Section 17: Genetic Evaluation of Cardiomyopathy*

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Overview

Substantial progress has been made recently in understanding the genetic basis of cardiomyopathy. Cardiomyopathies with known genetic cause include hypertrophic (HCM), dilated (DCM), restrictive (RCM), arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) and left ventricular noncompaction (LVNC). HCM, DCM, and RCM have been recognized as distinct clinical entities for decades, while ARVD/C and LVNC are relative newcomers to the field. Hence the clinical and genetic knowledge for each cardiomyopathy varies, as do the recommendations and strength of evidence.

The evidence indicating that HCM has a genetic basis is extensive: HCM is now understood largely to be a genetic disease of contractile proteins, although less commonly, infiltrative etiologies may also be causative (Table 17.1). The evidence supporting a genetic basis for DCM, after other more common causes have been excluded (e.g., ischemic disease, hypothyroidism, cardiotoxic agents such as doxorubicin), is now substantial for familial dilated cardiomyopathy (FDC), where FDC is defined as DCM of unknown cause in two or more closely related family members (Table 17.2). However, whether sporadic DCM has a genetic basis remains an open question, especially when detectable familial disease has been clinically excluded by testing closely related family members. Thus, while some recommendations formulated for the genetic evaluation of cardiomyopathy, such as the need for family history, apply to all entities, other recommendations must be tailored to account for these differences. This is particularly relevant as these guidelines use the generic term 'cardiomyopathy' to imply possible familial or genetic cause, assuming that all other detectable causes of cardiomyopathy have been ruled out. As noted above, multiple non-genetic causes are possible for DCM.

Recent discoveries indicate that ARVD/C is largely caused by mutations in genes encoding proteins of the desmosome (Table 3). Although initially recognized predominantly in the right ventricle, left ventricular involvement in 20−40% of patients has prompted the change in nomenclature from ARVD to ARVD/C.[1]

Discovering the genetic basis of restrictive cardiomyopathy (RCM) has been more challenging, as RCM is much less common than DCM or HCM, and less commonly presents with familial disease (Table 17.3).

LVNC is an anatomic abnormality of left ventricular myocardial development: left ventricular compaction is incomplete, leaving deep trabeculations in the LV myocardium. LVNC was categorized as a specific type of cardiomyopathy by an expert panel in 2006[2], and some genetic association has been observed (Table 17.3). Although initially reported to be a rare condition associated with adverse outcome[3], more recent reports [4−6] have called into question those preliminary conclusions.[7] Three different echocardiographic criteria have been utilized for diagnosis.[6] These authors suggested that the diagnostic criteria for LVNC might be too sensitive. Because of the uncertainty of diagnostic standards leading to difficulty clarifying its phenotype, we suggest that the LVNC recommendations be limited to those individuals with only the most prominent disease.

This section organizes recommendations by cardiac phenotype, recognizing that there is substantial overlap among phenotypes and some mutations are associated with more than one phenotype. Because therapeutic decision-making is generally dictated by phenotype, this approach was considered most helpful for the clinician.

The available clinical genetics data for each of the cardiomyopathies varies greatly in content and quality, and thus the quality and certainty of genetic counseling information is also variable. The evidence that supports clinical genetic testing varies greatly. While analytic validity (the ability of the test to detect a mutation) is attainable with current methods, evidence to support clinical validity (the ability of the test to detect the condition) remains quite limited for most cardiomyopathies, the exception being HCM. A separate measurement, clinical utility, defines the global risks and benefits of any test, asking the all-important question: how will the genetic information, whether positive or negative, affect clinical decision-making for the patient or the patient's family? Clinical utility remains to be defined for all genetic testing of cardiomyopathies.

While each recommendation has been designed for adult and pediatric patients, many of the references used to formulate these recommendations have focused primarily on adults. A section devoted to pediatric genetic cardiomyopathies provides additional specific information.

Despite these limitations, recent progress makes it possible to propose recommendations for the genetic evaluation of cardiomyopathy. These recommendations will evolve and mature as more robust clinical genetics knowledge becomes available.

HFSA Guideline Approach to Medical Evidence for Genetic Evaluation of Cardiomyopathy

Because genetic testing is relatively new, randomized clinical trials demonstrating that performing the specific genetic test improves outcomes are not available. Thus, we have used a different format for strength of evidence for clinical validity which asks the question "Does the test correlate with the outcome of interest?"[8] The hierarchy of types of evidence includes the following:

Table 17.1. Genetic causes of hypertrophic cardiomyopathy

Gene*	Protein	OMIM**	frequency, familial***	frequency, sporadic**	Comments	Selected References
AUTOSOMAL Dominant HCM - genes encoding sarcomeric proteins						
MYH7	β-myosin heavy chain	160760	30–40%	30–40%	wide age range; severe LVH; heart failure, SCD	10,11,37,38
MYBPC3	myosin-binding protein C	600958	30–40%	30–40%	usually milder disease, although can be severe; some older onset	10,11,38,39
TNNT2	cardiac troponin T	191045	10–20%	10–15%	mild LVH; SCD more common	10,11,38,40
TPM	α-tropomyosin	191010	2–5%	?		10,11,38,39
TNNI3	cardiac troponin I	191044	2–5%	?		10,11,38,41
MYL2	myosin regulatory light chain	160781	rare	rare		42
MYL3	myosin essential light chain	160790	rare	rare		42
ACTC	cardiac actin	102540	rare	rare		43
TTN	titin	188840	rare	rare		44
MYH6	α-myosin heavy chain	160710	rare	rare		45
TCAP	titin-cap or telethonin	604488	rare	rare		46
HCM caused by metabolic/infiltrative disease						
PRAGK2	AMP-activated protein kinase subunit	602743	?	?	HCM, with WPW	47
GLA	α-galactosidase	300644	?	?	Fabry disease, X-linked	48
LAMP2	lysosome associated membrane protein 2	309060	?	?	Danon disease, X-linked	49

*Genes within each category are ordered by publication.
**OMIM is Online Mendelian Inheriitance in Man (accessed via http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim.
***Rare denotes a frequency usually < 1%.

Strength A: The specific genetic test or clinical test has a high correlation with the cardiomyopathic disease of interest in reasonably large studies from multiple centers.

Strength B: The specific genetic test or clinical test has a high correlation with the cardiomyopathic disease of interest in small or single center studies.

Strength C: The specific genetic test or clinical test correlates with the cardiomyopathic disease of interest in case reports.

The criteria for clinical utility follow those used for overall strength of evidence in the other sections of this guideline (see Section 1), and pose the question, ''Does performing the test result in improved patient outcomes?''

Strength A: randomized, controlled, clinical trials. May be assigned on the basis of a single methodologically rigorous randomized trial.

Strength B: Cohort and case control studies. Post-hoc, subgroup analysis, and meta-analysis. Prospective observational studies or registries.

Strength C: Expert Opinion. Observational studies-epidemiologic findings. Safety reporting from large-scale use in practice.

However, as noted previously for clinical validity, randomized or controlled clinical trials or large cohort and case/control studies are seldom available from genetic cardiomyopathy studies. Hence the authors graded strength of evidence based upon the totality of information available.

Recommendation

17.1 A careful family history for ≥ 3 generations is recommended for all patients with cardiomyopathy.

Cardiomyopathy Phenotype	Strength of Evidence
Hypertrophic cardiomyopathy (HCM)	**A**
Dilated cardiomyopathy (DCM)	**A**
Arrhythmic right ventricular dysplasia (ARVD)	**A**
Left ventricular non-compaction (LVNC)	**A**
Restrictive cardiomyopathy (RCM)	**B**
Cardiomyopathies associated with extra-cardiac manifestations (Table 17.4)	**A**

Background

The family history, long established as an essential component of any medical evaluation, is particularly relevant for the cardiomyopathies.[9] The first goal of the family history is to ascertain if the cardiomyopathy is familial, and if

Table 17.2. Genetic causes of dilated cardiomyopathy

Gene*	Protein	OMIM	Frequency, familial**	Frequency, sporadic**	Comments***	References
AUTOSOMAL Dominant FDC						
Dilated cardiomyopathy phenotype						
ACTC	cardiac actin	102540	rare	rare		50–54
DES	desmin	125660	?	?		53,55–57
LMNA	lamin A/C	150330	7.3%	3.0%	5.5% overall (41/748, 6 studies, see text)	21-26,58–64
SGCD	δ-sarcoglycan	601411	rare	rare		56,65,66
MYH7	β-myosin heavy chain	160760	6.3%	3.2%	4.8% overall (22/455, 3 studies)	19,67–69
TNNT2	cardiac troponin T	191045	2.9%	1.6%	2.3% overall (15/644, 3 studies)	19,67,69–72
TPM1	α-tropomyosin	191010	rare	rare		73
TTN	titin	188840	?	?		74
VCL	metavinculin	193065	rare	rare		69,75
MYBPC3	myosin-binding protein C	600958	?	?		68
MLP/CSRP3	muscle LIM protein	600824	rare	rare		19,76
ACTN2	α-actinin-2	102573	?	?		77
PLN	phospholamban	172405	rare	rare		69,78,79
ZASP/LDB3	Cypher/LIM binding domain 3	605906	?	?		19,80
MYH6	α-myosin heavy chain	160710	?	?		45
ABCC9	SUR2A	601439				81
TNNC1	cardiac troponin C	191040	?	?		72
titin-cap TCAP	titin-cap or telethonin	604488	rare	rare		19,46
SCN5A	sodium channel	600163	?	?	2.3% overall (11/469, 2 studies)	82–84
EYA4	eyes-absent 4	603550	?	?		85
TMPO	thymopoietin	188380	?	?		86
PSEN1/PSEN2	presenilin 1/2	104311	?	?		87
X-LINKED FDC		300377				
DMD	dystrophin	300394				88,89
TAZ/G4.5	tafazzin	300394				90,91
AUTOSOMAL RECESSIVE FDC						
TNNI3	cardiac troponin I	191044	?	?		92

*Genes are ordered by publication year.
**Rare indicates less than 1%; frequencies are provided only with two or more publications.
***Overall frequencies may include studies that did not distinguish between familial and sporadic cases.

so, to identify those individuals who may be at risk. Because of reduced penetrance observed in some families with cardiomyopathy, a family history extending to at least 3 generations improves recognition that a cardiomopathy is inherited and helps define dominant or recessive transmission. Patients unprepared for a recitation of their family history may only provide general information suggestive of cardiovascular disease in their relatives. Not uncommonly, the cause of any cardiovascular condition resulting in hospitalization may be described as a 'heart attack,' as is the case with sudden cardiac death (SCD). Hence, when the diagnosis of cardiomyopathy is suggested, the patient should be requested to obtain additional information to confirm or exclude the cardiomyopathy diagnosis. Specific medical information pertinent to the patient's diagnosis should be sought regarding the patient's relatives. For example, in HCM or ARVD/C, targeted questions relating to SCD in teenagers and young adults should be sought. Increasingly, practitioners record a pedigree to illustrate the family history data.

When taking a family history it is imperative that the professional recording it make no a priori assumptions of which side of the family the disease originated[9] and should consider bilineal inheritance (transmission of a disease-causing mutation in the same or a different gene from both mother and father). In HCM, reports of large series of patients undergoing comprehensive genetic screening have shown compound or double mutations in 5%.[10–12] It has been suggested that some of these individuals may have had more severe disease related to a 'double-dose' effect incurred from the two mutations.[12]

A second goal, once a cardiomyopathy is suspected or proven to be familial, is to ascertain the inheritance pattern. Pedigree analysis is undertaken to determine if the inheritance is autosomal dominant or recessive, X-linked dominant or recessive, or mitochondrial[9] and thus provide an accurate risk assessment. Most genes known to cause cardiomyopathies are transmitted in an autosomal dominant manner. Autosomal dominant inheritance implies that only one copy of the mutation in needed to cause the disease phenotype and that each child has a 50% chance to inherit the mutation. For X-linked inheritance, the mutation is carried in a gene on the X-chromosome.

Expanding a family history beyond the 3rd generation and collecting medical data from relatives known or suspected to manifest clinical disease consistent with the

cardiomyopathy in question can be enormously informative. With additional family and clinical data, further analysis of the pedigree may suggest the age of onset, penetrance, lethality, response to treatment and other aspects of the condition. However, because obtaining a family history and related activities outlined above are time and effort intensive, busy practitioners may choose to refer patients with cardiomyopathy to centers expert in genetic cardiomyopathies. Such centers may also provide genetic counseling and genetic testing, compile clinical and genetic databases, and offer research opportunities that are essential for progress in the field.

Recommendation

17.2 Clinical screening for cardiomyopathy in asymptomatic first-degree relatives is recommended.

a.

Cardiomyopathy Phenotype	Strength of Evidence
Hypertrophic cardiomyopathy (HCM)	**A**
Dilated cardiomyopathy (DCM)	**A**
Arrhythmic right ventricular dysplasia (ARVD)	**A**
Left ventricular noncompaction (LVNC)	**B**
Restrictive cardiomyopathy (RCM)	**B**
Cardiomyopathies associated with extra-cardiac manifestations (Table 17.4)	**A**

b. Clinical screening for cardiomyopathy is recommended at intervals (see below) in asymptomatic at-risk relatives who are known to carry the disease-causing mutation(s). (Strength of Evidence = A)

c. Clinical screening for cardiomyopathy is recommended for asymptomatic at-risk first-degree relatives when genetic testing has not been performed or has not identified a disease-causing mutation. (Strength of Evidence = A)

d. It is recommended that clinical screening consist of:
- **History (with special attention to heart failure symptoms, arrhythmias, presyncope and syncope)**
- **Physical examination (with special attention to the cardiac and skeletal muscle systems)**
- **Electrocardiogram**
- **Echocardiogram**
- **CK-MM (at initial evaluation only)**
- **Signal Averaged ECG (SAECG) in ARVD only**
- **Holter monitoring in HCM, ARVD**
- **Exercise treadmill testing in HCM**
- **Magnetic resonance imaging in ARVD**

(Strength of Evidence =B)

e. Clinical screening for cardiomyopathy should be considered at the following times and intervals or at any time that signs or symptoms appear:

Cardiomyopathy Phenotype	Interval if genetic testing is negative and/or if clinical family screening is negative	Screening interval if a mutation is present	Strength of Evidence
Hypertrophic	Every 3 years until 30 years of age, except yearly during puberty; after 30 years if symptoms develop	Every 3 years until 30 years of age, except yearly during puberty; every 5 years thereafter	B
Dilated	Every 3–5 years beginning in childhood	Yearly in childhood; every 1–3 years in adults.	B
ARVD	Every 3–5 years after age 10	Yearly after age 10 to 50 years of age.	C
LVNC	Every 3 years beginning in childhood	Yearly in childhood; every 1–3 years in adults.	C
Restrictive	Every 3–5 years beginning in adulthood	Yearly in childhood; every 1–3 years in adults.	C

f. At-risk first-degree relatives with any abnormal clinical screening tests (regardless of genotype) should be considered for repeat clinical screening at one year. (Strength of Evidence = C)

Background

The basis for these extensive clinical screening recommendations (and the counseling and molecular recommendations in the sections that follow) is the fact that cardiomyopathy can be treated in almost all cases, improving survival and/or enhancing quality of life.[13,14] In contrast, many other genetic diseases have no useful medical treatment. Further, determining genetic risk of cardiomyopathy prior to disease presentation guides the recommendations for increased surveillance to detect early disease onset and medical intervention. All of these measures may delay disease presentation and progression, thereby avoiding advanced therapies such as cardiac transplantation, or averting the sequelae of life-threatening events, such as sudden cardiac death.[14]

Most cardiomyopathies are adult onset, and as is common for adult-onset genetic disease, show a variable age of onset and variable penetrance. Hence, clinical screening of first-degree relatives of adults diagnosed with cardiomyopathy is recommended, regardless of whether a disease-causing mutation has been identified in the index patient. Because of the variable age of onset, clinical screening repeated at intervals is recommended, even if clinical genetic

testing has not identified a disease-causing mutation in the family. If a disease-causing mutation is identified, the frequency of pre-symptomatic clinical screening in relatives known to be mutation carriers is recommended with increased frequency, as the probability of future disease is increased among carriers. Increased frequency of follow up clinical screening should also be undertaken for at-risk relatives if clinical screening has shown that the disease is familial, even if a mutation has not been found. This is because for genetic cardiomyopathy, familial disease strongly suggests genetic cause. Further, the sensitivity of genetic testing varies greatly (as noted in the background to Recommendation 17.3). Conversely, as the table above shows, if the clinical screening of first-degree relatives is negative, or a disease-causing mutation has not been identified, the intervals for clinical screening are recommended to be less frequent because of the reduced evidence of genetic risk.

The rationale for this latter recommendation, although reasonable, is based upon limited data. With clinical screening, whether the lack of clinical evidence of cardiomyopathy in first-degree family members is helpful to predict the presence or absence of genetic cause of the proband's cardiomyopathy has not yet been resolved. This is because of the variable age of onset and variable penetrance. Resolution of this issue will require data from additional large, rigorously designed clinical and genetic studies. Despite these uncertainties, we suggest that negative molecular genetic findings in the proband and/or no clinical evidence of disease in their family members, integrated with the type of cardiomyopathy, may be helpful to estimate the family members' genetic risk. We emphasize that these risk assessments will vary greatly with the type of cardiomyopathy, because of the varied sensitivity of genetic testing (reviewed in the background to Recommendation 17.3). Thus, we have recommended longer intervals between clinical screenings with less evidence of disease, recognizing that lack of evidence may not necessarily be synonymous with lack of risk. We also acknowledge that while genetic testing is recommended, in some circumstances genetic testing cannot be performed because of a variety of issues (eg, deceased or unavailable proband, funding issues). Hence, the clinician must integrate all data − clinical and genetic − from the patient and his/her family members, to support the clinical decision analysis in genetic cardiomyopathy.

Integration of all of these considerations, most importantly the type of cardiomyopathy, should be taken into account in screening of children, as well, While children can manifest clinical cardiomyopathy, most disease is adolescent- (HCM) or adult-onset. Hence these recommendations should be integrated with the type of cardiomyopathy, the age of onset of other affected members in the pedigree when such data are available, the identity of the cardiomyopathy gene, and other features.

The testing modalities by diagnosis given in Recommendation 17.2 are screening tests to be performed during an initial evaluation of someone of unknown disease status. If any cardiovascular abnormalities are detected, additional testing specific for the cardiomyopathy should be obtained in order to secure a diagnosis and prognosis and to formulate an appropriate treatment plan.

The risks for developing HCM after 50 years of age are reduced but not eliminated[15] as are those for ARVD after 50 years of age.[16] The utility and role of Holter monitoring and the signal-averaged ECG in the diagnosis of ARVD has been reviewed.[16] Magnetic resonance imaging is useful for the diagnosis of ARVD in centers experienced in its use and interpretation for ARVD[17]; data are not yet available to guide the frequency of its application for screening at-risk family members.

The patient should be encouraged to communicate with at-risk relatives regarding the presenting symptoms of cardiomyopathy, regardless of whether clinical genetic testing is undertaken or, if undertaken, whether the results are positive or negative. They should be counseled to seek medical assistance with symptoms, and in particular be counseled that potentially imminently life-threatening symptoms, such as presyncope or syncope, should be brought to immediate medical attention.

Less evidence is available to support of the genetic basis of RCM than for the other cardiomyopathies, hence its reduced strength of evidence in these recommendations.

Recommendation

17.3 Evaluation, genetic counseling, and genetic testing of cardiomyopathy patients are complex processes. Referral to centers expert in genetic evaluation and family-based management should be considered. (Strength of Evidence = B)

Background

The processes involved in clinical and genetic evaluation and testing for cardiomyopathies, integrated with up-to-date genetic counseling, are complex. This is in part because these recommendations are rapidly evolving. Those practicing cardiovascular genetic medicine must remain up to date with the accelerating developments in the field, integrating clinical and genetic evaluations with genetic counseling. This includes knowledge of recent discoveries of mutations in genes not previously implicated in the cardiomyopathies, as well as emerging gene-phenotype and genotype-phenotype correlations. Complexity also results from the extensive locus (many genes) and allelic (many different mutations within those genes) heterogeneity. Advances in genetic testing technology are also leading to a proliferation of new genetic tests for the cardiomyopathies, which are all confounded by this locus and allelic heterogeneity.

This recommendation states that referral to centers expert in genetic evaluation and family-based management should be considered. ''Should be considered'' language was selected because the strength of the evidence varies

with the cardiomyopathy phenotype, the details of the clinical and family information, and other aspects of each situation. Some practitioners with experience in the field may be able to provide appropriate care for cardiomyopathy patients without referral to a geneticist or a cardiomyopathy center with expertise in genetics. In addition to clinical care for the patient's cardiomyopathy, the practitioner will need to select the indicated genetic tests, counsel the patient on the purpose and outcomes of the possible results prior to the collection of blood or other tissue for the test, and then interpret the results to the patient upon receiving test results.[18] Whether results are positive or negative, the practitioner also will need to counsel the patient on potential reproductive risks should the patient wish to have children. Referral to genetic counseling services should be considered if these genetic counseling activities exceed the practitioner's skill, interest, or available time.

Several diverse patient situations help clarify this recommendation. The first is that of a cardiomyopathy patient whose parents are deceased and has no siblings or offspring. The primary need for this patient is reproductive counseling; that is, counseling on the risks of transmitting his/her cardiomyopathy to offspring. As presented below, genetic testing is primarily indicated for risk assessment in at-risk relatives, and since this patient has no first-degree relatives, counseling for genetic testing would be directed to reproductive risk assessment.

A second case is that of a patient with restrictive cardiomyopathy with no obvious family history. Since the genetic testing indicated for restrictive cardiomyopathy is much less established than that for HCM or DCM, efforts should be directed to acquiring a complete and comprehensive 3−4 generation family history. While the practitioner needs to understand that the only known genetic basis of familial restrictive cardiomyopathy stems from genes associated with HCM, in most other respects obtaining the family history is similar to that of the other cardiomyopathies.[9] A skilled practitioner can accomplish this, but if obtaining a complete and comprehensive family history exceeds the skill, interest or available time, then referral should be considered.

In contrast to RCM, the genetic information, genetic testing and counseling available for HCM is extensive. The professional ordering genetic testing for HCM must be skilled in interpreting the genetic test results and the subsequent counseling based upon the integration of the results (positive or negative), the family history, the clinical data of the patient and any other known affected or unaffected family members. Ideally, the practitioner will also be skilled in the management of the clinical aspects of HCM, integrating the clinical, diagnostic and therapeutic recommendations based on a synthesis of all data.[14] This latter point is particularly relevant with HCM because of the complexity of decision analysis for clinical interventions (eg, the assessment of outflow tract obstruction, and if present, selection of a treatment plan that may involve surgical or catheter-based interventions). In most centers expert in providing care for genetic cardiomyopathies, cardiovascular clinicians knowledgeable and skilled in genetics rely on genetic counselors or geneticists to provide comprehensive services.[13,14,18] If executing and completing these aspects of management exceed the practitioner's skill, training, interest or available time, then referral to a cardiovascular center specializing in dealing with genetic cardiomyopathy should be considered.

A final example is the question of genetic testing for a familial dilated cardiomyopathy. Even though mutations in >20 genes have been implicated as causative in familial dilated cardiomyopathy (Table 17.2), the role of genetic testing for DCM at this time remains less certain because of the low test sensitivity. Testing recommendations in 17.4 are based in part on the frequency of mutations of certain genes (Table 17.2) and in part on certain phenotypic characteristics of DCM (eg, the almost universal conduction system disease observed in LMNA cardiomyopathy, discussed below). The field is rapidly evolving, and no one simple, comprehensive standard for risk assessment or genetic testing is presently applicable. Referral to a cardiovascular center specializing in genetic cardiomyopathy can assist in defining the appropriateness of genetic testing for DCM patients.

Practitioners may also consider referral to cardiovascular genetics centers to promote the engagement of patients in research. Patient involvement is critical for continued discovery of unknown genes that cause cardiomyopathy, for establishing long-term natural history studies, and for harnessing this information to improve diagnosis and to improve treatments.

The recommendation for genetic counseling for cardiomyopathy follows later (17.6).

Molecular Genetic Testing

Recommendation

17.4 Genetic testing should be considered for the one most clearly affected person in a family to facilitate family screening and management.

a. Cardiomyopathy phenotype

Cardiomyopathy Phenotype	Strength of Evidence
Hypertrophic cardiomyopathy (HCM)	A
Dilated cardiomyopathy (DCM)	B
Arrhythmic right ventricular dysplasia (ARVD)	A
Left ventricular noncompaction (LVNC)	C
Restrictive cardiomyopathy (RCM)	C
Cardiomyopathies associated with other extracardiac manifestataions	A

b. Specific genes available for screening based on cardiac phenotype

Cardiomyopathy Phenotype	Gene tests available*	Yield of positive results
HCM	MYH7, MYBPC3, TNNT2 TNNI3, TPMI, ACTC, MYL2, MYL3.	MYH7, MYBPC3 each account for 30−40% of mutations, TNNT2 for 10−20%. Genetic cause can be identified in 35−45% overall; up to 60−65% when the family history is positive.
DCM	LMNA, MYH7, TNNT2, SCN5A, DES, MYBPC3, TNNI3, TPMI, ACTC, PLN, LDB3 and TAZ.	5.5%, 4.2%, 2.9%, for LMNA, MYH7, and TNNT2, respectively. All data are from research cohorts.
ARVD	DSP, PKP2, DSG2, DSC2	6−16%, 11−43%, 12−40%, for DSP, PKP2 and DSG2, respectively
LVNC	Uncertain − see discussion	Uncertain − see discussion
RCM	Uncertain − see discussion	Uncertain − see discussion

*GeneTests (www.genetests.org) is an NIH funded resource that lists clinical (and research) molecular genetic testing laboratories for the cardiomyopathies.

c. Screening for Fabry disease is recommended in all men with sporadic or non-autosomal dominant (no male-to-male) transmission of unexplained cardiac hypertrophy. (Strength of Evidence = B)

Background

This recommendation is quite restrictive despite the extensive genetic information available. The rationale for the strength of evidence is derived largely from the published sensitivity of genetic testing, as presented in Tables 17.1-17.3. These recommendations do not address molecular testing in prenatal, newborn screening or in-vitro fertilization settings. Additional information for specific genes or genetic diagnoses are available at the Online Mendelian Inheritance in Man (OMIM) website (http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim), which can be accessed using OMIM numbers assigned to genes (See Tables 17.1-17.3) or genetic condition (see Table 17.4) associated with cardiomyopathy.

Recommendation 17.4 states that the individual with the most evident disease should be the individual selected from a family to undergo genetic testing. This is a well established principle in clinical genetics, as selecting the individual with the most evident disease that has been clinically confirmed to a high degree of certainty decreases the probability of testing a phenocopy (someone who clinically has the disease from another cause and does not carry the family mutation) and thereby increases the likelihood of finding a genetic cause. Usually the individual

Table 17.3. Genetic causes of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy, Left Ventricular Noncompaction, and Restrictive Cardiomyopathy

Gene	Protein	OMIM	frequency*	Comments	Selected References
Arrrythmogenic Right Ventricular Dysplasia/Cardiomyopathy					
JUP	plakoglobin	173325	rare	Naxos disease, autosomal recessive	93−95
DSP	desmoplakin	125647	6−16%		1,96
PKP2	plakophilin-2	602861	11−43%		1,97,98
DSG2	desmoglein-2	125671	12−40%		1,99,100
DSC2	desmocollin-2	125645	rare		1,101,102
RYR2	ryanodine receptor	180902	rare		103
TGFB3	transforming growth factor beta-3	190230	rare		96,104
					105
Left Ventricular Noncompaction					
MYH7	β-myosin heavy chain	160760	?		106
LDB3	Limb domain binding protein 3	605906	?		80
DTNA	α-dystrobrevin	601239	?		107
TAZ	taffazzin	300394	?		107
Restrictive Cardiomyopathy					
MYH7	β-myosin heavy chain	160760	?		106,108
TNNI3	troponin I	191044	?		109

*frequency estimates for ARVD/C are from Genetests.

Table 17.4. Cardiomyopathies Associated with Systemic Disease

DCM
Duchenne Muscular Dystrophy
Becker Muscular Dystrophy
Emery-Dreifuss Muscular Dystrophy
Limb Girdle Muscular Dystrophy
Moyotonic Muscular Dystrophy
Mitochondrial Myopathy
Kearns-Sayre Syndrome
Myotubular (Centronuclear) Myopathy
Nemaline Myopathy
Cytochrome C Oxidase Deficiency
Barth Syndrome
Danon Disease
Fanconi Anemia
Diamond-Blackfan Syndrome
Sickle Cell Anemia
Medium Chain Acyl CoA Dehydrogenase Deficiency (MCAD)
Long Chain Acyl CoA Dehydrogenase Deficiency (LCAD)
Maroteaux-Lamy Syndrome
Fabry Disease
HCM
Fabry Disease
Friedreich's Ataxia
Noonan Syndrome
Costello Syndrome
LEOPARD Syndrome
Cardio-Facio-Cutaneous Syndrome
Hunter Syndrome
Hurler Syndrome
Hurler-Scheie Syndrome
Maroteaux-Lamy Syndrome
I-Cell Disease
Pompe Syndrome
Beckwith-Wiedemann Syndrome
Mitochondrial Myopathy
Cytochrome C Oxidase Deficiency
Barth Syndrome
Danon Disease
Down Syndrome
Proteus Syndrome
Yunis-Varon Syndrome
Pallister-Killian Mosaic Syndrome
Medium Chain Acyl CoA Dehydrogenase Deficiency (MCAD)
Long Chain Acyl CoA Dehydrogenase Deficiency (LCAD)
Multiple Sulfatase Deficiency
RCM
Amyloidosis
Sarcoidosis
Fabry Disease
Endomyocardial Fibrosis
Loffler's Eosinophilic Endomyocardial Disease
Pseudoxanthoma Elasticum
Desmin Myopathy
Gaucher Disease
LVNC
Mitochondrial Myopathy
Barth Syndrome
ARVD
Naxos Disease
Carvajal Syndrome

with more evident disease will also provide a more compelling phenotype, typically with more disease features, enabling the most accurate classification of the cardiomyopathy. Procurement of a tissue sample (preferentially tissue that has not been fixed) from an autopsy specimen can provide DNA for genetic testing. At times a DNA-containing sample from the family member with the most evident disease is not available, commonly because of death antecedent to the genetic analysis. Thus, another individual from the family must be selected for testing. Selection of a secondary individual for testing requires careful consideration, especially because of the low sensitivity for genetic testing for many cardiomyopathies. The professional selecting the individual for testing will need to consider the implications of negative genetic test results for that subject and have a plan for any additional testing for the remaining at-risk family members. On the other hand, if a mutation can be identified and the evidence supports its role as the disease-causing mutation, testing can be performed in relatives regardless of their clinical status.

Recommendation 17.4 also restricts the indication for genetic testing to that of *facilitation of family screening and management*. Simply put, this recognizes that currently the primary value, the primary reason to seek genetic testing for the genetic cardiomyopathies, is to more accurately predict the risk of a family member developing cardiomyopathy who currently has little or no clinical evidence of cardiovascular disease.

If a disease-causing mutation is identified in the affected family member initially tested, and subsequent genetic testing of an at-risk but presymptomatic family member is negative, that family member's risk of developing the cardiomyopathy is substantially reduced. In this situation the need for ongoing clinical screening in such a mutation-negative family member is not recommended. On the other hand, if a disease-causing mutation is identified in an asymptomatic, at-risk family member, the confidence is much greater to infer risk for that individual. The individual should be counseled on the presenting signs and symptoms of the specific cardiomyopathy, the associated reduced penetrance and variable expressivity, and the rationale and frequency of the recommended clinical surveillance.

Notably these recommendations are silent for any additional interventions specific for a disease-causing mutation. The reason for this stems from the lack of validated genotype-phenotype correlations of specific mutations with specific clinical cardiovascular outcomes. Unless or until specific mutations have been shown to reliably predict specific clinical outcomes (eg, increased or reduced risk of a specific event such as the development of symptomatic heart failure or the high probability of sudden cardiac death), the recommendations will refer to the general behavior of each disease gene.

The general characteristics of disease presentation and progression may suggest involvement of specific genes. We refer to this as 'gene-phenotype relationships' in contrast to the more commonly used 'genotype-phenotype relationships,' commonly used to indicate phenotypic characteristics of specific mutations. The strongest

evidence for gene-phenotype relationships is present for HCM and DCM (Table 17.5).

Recommendation 17.4, focused on genetic testing to facilitate family screening and management, is also silent for specific recommendations for apparent sporadic (non-familial) disease. However, considerable evidence suggests that HCM results from both sporadic and familial genetic disease.[11] In contrast, the etiology of DCM that does not appear to be familial remains enigmatic, as is the evidence to support an underlying genetic cause. Some patients with DCM, but without a positive family history, have been shown to harbor mutations consistent with genetic causation of their disease (Table 17.2). Further, the largest genetic survey to date of six DCM disease genes in 313 unrelated probands observed a similar frequency of mutations attributed to familial vs sporadic disease.[19] However, patient acquisition for that study was not specifically designed to address the frequency of the genetic basis of sporadic DCM versus familial disease, and familial disease was not excluded with prospective clinical screening of first-degree relatives in those assigned to have sporadic DCM. This is particularly relevant, as conducting clinical screening of first-degree family members with echocardiograpy and ECG has been shown to have four-fold greater sensitivity to detect familial DCM compared to obtaining a careful 3-generation family history.[20] Thus, a genetic etiology for the bulk of non-ischemic, presumably non-familial (sporadic) DCM, while plausible, is not yet supported by rigorous studies that provide robust, reliable estimates of the frequency of genetic causation.

HCM has the strongest evidence to support genetic testing (Table 17.1). ARVD/C, although quite rare, also has good evidence to support genetic testing (Table 17.3).

Testing for DCM is confounded by the question of etiology of sporadic DCM discussed above. It is also greatly confounded by the extensive genetic heterogeneity, as well as the relatively low frequency of involvement of any one gene in DCM. Technological advances will continue to improve testing methods, thereby dramatically decreasing costs. While such progress will make it possible to test many DCM genes simultaneously, it is likely that sequence variations of unknown significance will be discovered that may confound test interpretation.

However, testing for the *LMNA* gene is recommended in patients with prominent conduction disease with or without supraventricular or ventricular arrhythmias (Table 17.5), or with signs of skeletal muscle involvement, shown most commonly by elevated creatine kinase (CK-MM) because in both groups *LMNA* mutations appear to be at higher frequency (Table 17.5). *LMNA* molecular genetic testing may be considered for all DCM patients based on its overall higher frequency in DCM (Table 17.5: a mean of 7.3% of those with familial disease, or 3.0% of those with apparent sporadic disease, or 5.5% overall, as summarized from six studies [21–26]), and because of its diagnosis on prognosis and management.[27]

Data are only now emerging describing the genetic basis of LVNC, limiting strength of recommendations, as is the case for RCM (Table 17.3).

Clinical genetic testing should be carried out in a fully accredited molecular genetic testing laboratory that has met Clinical Laboratory Improvement Amendment (CLIA) standards. Clear distinctions should be made between testing for clinical purposes, as advocated by these recommendations, in CLIA-accredited laboratories and that undertaken for research purposes that cannot be used to direct clinical care (unless conducted in a CLIA-certified research laboratory that provides clinical reports). Because the genetic knowledge base of cardiomyopathy is still emerging, practitioners caring for patients and families with genetic cardiomyopathy are encouraged to consider research participation. Referral centers expert in genetic cardiomyopathy are experienced in explaining the roles and outcomes of clinical testing versus research participation, which may include research genetic testing, and are able to facilitate both objectives.[28]

Table 17.5. Cardiomyopathy Phenotypes Suggestive of Specific Disease Genes

Gene	Protein	Phenotype Summary*	Comments*	References
Dilated cardiomyopathy phenotype				
LMNA	lamin A/C	Prominent conduction system disease and arrhythmias, then DCM and heart failure	Asymptomatic ECG abnormalities, then sinus/AV node dysfunction; 1st, 2nd, 3rd degree heart block; Aflutter/Afib, tachy/brady syndrome, pacemakers common. Onset of DCM, with mild - severe LV dysfunction, then HF, SCD, advanced disease requiring cardiac transplantation	21–26,58–64
Hypertrophic cardiomyopathy phenotype				
MYH7	β-myosin heavy chain	wide age range; severe LVH; heart failure, SCD		10,11,37,38
MYBPC3	myosin-binding protein C	usually milder disease; some older onset		10,11,38,39
TNNT2	cardiac troponin T	mild LVH; SCD common		10,11,38,40

*Aflutter/Afib is atrial flutter and atrial fibrillation; AV is atrioventricular; SCD is sudden cardiac death; LVH is left ventricular hypertrophy.

Genetic Counseling

Recommendation

17.5 Genetic and family counseling is recommended for all patients and families with cardiomyopathy. (Strength of Evidence = A)

Background

Genetic counseling is the process of communicating relevant genetic information, including genetic risks, to patients and their families, so that they may understand the genetic information presented and use it to make informed decisions regarding genetic testing or other therapeutic decisions. The process also helps individuals to adapt to the medical, psychological and familial implications of genetic contributions to disease.[29] The majority of genetic counseling is performed by board-certified Master's level genetic counselors or by board-certified medical geneticists. Genetic counseling for the cardiomyopathies is best undertaken by genetic counselors, geneticists who are knowledgeable of the cardiovascular clinical features of the type of cardiomyopathy in question, or cardiologists who are expert in the cardiomyopathy in question and are fluent in the content and nature of genetic counseling for the patient and their family members.[13,18,30] Alliances of cardiologists with special interest and expertise in genetic cardiomyopathies with genetics professionals, usually Master's level trained genetic counselors or nurses trained in genetics, are beginning to emerge. In a survey of Dutch cardiologists and geneticists regarding the provision of care for HCM, most cardiologists preferred that pedigree construction, counseling and genetic testing be handled by geneticists, although a significant trend for collaborative arrangements between geneticists and cardiologists was also noted.[31]

Regardless of who provides it, genetic counseling is an essential component of the evaluation, diagnosis, and management of the cardiomyopathies.[13,18,30] Essential activities completed by a genetic counselor are obtaining a careful and comprehensive 3- to 4-generation family history; educating the patient and family regarding disease transmission and family risks; counseling regarding any genetic testing to be undertaken including the implications of positive, negative, or uncertain results; providing key information to other at-risk family members as identified by the index patient; and assisting with the interpretation of genetic test results and their integration into the overall treatment plan. Counseling is designed to promote informed choices and adaptation to the risk or condition by providing medical facts and options and social implications.

The first essential activity, obtaining a comprehensive family history, has already been was addressed earlier. The next objective is to educate the patient and family regarding the disease transmission and family risks. If genetic testing has identified a plausible genetic cause, counseling regarding transmission is conducted (autosomal or X-linked, either dominant or recessive). The pedigree is commonly utilized to inform the patient and family of at-risk members. If the patient presents without prior genetic testing, but testing is indicated, counseling is undertaken regarding the utility, sensitivity, analytic validity, and the implications of all possible testing outcomes based on the prior items. The patient, family members, or both need to be counseled on the possibility of identifying genetic variants of unknown significance. Counseling also involves exploring the psychosocial issues that are relevant to the condition or risk that the individual is facing, as well as addressing family dynamics, which could potentially impact dissemination of genetic information to at-risk family members.

Therapy Based on Genetic Testing

As already discussed, the finding of any specific mutation as the cause of the cardiomyopathy does not in itself guide therapy. However, the clinical characteristics associated with some disease genes (Table 17.5), when integrated with the clinical and family data, may influence the overall case assessment, and may appropriately impact all aspects of the clinical recommendations. This includes the frequency and stringency of presymptomatic screening for signs of disease, the strength of interventions to educate family members of risks and symptoms, the threshold for presymptomatic initiation of preventive (eg, ICDs in certain HCM, DCM or ARVD/C settings) or therapeutic interventions (eg, beta blockers or ACE inhibitors in presymptomatic DCM).

Therapy Based on Cardiac Phenotype

Recommendations

17.6 Medical therapy based on cardiac phenotype is recommended as outlined in the general guidelines. (Strength of Evidence = A)

17.7 Device therapies for arrhythmia and conduction system disease based on cardiac phenotype are recommended as outlined in the general guidelines. (Strength of Evidence = B)

17.8 In patients with cardiomyopathy and significant arrhythmia or known risk of arrhythmia an ICD may be considered before the left ventricular ejection fraction falls below 35%. (Strength of Evidence = C)

Background

Guidelines for clinical care of the patient with cardiomyopathies are available for HCM[32] and DCM (Sections 4−16, 34). These guidelines provide comprehensive guidance for care of those who are presymptomatic or have had the onset of clinical disease. Guidelines for the clinical care for ARVD, LVNC and RCM are not yet available.

In brief, implantable cardiac defibrillators (ICDs) are indicated for symptomatic or life-threatening arrhythmias

regardless of the type of cardiomyopathy diagnosis or ventricular function. The indications for ICDs are summarized for DCM in Section 9 and elsewhere.[33] For DCM, a left ventricular ejection less than 30-35% is usually an indication for an ICD, regardless of etiology.

Electrophysiological disease can be considered broadly as conduction system disease and arrhythmia. Conventional guidelines apply for symptomatic or pre-symptomatic conduction system disease regardless of other aspects of the patient's clinical situation.[34] Pacemakers are indicated for symptomatic bradycardia, high grade AV block regardless of symptoms, for any other symptomatic conduction system disease. In this setting of lamin A/C cardiomyopathy requiring pacemaker placement, the use of an ICD rather than a pacemaker has been recommended.[36] Such a course appears reasonable. Patients with a dilated cardiomyopathy but with EF $>$ 30−35% may be considered for an ICD if the family history is positive for SCD or for patients with LMNA mutations.[35]

Pediatric Forms of Inherited Cardiomyopathies

All phenotypes of cardiomyopathy presenting in childhood can occur as a genetic disorder. Unlike adult disease, pediatric cardiomyopathies, particularly those presenting in the first year of life, have an increased likelihood of being mitochondrial or metabolic-based. Evaluation of these young children must include studies aimed at determining whether mitochondrial dysfunction or metabolic derangement is central to the underlying basis of the cardiac disorder. In the case of mitochondrial disease, mitochondrial DNA (mtDNA) mutations inherited from the mother (maternal inheritance) or autosomal recessive inheritance underlie these disorders. Metabolic defects most commonly are inherited as autosomal recessive traits.

In the remaining cases of inherited cardiomyopathies of childhood, the same inheritance patterns as seen in adulthood are expected.

HCM of Childhood. Young children with left ventricular hypertrophy (LVH) may have an underlying mitochondrial or metabolic disease, while others have early clinical expression of HCM due to a sarcomere gene mutation. For instance, the deadly infiltrative lysosomal storage disorder, Pompe disease, or the benign infant of a diabetic mother form of LVH may appear to be similar by echocardiography. In addition, syndromes such as Noonan syndrome, overgrowth disorders such as Beckwith-Wiedeman syndrome or Sotos syndrome, or children with chromosomal disorders may present with LVH. A subgroup of these young children with LVH, however, has the typical ''adult form'' of disease caused by mutations in genes encoding sarcomere proteins.[36] Children can inherit these mutations or the gene defects can arise de novo and cause sporadic disease.

Children with HCM from mutations in sarcomeric genes typically demonstrate the classical clinical phenotypic features of HCM seen in adults. Phenotypic heterogeneity is common in children with familial forms of disease, both in clinical expression and outcome. For these reasons, the clinical follow-up of children with HCM tends to differ from that outlined for adults. Children younger than 1 year of age with HCM are usually seen frequently, commonly every 3 months. Siblings without clinical features of disease are followed yearly in most cases until reaching puberty. At that time, follow-up is every 1−2 years depending on their specific clinical, echocardiographic and electrocardiographic features. In cases where HCM presents in older children, the siblings are usually seen every 3 years unless a defect is identified.

DCM of Childhood. Inherited forms of DCM in childhood appear to exist in approximately 50% of affected subjects presenting by 18 years of age. Like HCM, mitochondrial and metabolic disease, as well as chromosomal defects and dysmorphic syndromes may be responsible for a substantial subgroup of cases. In the remaining inherited forms, autosomal and X-linked inheritance is most common. A substantial subgroup of children has associated skeletal myopathy, and some of these will also have conduction system disease. In inherited cases, similar to that described for HCM, onset of clinical features is age-dependent. In families with earlier onset of symptoms, follow-up of at-risk relatives should begin earlier. Relatives, particularly siblings, also follow a similar pattern as those outlined for relatives of HCM patients.

RCM of Childhood. Restrictive cardiomyopathy in childhood is an uncommon but serious form of cardiomyopathy. Inherited forms are infrequent, but when they occur appear to be associated with defective sarcomeric genes or mutations in desmin. Associated skeletal myopathy is common. In children with RCM, autosomal dominant inheritance predominates. Family evaluation for siblings tends to be approximately every 3 years unless a defect is identified.

LVNC of Childhood. Left ventricular noncompaction is seen during all ages of childhood from birth onward. Mitochondrial, metabolic, syndromic, chromosomal, and neuromuscular abnormalities are common. In addition, autosomal dominant inheritance is notable. LVNC is subdivided into dilated, hypertrophic, and hypertrophic/dilated forms, isolated LVNC without other abnormalities of size, thickness or function, and LVNC associated with congenital heart disease. Family members are followed every 3 years unless a defect is identified.

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