically pathogenic.

One goal of genetic testing for DCM is to assist the patient with family planning through excluding a known genetic mutation or establishing the mode of inheritance if an underlying genetic mutation is found. Another important diagnostic implication of DCM genetic testing is to facilitate family screening by identifying at-risk relatives who carry the disease-causing mutation. Hence, mutation-specific genetic testing is recommended for family members, following the identification of a DCM-causative mutation in the proband [5••]. The genetic testing result of the family members should always be integrated into information derived from clinical screening. It has been presumed, albeit unconfirmed that standard heart failure pharmacological treatment of mutation-positive, preclinical subjects can prevent or delay manifestation of the disease.

HCM

Genetics

HCM is the most common inherited cardiac disease, with a prevalence of approximately 1 in 500 in the general population [29]. It is usually inherited in an autosomal dominant pattern and is highly penetrant: An HCM mutation conveys substantial (>95 %) risk over a lifetime for developing clinical and/or phenotypic evidence of HCM. However, the severity of the disease and the age of onset are unpredictable due to variable expressivity and age-dependent penetrance [30]. HCM is primarily a disease of the sarcomere, and around 1400 mutations in the genes encoding sarcomere proteins have been identified to date (Table 1) [31, 32]. Mutations in the sarcomere genes encoding cardiac β-myosin heavy chain (*MYH7*, often earlier onset and more malignant) and cardiac myosin binding protein C (*MYBPC3*, later onset with variable clinical course) are the two most common and account for approximately 70 % of HCM disease genes [33]. Nonsarcomeric genes associated with HCM have been reported but are uncommon, and they include genes encoding Z-disk proteins and proteins located in the sarcoplasmic reticulum and plasma membrane [14].

Family History

A detailed family history for more than three generations should be obtained from HCM patients [6••]. Attention should be directed to identifying relatives with a history of heart failure, HCM, cardiac transplantation, unexplained sudden death, cardiac conduction system disease and/or arrhythmia, or unexplained stroke or other thromboembolic disease. Family history is important to prove that HCM is familial in origin; however, rare de novo mutations can occur [34]. Both sides of the family should be considered as possibly contributing to familial HCM, and bilineal inheritance (transmission of a disease causing mutation in the same or a different gene from both father and mother) with compound or double mutations has been reported [33, 35]. Family history of sudden cardiac death also plays a role in risk stratification for ICD implantation in HCM patients, as well as guiding the clinical screening of family members [36]. However, the natural history of a specific HCM mutation in a family may also vary.

Genetic Counseling

As one of the most common forms of inherited cardiomyopathy, genetic counseling is highly recommended and almost a routine part of the assessment of HCM patients and their family members [6••, 7, 36]. Based on family history, clinical screening, and pedigree analyses, relatives are counseled on the pattern of inheritance and the risk of inheriting HCM. Genetic counseling is also indicated before planned conception for reproductive risk assessment. As HCM is an autosomal dominant disorder, the chance that an affected patient will transmit disease to each offspring is 50 %. Genetic counseling should precede genetic testing for HCM to increase patient's understanding of the medical, psychological, and familial implications of test results.

Clinical Cardiovascular Screening for Family Members

Due to autosomal dominant inheritance nature of HCM, clinical screening with history, physical examination, electrocardiogram, and echocardiogram in asymptomatic first-degree relatives is recommended. As the clinical expression of HCM usually increases with age, periodic clinical screening should be performed generally every 2–5 years, except during puberty where more frequent screening at yearly interval is suggested. Screening can be stopped if the family members tested negative for HCM mutations or have reached 50–60 years of age [6••, 7, 36].

Molecular Genetic Testing

The molecular era for HCM emerged more than 25 years ago with identification of disease-causing mutations in cardiac sarcomere proteins [37]. The use of genetic testing for HCM was initially confined to research laboratories for the purpose of understanding the genetic basis of the disease. It was not until 2003 when clinical utility of HCM genetic testing became more widespread with the availability of newer

sequencing technologies that provide rapid, reliable, and comprehensive molecular diagnosis [38]. Alternative techniques used for molecular diagnosis of HCM include high-resolution melting, mutation detection using DNA arrays, and NGS approaches [32]. Most institutional and commercial laboratories screen 5–10 of the more frequently mutated sarcomere genes as panel testing, while NGS testing provides additional opportunities to identify selective rare variants. Overall, *MYBPC3* and *MYH7* are far more common (accounting for about 80 % of familial HCM), whereas *TNNT2*, *TPM1*, *TNNI3*, *MYL2*, *MYL3*, *ACTC*, *CSRP3*, and *TCAP* are less common. The detection rates of a pathogenic mutation in sporadic and familial HCM cases ranged from 40 to 60 % [33]. Depending on the genes included in the testing panel, the detection rate may vary between laboratories and over time within the same laboratory. The pretest probability of genetic testing for HCM is dependent on a number of clinical factors as well as morphologic manifestations (Fig. 1).

Practical Considerations for HCM Genetic Testing

It is recommended that patients with a clinical diagnosis of HCM or atypical clinical presentation of HCM undergo a comprehensive or targeted (MYBPC3, MYH7, TNNT2, TPM1, TNNI3) HCM genetic testing [5••, 6••, 36]. The principal role of HCM genetic testing in the proband is to ascertain the definitive genetic status and diagnosis of HCM. Yet, knowledge of the underlying HCM genetic mutation still has somewhat limited prognostic relevance as the genotype-phenotype correlations are not well established. Furthermore, medical therapy and surgical myomectomy should be considered in those with clinically significant septal hypertrophy regardless of genotype. On the other hand, a negative genetic testing provides some reassurance, as it may indicate a milder phenotype from a rare variant with better prognosis or a non-genetic etiology [30, 39]. There is currently no specific therapy specifically designed to target-specific HCM-causing gene mutations—a topic of active clinical and preclinical investigation. Furthermore, the implication of genetic testing in the assessment of risk of sudden cardiac death in HCM remains uncertain, and the genetic test result does not guide the indication for implantable cardiac defibrillator implantation, which is largely based on clinical risk factors. If an HCM-causing mutation is established in an index case, mutation-specific genetic testing should be performed in all first-degree family members and appropriate relatives to identify those with unrecognized disease. Mutation-specific genetic testing of the relatives is more sensitive than clinical screening, as ECG or echocardiographic abnormalities may be absent or subtle, or develop late in life. If a family member without clinical evidence of HCM tests positive for the index case's mutation (genotype positive/phenotype negative), lifelong clinical screening will be necessary due to the highly penetrance of the disease. Periodic assessment of arrhythmias with exercise stress testing or Holter monitoring may be appropriate in genotype-positive/phenotype negative individuals, especially if the family history indicates a high risk for sudden cardiac death. Mutation-negative family members and their descendants have no risk for developing HCM and do not require further clinical surveillance [5••, 27, 30]. It has been shown that genetic screening in families with a known-mutation is cost-effective, allowing half of the relatives tested to be discharged without need for clinical investigations or long-term follow-up [40]. Genetic testing, however, is not indicated in relatives when the index patient does not have a definitive pathogenic mutation [5••, 27].

ARVC

Genetics

The prevalence of ARVC is estimated to be 1 in 1000 to 2000, with >50 % of cases being familial [41, 42]. ARVC is typically inherited in an autosomal dominant pattern with age-

Clinical markers for positive genetic test results

Marker	Points
Age at Dx < 45 y	1
MLVWT ≥ 20 mm	1
Family Hx of HCM	1
Family Hx SCD	1
Reverse-curve HCM	1
Hx of hypertension	-1

Scoring range: -1 to 5 points

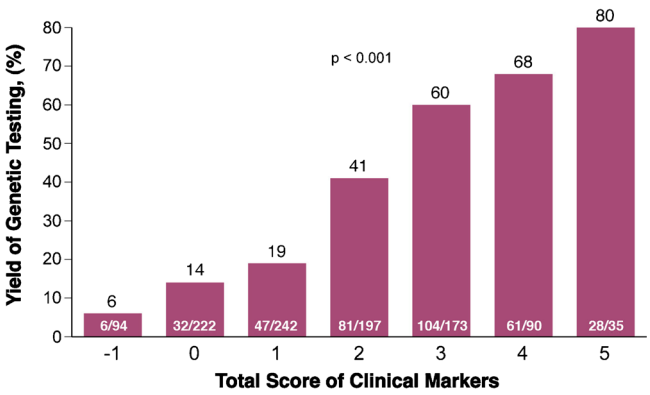

Fig. 1 Yield of panel genetic testing for HCM: The Mayo Hypertrophic Cardiomyopathy Predictor Score (reprinted with permission from Bos et al., *Mayo Clin Proceed* 2014). *Dx* diagnosis, *MLVWT* maximal left ventricular wall thickness, *Hx* history, *HCM* hypertrophic cardiomyopathy, *SCD* sudden cardiac death

dependent, low penetrance, and variable expressivity [3, 43]. Less commonly, ARVC can be inherited in autosomal recessive form, in which ARVC is part of cardiocutaneous disorders—Naxos disease and Carvajal syndrome, which are characterized by palmoplantar keratoderma and wolly hair [4]. ARVC is classically described as a disease of the desmosome, a multiprotein complex that forms cell-to-cell junctions and links intermediate filaments of adjacent cells. Mutations in five genes that encode desmosomal proteins (plakoglobin, desmoplakin, plakophilin-2, desmoglein-2, and desmocollin-2) have been found in ARVC. Three nondesmosomal genes have been implicated in ARVC: transforming growth factor β3 (*TGF-β3*), transmembrane protein 43 (*TMEM43*), and ryanodine receptor-2 (*RYR-2*) (Table 1) [4, 44].

Family History

Family history forms an important part of the diagnostic criteria for ARVC as proposed in the 2010 modified Task Force criteria [45]. Like in other inherited cardiomyopathies, a careful family history for >three generations is recommended for ARVC patients [6••]. A patient fulfills major diagnostic criteria if there is a first-degree relative who has ARVC based on current Task Force criteria or diagnosed pathologically at autopsy or surgery. History of ARVC in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria; premature sudden death (age <35 years) due to suspected ARVC in a first-degree relative and ARVC confirmed pathologically or by current Task Force criteria in second-degree relative constitute minor diagnostic criteria [45].

Genetic Counseling

Genetic counseling is strongly advised for affected individuals and family members to provide them with information on the autosomal dominant inheritance of ARVC, chance of family members being affected and the risk of transmission to subsequent generations [6••, 7]. However, a proband with autosomal dominant ARVC may have the disorder as a result of a de novo mutation. The proportion of ARVC cases caused by de novo mutation is unknown. Patients with ARVC associated with Naxos disease or Carvajal syndrome should be counseled for the autosomal recessive nature of the disease. The decision of persons with ARVC to conceive a child is difficult and should be made on a case-by-case basis [46]. It is important to emphasize that ARVC can express late in life (in the fifth decade of life and beyond in about 50 % of patients) [47].

Clinical Cardiovascular Screening for Family Members

Clinical screening with history, physical examination, electrocardiogram, and echocardiography is indicated in family members of ARVC patients every 2–5 years. As ARVC carries higher risk of arrhythmias compared with other cardiomyopathies, Holter monitor and signal-averaged ECG are recommended as part of clinical screening [5••]. Clinical screening of gene-positive relatives beyond the age of 50–60 years may be appropriate as half of the relatives may develop late-onset of disease [47]. It is suggested that magnetic resonance imaging be incorporated in the clinical screening of gene-positive relatives [6••, 48].

Molecular Genetic Testing

Due to the limited diagnostic yield of the genetic testing, failure to identify a mutation does not exclude ARVC. Nevertheless, identification of at-risk relatives remains to be the most important clinical utility of ARVC genetic testing. The ability of a multi-gene panel to detect a causative ARVC mutation in any given individual varies between laboratories based on different methods used and genes included in the panel. Sequence analysis and mutation scanning of the entire gene are the commonly used testing methods. The overall yield of genetic testing for all available genes in probands who meet the revised Task Force criteria for ARVC approximates 50 % [47].

Practical Considerations for ARVC Genetic Testing

Comprehensive or targeted mutation screening of known ARVC genes is recommended for patients satisfying definite or possible Task Force diagnostic criteria, with the main applications being confirmatory testing in index cases and cascade screening of families [5••, 6••]. Identification of a pathogenic mutation in the person with some features of ARVC fulfills major Task Force diagnostic criteria and may help to establish the diagnosis. There is a groundswell that patients meeting Task Force criteria should be offered an implantable cardiac defibrillator, although it is still debatable [48]. A person with ARVC who clearly has the disease may not personally benefit from genetic testing because the presence or absence of a gene defect would not alter the treatment [49]. In terms of prognostic implication, genotype-phenotype studies suggested that plakophilin-2 (*PKP2*) mutations are associated with earlier onset of symptoms and ventricular arrhythmia, while desmoplakin (*DSP*) mutations are associated with more left ventricular involvement [49, 50]. If a variant of uncertain clinical significance is identified in an index case, mutation-specific genetic testing is not recommended for at-risk family members. However, testing of other family members with ARVC to see if the mutation tracks with the disease in the family is appropriate [5••]. The finding of a pathogenic ARVC

mutation in at-risk family members indicates that they are at risk for developing ARVC and should be screened clinically at a more infrequent interval (yearly) rather than every 2–5 years even if their initial screen is normal. Family members who test negative for the pathogenic mutation do not require additional screening [6••]. It has been reported that as high as 6 % of healthy controls have variants identified in ARVC genes, further highlighting the complexity of the genetics of ARVC and the concerns with falsely labeling patients [51, 52]. This highlights the need for genetic counseling to aid in the interpretation of the genetic testing results and appropriate use of genetic testing in at-risk relatives.

RCM

Genetics

RCM due to familial cause is rare and is most commonly transmitted as autosomal dominant trait, but autosomal recessive and X-linked inheritance can occur [53, 54]. Genetic mutations in familial RCM are not well-defined, and there is significant overlap in the mutations between RCM, DCM, and HCM (Table 1) [55]. RCM-associated mutations have been reported in genes encoding sarcomere (*TNNI3*, *TNNT2*, *MYH7*, *ACTC1*, *TPM1*, *MYL3*, *MYL*, and *MYBPC3*), Z-disk proteins (*MYPN*, *TTN*, and *BAG3*), and intermediate filament network (DES) [15, 53].

It is important to recognize that some secondary cardiomyopathies due to systemic diseases may present with RCM (or HCM). Clinically relevant examples include transthyretin amyloidosis (*TTR*), metabolic disorders such as Fabry disease (alpha-galactosidase A, *GLA*), hemochromatosis (human hemochromatosis, *HFE*), lysosome-associated membrane protein 2 (*LAMP*) gene, and AMP-dependent protein kinase (*PRKAG2*) gene mutations [53, 56]. Genetic testing plays a vital role in diagnosing these secondary causes of RCM, since there are important treatment considerations and benefits of early detection for these conditions (e.g., specific drug therapy or early considerations for advanced therapeutic options).

Family History, Genetic Counseling, and Clinical Screening of Family Members

Despite the rarity of familial RCM, efforts should still be made to acquire a comprehensive three to four-generation family history to determine if the RCM is hereditary and the mode of inheritance. The strength of evidence for this recommendation is less well established [6••]. Genetic counseling should also be provided to the patients and family members although the knowledge of the underlying genetic information about RCM is limited. Clinical screening of asymptomatic first-degree relatives at interval of one to three yearly is recommended, although there is limited evidence to support the recommendation [6••].

Molecular Genetic Testing for RCM and Practical Considerations

As the genetic etiology of RCM is only beginning to be defined, the recommendation of genetic testing in patients with RCM and the diagnostic yield remains uncertain [5••, 6••]. Genetic testing may be useful to confirm the diagnosis of familial RCM, which is associated with poor prognosis [57]. As with other inherited cardiomyopathies, mutation-specific genetic testing should be pursued for family members [5••].

LVNC

Genetics

LVNC is a genetically heterogeneous cardiomyopathy, with both familial and sporadic forms [58]. The prevalence of LVNC is unclear, and the familial forms accounted between 18 and 50 % of the cases [58–60]. Autosomal dominant is the most common form of inheritance, but autosomal recessive, X-linked, and maternally inherited (matrilineal) mitochondrial inheritance have been reported [15, 59]. Mutations have been identified in genes coding for sarcomeric, cytoskeletal, Z-line, ion channel, and mitochondrial proteins [61]. More than ten genes have been described in LVNC, and some of the genetic mutations are associated with overlapping phenotype with HCM and DCM (Table 1) [15].

Family History, Genetic Counseling, and Clinical Screening of Family Members

Family history and genetic counseling are recommended for patients with LVNC, although up to 44 % of familial disease remained undetected by ascertainment of family history [5••, 7, 62]. Clinical screening of family members can improve the sensitivity of identifying familial LVNC to 64 % and is recommended to be done periodically every 3–5 years [7, 62].

Molecular Genetic Testing for LVNC and Practical Considerations

The diagnostic yield of genetic testing for LVNC ranges from 17 to 41 %, depending on the number of genes included in the testing panel [62, 63]. Given this relatively low rate of diagnostic yield, the isolated utility of genetic testing for the definitive diagnosis of the index patient is probably of limited use. That being said, the differential diagnosis of significant right ventricular dystrophy is limited; thus, underlying inflammatory cardiomyopathy (such as sarcoidosis and myocarditis)

should also be considered when genetic testing is negative for the most common mutations. Nevertheless, combining genetic testing with clinical screening of family members can greatly enhance the detection rate of familial LVNC to 67 % [62]. Mutation-specific genetic testing for family members following the identification of a causative mutation in the index case is very useful and is highly recommended [5••]. LVNC genetic testing has no prognostic and therapeutic implications, as clear genotype–phenotype correlations have not been identified. In contrast, clinical manifestations such as progression to DCM or systolic dysfunction, ventricular arrhythmia leading to SCD, or thromboembolic events as a consequence of large trabeculae large determine the therapeutic approach of this disorder.

Conclusion

Genetic testing has gained significant enthusiasm and has been incorporated in the recent clinical practice for the evaluating inherited cardiomyopathies. Like most genetic disorders, the fundamental framework of genetic evaluation of inherited cardiomyopathies consists of family history collection, genetic counseling, clinical screening of family members, and molecular genetic testing. The understanding of the genetic basis of DCM, HCM, and ARVC is much better established compared with RCM and LVNC. Hence, the strength of evidence supporting the recommendations of the genetic evaluation varies significantly between specific hereditary cardiomyopathies. Therefore, molecular profiling is likely going to be more holistic than segregated. There are also considerable differences in the diagnostic, prognostic, and therapeutic implications of molecular genetic testing in each distinct genetic cardiomyopathy. Genetics in cardiomyopathy continue to evolve rapidly, and comprehensive genetic testing for many genes is now readily available at a reasonable cost.

The use of NGS approaches in molecular genetic testing may identify more rare mutations that do not belong to specific categories in syndromic patients. Next-generation sequencing also allows combined test panels (cardiomyopathy together with others including arrhythmia and connective tissue diagnostics) to provide a more comprehensive look of cardiovascular genetic predisposition at relatively low-cost increments. However, recent evidence with broad adoption of genetic testing in HCM patients and their at-risk relatives has implied that expansion of genes sequenced by NGS approaches still did not significantly expand the diagnostic yield of genetic testing [56]. While there are currently limited approaches to target genotypes for both treatment and prevention of specific cardiomyopathies, studies have started to consider such strategies as clinical adoption is evolving and available [64] (https://www.clinicaltrials.gov/ct2/show/NCT02319005, https://clinicaltrials.gov/ct2/results?term=myokardia).

Compliance with Ethical Standards

Conflict of Interest Loon Yee Louis Teo and Rocio T. Moran declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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