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Progress With Genetic Cardiomyopathies

Screening, Counseling, and Testing in Dilated, Hypertrophic, and Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

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***Abstract*—**This review focuses on the genetic cardiomyopathies: principally dilated cardiomyopathy, with salient features of hypertrophic cardiomyopathy and arrhythmogenic right ventricular dysplasia/cardiomyopathy, regarding genetic etiology, genetic testing, and genetic counseling. Enormous progress has recently been made in identifying genetic causes for each cardiomyopathy, and key phenotype and genotype information is reviewed. Clinical genetic testing is rapidly emerging with a principal rationale of identifying at-risk asymptomatic or disease-free relatives. Knowledge of a disease-causing mutation can guide clinical surveillance for disease onset, thereby enhancing preventive and treatment interventions. Genetic counseling is also indicated for patients and their family members regarding the symptoms of their cardiomyopathy, its inheritance pattern, family screening recommendations, and genetic testing options and possible results. **(*Circ Heart Fail*. 2009;2:253-261.)**

Key Words: arrhythmia ■ cardiomyopathy ■ genetics ■ genetic counseling ■ genetic testing

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Enormous progress has recently been made in identifying the genetic causes of cardiomyopathy, which, in turn, has enabled greater understanding of molecular mechanisms underlying each disease. This progress has also increased the probability of establishing specific genetic diagnoses, thereby providing new opportunities for practitioners, patients, and families to use this genetic information.

When considering whether a patient may have a cardiomyopathy, the approach is guided foremost by the patient's phenotype (clinical features). These clinical features include cardiovascular data, such as those derived from echocardiographic studies (ventricular size, function, wall thickness, and wall motion), and ECG findings. More elegant studies, such as MRI, may also complement a cardiomyopathy evaluation. A detailed medical history (including age of onset, type of symptoms), a physical examination (to rule out syndromic disease), and a 3- to 4-generation family history are also important. This cumulative phenotypic information drives assignment of a specific cardiomyopathy diagnosis.

Although most genetic cardiomyopathies only involve the heart, establishing a phenotypically driven cardiomyopathy diagnosis at times requires recognition of key features of syndromic forms. A syndrome is a recurring pattern of defects that most likely represents a single etiology. In most cases of cardiovascular syndromic disease, multiple tissues and/or organ systems are involved. Thus, the cardiovascular practitioner must be alert for signs and symptoms beyond the cardiovascular system. For example, Noonan syndrome, which can be associated with 4 genes (none associated with isolated hypertrophic cardiomyopathy [HCM]), presents with cardiac hypertrophy, short stature, variable degrees of developmental delay, and dysmorphic features (see link within[1] for references, and Table 1).

In addition to phenotypic data, a great deal of information regarding the genotype—the genetic makeup—of individuals with cardiomyopathy is now available that can provide a genetic cause to a newly rendered, carefully phenotyped clinical diagnosis. Different mutations in the same gene (allelic heterogeneity) may give rise to virtually identical phenotypes; however, this can also lead to strikingly different phenotypes. This is exemplified by *LMNA* mutations, which lead to multiple allelic phenotypes, collectively referred to as laminopathies (see links within[2] for references). *LMNA* allelic disorders include isolated dilated cardiomyopathy (DCM), syndromes that may involve DCM (eg, Emery-Dreifuss muscular dystrophy) or disorders not associated with DCM (eg, lipodystrophy and Hutchinson-Gilford progeria; Tables 1 and 2).

With a causal genetic mutation identified in a proband, closely related at-risk family members can choose to undergo genetic testing to determine whether they carry the same mutation. Such information may be extremely helpful in guiding clinical screening for evidence of disease in presymptomatic individuals, counseling patients regarding disease presentation, and facilitating life-saving interventions.

Guidelines for the care of patients with suspected or known genetic cardiomyopathy are only now emerging, usually organized by phenotype rather than by genotype. However, as much larger studies linking clinical and genotype data are

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Table 1. Selected Syndromic/Multisystem Forms of Cardiomyopathy

Gene	Locus	OMIM*	Gene Product	Associated Syndromes	Inheritance Pattern	Additional Clinical Features
DCM						
HFE	6p21.3	235200	Hereditary hemochromatosis	Hemochromatosis	AR	Cirrhosis, diabetes, hypermelanotic pigmentation, ↑ serum iron, ferritin
LMNA†	1q21.2	150330	Lamin A/C	Emery-Dreifuss muscular dystrophy types 2 and 3 (EMD2 and EMD3), limb girdle muscular dystrophy (LGMD) 1B	EMD2, AD; EMD3, AR; LGMD1B, AD	EMD: joint contractures (elbow, achilles tendon, neck), ↑ CK, arrhythmias, childhood muscle weakness; LGMD1B: mild joint contractures, ↑ CK, arrrhythmias, shoulder/hip-girdle weakness
MYH7†	14q12	160760	β-myosin heavy chain	Laing distal myopathy	AD	Childhood onset weakness of ankles and great toes, followed by the finger extensors. Neck flexors and facial weakness
DSP†	6p24	125647	Desmoplakin	Carvajal syndrome	AR	Woolly hair, keratoderma
DMD†	Xp21.2	300377	Dystrophin	Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD)	XL	DMD: males: ↑ CK, childhood muscle weakness, wheelchair bound by age 12, DCM after age 18; BMD: ↑ CK, skeletal muscle weakness in 20s or later; females can be affected with milder phenotype or DCM alone
TAZ/G4.5†	Xq28	300394	Tafazzin	Barth syndrome	XL	Growth retardation, intermittent lactic acidemia, granulocytopenia, recurrent infections
MTTY	mtDNA	590100	$tRNA^{Tyr}$	Focal segmental glomerulosclerosis and dilated cardiomyopathy	Maternal	Focal segmental glomerulosclerosis, migraines
Variable (eg, *MTND5*, *MTND4*, *MTND3*, *MTCD3*, *MTATP6*, *MTATP8*)	mtDNA multigene deletion	530000	NADH dehydrogenase subunit 3, 4, & 5; Cytochrome c oxidase subunit 3	Kearns-Sayre syndrome	De novo	Progressive external ophthalmoplegia, muscle weakness, cerebellar ataxia, diabetes mellitus
HCM						
GLA†	Xq22	300644	α-galactosidase A	Fabry disease	XL	Acroparesthesia, angiokeratomata, tinnitus/deafness, renal insufficiency, hypo/anhidrosis, corneal and lenticular opacities, stroke; females may have milder phenotype or HCM alone
LAMP2†	Xq24	309060	Lysosome-associated membrane protein 2	Danon disease	XL	Developmental delay (DD), mental retardation (MR), skeletal muscle weakness
PRKAG2†	7q36	602743	AMP-activated protein kinase γ 2	Wolf-Parkinson-White syndrome	AD	Preexcitation
PTPN11/ *RAF1*	12q24.1/ 3p25	176876/ 164760	tyrosine-protein phosphatase non-receptor type 11/*RAF* proto-oncogene serine/threonine-protein kinase	Noonan (NS)/Leopard (LS) syndromes	AD	NS: short stature, DD, MR, characteristic facies, neck webbing, pectus carinatum/excavatum, delayed puberty, cryptorchidism/LS: lentigines, ECG conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, growth retardation, sensorineural deafness, skeletal abnormalities, cognitive dysfunction
FRDA	9q13	606829	Frataxin	Friedreich ataxia	AR	Progressive gait/limb ataxia, progressive muscle weakness, fatigue, sensory neuropathy, cognitive dysfunction, emotional liability, deafness, decreased visual acuity, dysarthria, myocardial fibrosis, diabetes mellitus, foot deformities, scoliosis

(*Continued*)

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Table 1. Continued

Gene	Locus	OMIM*	Gene Product	Associated Syndromes	Inheritance Pattern	Additional Clinical Features
ANT1	4q35	103220	Adenine Nucleotide Translocator 1	Progressive external ophthalmoplegia with ragged red fibers	AD	Lactic acidosis, mild myopathy
MTTK	mtDNA	590060	$tRNA^{Lys}$	MERRF	Maternal	Myoclonic epilepsy with ragged red fibers (MERRF), hearing loss
MTATP6	mtDNA	516060	ATP synthase 6	Leigh syndrome	Maternal	Progressive neurodegeneration
MTTL1	mtDNA	590050	$tRNA^{Leu\text{-}UUR}$	MELAS	Maternal	Encephalopathy, lactic acidosis, stroke (MELAS)
MTTG	mtDNA	590035	$tRNA^{Gly}$	Maternally inherited HCM	Maternal	Bowel dysmotility
MTND1	mtDNA	516000	NADH dehydrogenase, subunit 1	Multisystem mitochondrial diseases	Maternal	MR, type 2 diabetes
ARVD/C						
JUP†	17q21	173325	Junction plakoglobin	Naxos syndrome	AR	Palmoplantar keratoderma, woolly hair

mtDNA indicates mitochondrial DNA.

*OMIM is Online Mendelian Inheritance in Man, URL: http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim, where additional information for each gene can be found.

†Mutations in these genes can also cause nonsyndromic cardiomyopathies.

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conducted, genotype-based diagnoses will become more routinely used to characterize cardiomyopathies.

DCM

DCM Clinical Features

Discoveries of mutations in genes that cause DCM were made possible from early studies in families with idiopathic dilated cardiomyopathy (IDC). In the early 1980s only 1% to 2% of IDC cases were thought to be familial, as previously reviewed in detail.[4] Studies in the later 1980s showed that 5% to 10% of IDC cases were familial, whereas in the 1990s, with more rigorous study designs and larger cohorts, the familial rate was shown to range from 20% to 50% when comprehensive clinical screening (history, examination, ECG, and echocardiogram) of relatives was undertaken (see Ref. 4 for extensive review).

Familial dilated cardiomyopathy (FDC) has been defined as 2 or more closely related family members meeting diagnostic criteria for IDC.[4,5] Genetic etiology was suspected in these families because of the multigenerational nature of the disease and transmission usually indicating an autosomal dominant pattern of inheritance.

Previous comprehensive reviews have summarized the clinical features and presentation of IDC.[6] Most studies have failed to identify significant features that differ between patients with IDC and those with FDC, including age, gender, or clinical signs or symptoms at presentation.[7,8]

A 3- to 4-generation family history has been recommended with a new diagnosis of IDC, despite recognition that family history alone is insensitive compared with full clinical screening (history, examination, ECG, and echocardiogram).[4,9]

Clinical onset of FDC is usually in the adult years (30s to 50s), but varies widely, occasionally even presenting in infants, small children, and the elderly. Like IDC,[6] FDC most commonly presents with advanced disease, including heart failure, arrhythmia, stroke, or embolus, the latter from mural thrombus.[4] Family studies have demonstrated that clinically silent FDC can be present for years, but large natural history studies of asymptomatic individuals with either IDC or FDC are not available.[6]

DCM Genetics

More than 20 genes have been identified as causes of DCM, representing marked locus heterogeneity (Tables 1 and 2). For most of these genes, allelic heterogeneity is the rule. The genes implicated in DCM code for a variety of proteins expressed within the cardiomyocyte, ranging from the nuclear envelope, the cardiac sarcomere, ion channels, transcription factors, and the dystrophin-associated cytoskeletal complex (Table 2). Numerous excellent reviews are available that provide additional detail.[4,10–17] Mitochondrial defects have also been identified[4,13,17] (Tables 1 and 2).

One of the genes associated with DCM, the *LMNA* gene, which encodes the type A lamins, A and C, has been reported to be causative of DCM in 4% to 8% of patients with IDC/FDC (Table 2). The lamins are critical, structural elements of the inner nuclear membrane. *LMNA* mutations were observed in 5.9% of probands in a cohort of 324 unrelated patients with IDC/FDC, the largest series to derive a frequency estimate to date.[18] Other common genetic causes of DCM include mutations in β-myosin heavy chain (*MYH7*) and cardiac troponin T (*TNNT2*) (Table 2). Numerous other genes have been associated with FDC, most of which are autosomal, although 2 X-linked genes are also included. The mutation frequencies provided in most cases should be considered preliminary, as usually only 1 or 2 primary reports focusing on single genes are available from which to estimate frequencies. One larger cohort[8] has been sequenced for 7 genes.[18,19]

Penetrance of disease in families with FDC is highly variable, and, common to most adult-onset genetic disease, age dependent. Penetrance estimates have been suggested to be 10% at <20 years, 34% between 20 to 30 years, 60% between 30 to 40 years, and 90% at 40 years, although genetic screening was not accomplished in this report.[20]

Table 2. Genetic Causes of Dilated Cardiomyopathy (DCM)

Gene	Locus	OMIM*	Gene Product	Frequency†	Allelic Disorders
Autosomal dominant DCM					
LMNA	1q21.2	150330	Lamin A/C	4–8%	Lipodystrophy, Charcot-Marie-Tooth 2B1, Emery-Dreifuss muscular dystrophy, Hutchinson-Gilford progeria syndrome, limb girdle muscular dystrophy (LGMD) 1B
MYH7	14q12	160760	β-myosin heavy chain	4–6%	Laing distal myopathy, HCM
TNNT2	1q32	191045	Cardiac troponin T	3%	HCM
SCN5A	3p21	600163	Sodium channel	2–3%	Long QT syndrome type 3, Brugada syndrome, idiopathic ventricular fibrillation, sick sinus syndrome, cardiac conduction system disease
MYH6	14q12	160710	α-myosin heavy chain	? 2–3%	HCM, dominantly inherited atrial septal defect
DES	2q35	125660	Desmin	<1%–1%	Desminopathy, myofibrillar myopathy
VCL	10q22.1-23	193065	Metavinculin	<1%–1%	HCM
LDB3	10q22.2-23.3	605906	LIM domain-binding 3	<1%–1%	HCM, myofibrillar myopathy
TCAP	17q12	604488	Titin-cap or telethonin	<1%–1%	LGMD2G, HCM
PSEN1/PSEN2	14q24.3/1q31-q42	104311/600759	Presenilin 1/2	<1%–1%	Early-onset Alzheimer disease/early- and late-onset Alzheimer disease
ACTC	15q14	102540	Cardiac actin	<1%	HCM
TPM1	15q22.1	191010	α-tropomyosin 1	<1%	HCM
SGCD	5q33–34	601411	δ-sarcoglycan	<1%	Delta sarcoglycanopathy (LGMD2F)
CSRP3	11p15.1	600824	Muscle LIM protein	<1%	HCM
ACTN2	1q42-q43	102573	α-actinin-2	<1%	HCM
ABCC9	12p12.1	601439	SUR2A	<1%	NA
TNNC1	3p21.3-p14.3	191040	Cardiac troponin C	<1%	NA
TTN	2q31	188840	Titin	?	Udd distal myopathy, HCM, Edstrom myopathy, early onset myopathy with fatal cardiomyopathy
MYBPC3	11p11.2	600958	Myosin-binding protein C	?	HCM
PLN	6q22.1	172405	Phospholamban	?	HCM
EYA4	6q23	603550	Eyes-absent 4	?	NA
TMPO	12q22	188380	Thymopoietin	?	NA
X-linked FDC					
DMD	Xp21.2	300377	Dystrophin	?	Dystrophinopathies (Duchenne muscular dystrophy, Becker muscular dystrophy)
TAZ/G4.5	Xq28	300394	Tafazzin	?	Barth syndrome, endocardial fibroelastosis type 2, familial isolated noncompaction of the left ventricular myocardium
Autosomal recessive DCM					
TNNI3	19q13.4	191044	Cardiac troponin I	<1%	HCM, restrictive cardiomyopathy

NA indicates not applicable.

*OMIM is Online Mendelian Inheritance in Man, URL: http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim, where additional information for each gene can be found.

†These estimates have been generated from primary and available secondary reports. See Ref. 3 for additional on-line gene-specific genetic testing information.

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HCM

HCM Clinical Features

HCM is a genetic cardiomyopathy structurally characterized by left ventricular (LV) hypertrophy, predominantly of the interventricular septum, myocyte disarray, and fibrosis. It affects ≈1/500 (0.2%) individuals. Although the HCM designation is commonly restricted to hypertrophy arising from mutations in genes encoding sarcomeric contractile proteins, other nonsyndromic, genetic causes of the hypertrophic phenotype are additionally captured by this nomenclature (Tables 1 and 3).

Unlike DCM, which is primarily an adult-onset disease, HCM arising from mutations of genes encoding sarcomeric proteins most commonly occurs at puberty. Diastolic dysfunction typically precedes overt hypertrophy or symptoms of heart failure. Approximately 20% of individuals will develop atrial fibrillation, which can be associated with embolic stroke. Approximately 25% of individuals with HCM survive to age 75 or older with low (1%) overall annual mortality

Table 3. Genetic Causes of Hypertrophic Cardiomyopathy (HCM)

Gene	Locus	OMIM*	Gene Product	Frequency†	Allelic Disorders
Autosomal dominant HCM					
MYH7	14q12	160760	β-myosin heavy chain	30% to 40%	DCM, Laing distal myopathy
MYBPC3	11p11.2	600958	Myosin-binding protein C,	30% to 40%	DCM
TNNT2	1q32	191045	Cardiac troponin T	5%	DCM
TNNI3	19q13.4	191044	Cardiac troponin I	5%	DCM, restrictive cardiomyopathy
TPM1	15q22.1	191010	α-tropomyosin 1	≈1% to 2%	DCM
MYL2	12q23-q24.3	160781	Cardiac myosin light chain 2	?	NA
MYL3	3p	160790	Myosin light chain 3	≈1%	NA
ACTC	15q14	102540	Cardiac actin	≈1%	DCM
TTN	2q31	188840	Titin	Rare	DCM, Udd distal myopathy, Edstrom myopathy, early onset myopathy with fatal cardiomyopathy
MYH6	14q12	160710	α-myosin heavy chain	<1%	DCM, dominantly inherited atrial septal defect
TCAP	17q12	604488	Titin cap or telethonin	<1%	DCM, limb girdle muscular dystrophy (LGMD) 2G
MYOZ2	4q26-q27	605602	Myozenin 2	<1%	NA
CSRP3	11p15.1	600824	Muscle LIM protein	Rare	DCM
MYLK2	20q13.3	606566	Myosin light chain kinase 2	Rare	NA
LDB3	10q22.2-q23.3	605906	LIM domain-binding 3	Rare	DCM, myofibrillar myopathy
VCL	10q22.1-q23	193065	Metavinculin	Rare	DCM
ACTN2	1q42-q43	102573	α-actinin 2	Rare	DCM
PLN	6q22.1	172405	Phospholamban	Rare	DCM
JPH2	20q12	605267	Junctophilin 2	Rare	NA
CAV3	3p25	601253	Caveolin 3	Rare	Long QT syndrome 9, LGMD1C, isolated persistent hyperCKemia, rippling muscle disease
CALR3	19p13.12	611414	Calreticulin 3	Rare	NA

NA indicates not applicable.

*OMIM is Online Mendelian Inheritance in Man, URL: http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim.

†These estimates have been generated from primary and available secondary reports. See Ref. 1 for additional on-line gene-specific genetic testing information.

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rates. LV outflow tract obstruction confers a higher risk for morbidity and mortality. Sudden cardiac death, primarily resulting from ventricular arrhythmias, is also a common cause of mortality and often serves as the presenting manifestation of disease.

Cardiac hypertrophy is a major phenotypic component of a number of syndromes, including various mitochondrial disorders (Tables 1 and 3). Some syndromic forms, such as Fabry and Danon diseases, display X-linked patterns of inheritance, which can aid in distinguishing them from HCM, particularly in cases where syndromic features are absent.[21,22]

Clinical management for HCM involves not only amelioration of symptoms, but also prevention of SCD and screening of at-risk family members. These topics are covered in reviews[23,24] and consensus guidelines.[25]

HCM Genetics

HCM usually follows an autosomal dominant pattern of inheritance, characterized by substantial variation in expressivity and age-dependent penetrance. It is caused primarily by missense mutations in genes encoding components of the cardiac sarcomere, although causative nonsense, frameshift, and in-frame insertion/deletion mutations have also been observed, particularly in *MYBPC3,* which encodes cardiac myosin-binding protein C[26] (Table 3).

Unlike DCM, mutations in 2 genes, *MYH7* and *MYBPC3*, account for ≈80% of HCM cases when genetic cause is found,[1,26,27] but similar to DCM, marked allelic heterogeneity of these genes is the rule with most mutations occurring privately or at frequencies <1%. Mutations in 3 other genes, *TNNT2*, *TNNI3*, and *TPM1*, encoding components of the troponin complex, are also relatively common (collectively ≈10% to 15% when genetic cause is found).[1,26–28] Mutations have been identified rarely in additional sarcomeric genes[29] (Table 3). Currently, 9 genes are available for clinical genetic testing,[1] and of all patients who undergo genetic testing, a mutation is identified in 40% to 60% of sporadic and familial cases when testing is performed for these genes.[26,27]

Some patients (2% to 5%) harbor 2 mutations in causative sarcomeric genes.[26,30,31] Because these patients exhibit more severe and earlier onset hypertrophy,[30] it has been proposed that 1 mutation may act as a modifier to the other.[26]

Mitochondrial etiologies, though less frequently involved, have also been implicated[28,32,33] (Table 1), including coexistence of *MYH7* and mitochondrial DNA mutations.[34]

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

ARVD/C Clinical Features

ARVD/C is an uncommon disease characterized by right ventricular (RV) fibrofatty replacement, RV myocyte loss,

Table 4. Genetic Causes of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)

Gene	Locus	OMIM*	Gene Product	Frequency†	Allelic Disorders
Autosomal dominant ARVD/C					
PKP2	12p11	602861	Plakophilin 2	11% to 43%	NA
DSG2	18q12	125671	Desmoglein 2	12% to 40%	NA
DSP	6p24	125647	Desmoplakin	6% to 16%	Carvajal syndrome
DSC2	18q12	125645	Desmocollin 2	Rare	NA
JUP	17q21	173325	Junction plakoglobin	Rare	Naxos syndrome
RYR2	1q42	180902	Ryanodine receptor 2	Rare	NA
TGFB3	14q24	190230	Transforming growth factor β-3	Rare	NA
TMEM43	3p25	612048	Transmembrane protein 43	Unknown	NA
Autosomal recessive ARVD/C					
PKP2	12p11	602861	Plakophilin 2	Rare	NA

NA indicates not applicable.

*OMIM is Online Mendelian Inheritance in Man, URL: http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim.

†These estimates have been generated from primary and available secondary reports. See Ref. 40 for additional on-line gene-specific genetic testing information.

and RV wall thinning.[35] Standard diagnostic criteria have been established[35] and revised,[36] and include functional and structural alterations of the RV (principally fibrofatty replacement of the free wall), ECG depolarization/repolarization changes, arrhythmias/conduction abnormalities, and family history. Onset usually occurs during adolescence or young adulthood, although presentation during the fifth decade has been observed. Sudden cardiac death and/or exercise-induced ventricular arrhythmia are often presenting features. Death usually occurs as a result of ventricular tachycardia or, less commonly, heart failure. Despite being primarily a disease of the RV, LV involvement may also be present and can precede RV manifestations[37] or even be the presenting feature.[38] Management guidelines have been established as a component of more general arrhythmia guidelines. Family history intake is recommended[9,35,39]; however, given low penetrance and clinical variability, as well as the possibility of nonsyndromic autosomal recessive ARVD/C, absence of familial disease does not rule out genetic risk. Because of this, clinical screening of first-degree relatives is recommended at intervals.

ARVD/C Genetics

One third to one half of ARVD/C cases are familial. The pattern of inheritance is autosomal dominant with variable expressivity and reduced penetrance (20% to 30% or higher, particularly in males). Eight causative genes have been identified, most of which encode cardiac desmosomal proteins (Table 4).

Pathologically, ARVD/C may be mediated by desmosomal defects predisposing to myocyte damage,[39,41] followed by inflammation and fibrofatty replacement.[39] Other arrhythmogenic mechanisms may involve gap junction remodeling[42] and Wnt signaling defects.[43] A genetic cause remains unknown in ≈50% of cases (Table 4).

Clinical Screening, Counseling, Genetic Testing, and Guideline Recommendations for the Genetic Cardiomyopathies

Guidelines for HCM,[25,44,45] DCM,[45,46] and ARVD/C[45] are available, as is expert opinion and currently available genetic testing at the GeneTests website (www.genetests.org) for HCM,[1] DCM,[3] and ARVD/C.[40] Generic guidelines for all practitioners who diagnose and manage these cardiomyopathies can be summarized as: (1) obtain a careful family history of at least 3 to 4 generations; (2) recommend clinical screening in at-risk-relatives (eg, echocardiogram, ECG, history, examination, and other specialized testing as appropriate for the cardiomyopathy); (3) counsel the patient that the condition may have a heritable genetic basis, and discuss its likely pattern of inheritance, the typical age of onset, presenting symptoms, and other relevant features; and (4) consider and conduct genetic testing, as appropriate.

In some patients, these recommendations are straightforward, whereas in others, gaining family history data, providing counseling, or undertaking decisions regarding genetic testing are more complex and problematic. Especially in the latter cases, referrals to geneticists or cardiologists specializing in cardiovascular genetic medicine[47] may be desirable and should be considered.

Genetic Counseling

Genetic counseling is a helpful adjunct to assist with the diagnosis and management of the cardiomyopathies.[48–50] It is also an essential component of any genetic testing process.[50] In North America, genetic counseling is traditionally carried out by board certified, masters-trained counselors (an increasing number specializing in cardiovascular genetic medicine)[47] in collaboration with physicians.

The genetic counseling process has 4 principal components, including (1) acquiring a complete family history; (2) providing information regarding the modes of inheritance and clinical features of the cardiomyopathy; (3) presenting the benefits, risks, limitations, and possible outcomes if genetic testing will be offered; and (4) discussing with the patient and family the potential psychosocial impact of a heritable disease. Recent reviews provide comprehensive information regarding these topics, including genetics glossaries for those less familiar with genetic terminology.[9,50]

A thorough family history of cardiomyopathy and any other cardiovascular or genetic disease is obtained as a 3- to

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4-generation pedigree. Pedigree analysis follows, which allows clinicians to observe familial patterns, discover possible genetic risk factors, and identify at-risk family members for whom clinical screening and genetic testing may be indicated.

Genetic Testing for the Cardiomyopathies

The rationale for genetic testing in cardiomyopathy at this time is principally to identify a disease-causing mutation in those at-risk family members who have little or no evidence of disease, so that heightened clinical surveillance, more informed medical management, and/or reproductive decision-making can be undertaken.[45,47] Increased clinical surveillance, in turn, can lead to early intervention, thereby preventing sequelae of advanced disease. The bedrock underlying this rationale is that treatment interventions are available that can prevent, delay or treat almost all of the morbid or mortal aspects of the cardiomyopathies.[45,47] In this respect, cardiovascular genetic disease varies from many other genetic diagnoses that have no known interventions to affect their natural history.[47]

Genetic testing may be useful for the sole purpose of clarification or confirmation of disease etiology in an affected individual with cardiomyopathy; knowledge of causation in a disease considered to be idiopathic, for example IDC, may have considerable intrinsic value. Genetic testing may also be useful for diagnosis or clinical management, such as distinguishing between adaptive hypertrophy to exercise (athlete's heart) and HCM, or assessing risk for progressive conduction system disease and/or arrhythmia in a person with DCM.

Genetic testing, although rapidly emerging into clinical practice, is currently undertaken at only a few centers.[47] Further, because of the relative insensitivity of genetic testing for DCM, and intermediate sensitivity for HCM and ARVD/C, testing is usually limited to the most common causative genes.[50] This approach may be rapidly changing as more cost-effective screening methods, such as chip-based or next generation sequencing, become available. Also, with the recent passage of the Genetics Information Nondiscrimination Act, interest in and utilization of genetic testing services is likely to increase. Time and cost, however, remain pertinent considerations.[51] In addition, insurance coverage is variable, further confounding access to testing. Research genetic testing, the mainstay for most of the past 15 years, may be an option if clinical genetic testing is unavailable or is otherwise uninformative; however, this testing typically takes months to years to complete, and often requires mutation confirmation through a Clinical Laboratory Improvement Amendment (CLIA)-certified laboratory.[50] Nevertheless, research testing of large cohorts of patients and family members is essential to continued progress in the field, and referrals of patients with genetic cardiomyopathies for clinical research and longitudinal follow-up have been advocated.[45] Clinical and research testing availability are catalogued by GeneTests (www.genetests.org), a continually updated medical genetics resource.

To increase the likelihood of finding a causative mutation, genetic testing should begin with the family member manifesting the most obvious disease.[50] If the proband's results are negative, further testing in the family is often of little utility, particularly testing of asymptomatic relatives. For autosomal dominant disease, a positive result implies that the proband's offspring will be at 50% risk of inheriting the disease and testing should be made available to them.

Although causative mutations for DCM have been identified in >20 genes, preliminary data suggest that mutations in these genes account for a minority of cases, probably at best 20% to 25% (Table 2). Depending on the phenotype and family history, testing may begin with *LMNA, MYH7,* and *TNNT2* because of their higher frequencies (Table 2). Negative results for these 3 genes may then warrant reflex testing to the remaining genes.

Of particular note, onset of conduction system disease with minimal cardiac dilatation is suggestive of *LMNA*-related DCM. It has also been suggested that all individuals with IDC should undergo genetic testing for mutations in *LMNA*,[2,18,45,50] given relatively higher mutation frequencies in this gene.

Clinical testing is available for 9 sarcomeric genes associated with HCM, with genetic causation identifiable in ≈40% to 60% of families.[26,27] Genetic workup may begin with *MYH7, MYBPC3*, and *TNNT2*, because mutations in these genes account for most cases (Table 3). As with DCM, definitive genotype-phenotype correlations remain elusive, in part because of extreme genetic heterogeneity, rarity of individual mutations, and substantial variation in penetrance and expressivity, even among related individuals carrying identical mutations. *TNNT2* testing may be considered first if a family presents with SCD or mild hypertrophy. If no mutation is found in these 3 genes, testing can reflex to the remaining clinically available sarcomeric genes. Because any LV wall thickness can be associated with an HCM mutation, genetic testing is feasible for any level of hypertrophy.[25]

Genetic testing can be useful in the setting of ARVD/C, where SCD is a common presenting feature. Results compiled from multiple cohorts tested for *DSP, PKP2, DSG2*, *DSC2*, and *TGFB3* suggest that the detection rate is 40% to 50%.[41] Because *PKP2* mutations are identified in relatively higher proportions[43] (Table 4), it is reasonable to begin testing with *PKP2* and, if negative, consider reflex testing. A few genotype/phenotype correlations have been suggested: *RYR2* has been associated with early-onset cardiac death and effort-induced polymorphic ventricular tachycardia, *TMEM43* with fully penetrant disease, and *DSP* or *DSG2* with LV involvement.

Genetic testing should be considered in the context of strong clinical data. Furthermore, although DCM, HCM, and ARVD/C tend to follow an autosomal dominant inheritance pattern, multigenic and homozygous forms have been reported.[26,28,30,31,37] Thus, the complexity of testing options and inheritance patterns in hereditary cardiomyopathies warrants involvement of cardiovascular genetics experts and ongoing collaboration between cardiologists and genetic professionals.

Epilogue

Enormous progress has been made in identifying and understanding the genetic basis of cardiomyopathy. The field is rapidly evolving and the future appears bright. Ongoing

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research efforts now aim to identify additional genetic cause, particularly for DCM. Newer, faster sequencing methods are being developed that will help us achieve more rapid and cost-effective molecular genetic diagnoses. Also critical for progress will be the conduct of long-term natural history studies with large cohorts of patients and their family members known to carry disease-causing mutations. This future is underway; although still incomplete, genetic cardiomyopathy knowledge has already led to relevant, achievable clinical recommendations for the screening of at-risk family members, genetic counseling, and genetic testing.

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Disclosures

None.

References

1. *Familial Hypertrophic Cardiomyopathy Overview*. Seattle, Wash: University of Washington; 2008. Available at: http://www.genetests.org. Accessed January 18, 2009.
2. *LMNA-Related Dilated Cardiomyopathy*. Seattle, Wash: University of Washington; 1997–2008. Available at: http://www.genetests.org. Accessed January 18, 2009.
3. *Dilated Cardiomyopathy Overview*. Seattle, Wash: University of Washington; 1997–2008. Available at: http://www.genetests.org. Accessed January 18, 2009.
4. Burkett EL, Hershberger RE. Clinical and genetic issues in familial dilated cardiomyopathy. *J Am Coll Cardiol*. 2005;45:969–981.
5. Mestroni L, Maisch B, McKenna WJ, Schwartz K, Charron P, Rocco C, Tesson F, Richter A, Wilke A, Komajda M. Guidelines for the study of familial dilated cardiomyopathies. Collaborative Research Group of the European Human and Capital Mobility Project on Familial Dilated Cardiomyopathy. *Eur Heart J*. 1999;20:93–102.
6. Dec G, Fuster V. Idiopathic dilated cardiomyopathy. *N Engl J Med*. 1994;331:1564–1575.
7. Michels VV, Moll PP, Miller FA, Tajik J, Chu JS, Driscoll DJ, Burnett JC, Rodeheffer RJ, Chesebro JH, Tazelaar HD. The frequency of familial dilated cardiomyopathy in a series of patients with idiopathic dilated cardiomyopathy. *N Engl J Med*. 1992;326:77–82.
8. Kushner JD, Nauman D, Burgess D, Ludwigsen S, Parks S, Pantely G, Burkett EL, Hershberger R. Clinical characteristics of 304 kindreds evaluated for familial dilated cardiomyopathy. *J Cardiac Failure*. 2006; 12:422–429.
9. Morales A, Cowan J, Dagua J, Hershberger RE. Family history: an essential tool for cardiovascular genetic medicine. *Congest Heart Fail*. 2008;14:37–45.
10. Morita H, Seidman J, Seidman CE. Genetic causes of human heart failure. *J Clin Invest*. 2005;115:518–526.
11. Taylor MR, Carniel E, Mestroni L. Cardiomyopathy, familial dilated. *Orphanet J Rare Dis*. 2006;1:27.
12. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. *Circulation*. 2006; 113:1807–1816.
13. Richard P, Villard E, Charron P, Isnard R. The genetic bases of cardiomyopathies. *J Am Coll Cardiol*. 2006;48(supple A):A79–A89.
14. Karkkainen S, Peuhkurinen K. Genetics of dilated cardiomyopathy. *Ann Med*. 2007;39:91–107.
15. Ashrafian H, Watkins H. Reviews of translational medicine and genomics in cardiovascular disease: new disease taxonomy and therapeutic implications cardiomyopathies: therapeutics based on molecular phenotype. *J Am Coll Cardiol*. 2007;49:1251–1264.
16. van Spaendonck-Zwarts KY, van den Berg MP, van Tintelen JP. DNA analysis in inherited cardiomyopathies: current status and clinical relevance. *Pacing Clin Electrophysiol*. 2008;31(suppl 1):S46–S49.
17. Judge DP, Johnson NM. Genetic evaluation of familial cardiomyopathy. *J Cardiovasc Trans Res*. 2008;1:144–154.
18. Parks SB, Kushner JD, Nauman D, Burgess D, Ludwigsen S, Peterson A, Li D, Jakobs P, Litt M, Porter CB, Rahko PS, Hershberger RE. Lamin A/C mutation analysis in a cohort of 324 unrelated patients with idiopathic or familial dilated cardiomyopathy. *Am Heart J*. 2008;156:161–169.
19. Hershberger R, Parks S, Kushner JD, Li D, Ludwigsen S, Jakobs P, Nauman D, Burgess D, Partain J, Litt M. Coding sequence mutations identified in MYH7, *TNNT2, SCN5A, CSRP3, LBD3,* and *TCAP* from 313 patients with familial or idiopathic dilated cardiomyopathy. *Clin Translational Sci*. 2008;1:21–26.
20. Mestroni L, Rocco C, Gregori D, Sinagra G, DiLenarda A, Miocic S, Vatta M, Pinamonti B, Muntoni F, Caforio L, McKenna W, Falaschi A, Giacca M, Camerini F. Familial dilated cardiomyopathy: evidence for genetic and phenotypic heterogeneity. *J Am Coll Cardiol*. 1999;34: 181–190.
21. Sachdev B, Takenaka T, Teraguchi H, Tei C, Lee P, McKenna WJ, Elliott PM. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. *Circulation*. 2002;105:1407–1411.
22. Arad M, Maron BJ, Gorham JM, Johnson WH Jr, Saul JP, Perez-Atayde AR, Spirito P, Wright GB, Kanter RJ, Seidman CE, Seidman JG. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med*. 2005;352:362–372.
23. Brown ML, Schaff HV. Surgical management of obstructive hypertrophic cardiomyopathy: the gold standard. *Expert Rev Cardiovasc Ther*. 2008; 6:715–722.
24. Seggewiss H, Rigopoulos A. Management of hypertrophic cardiomyopathy in children. *Paediatr Drugs*. 2003;5:663–672.
25. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH, III, Spirito P, Ten Cate FJ, Wigle ED. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol*. 2003;42: 1687–1713.
26. Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C, Benaiche A, Isnard R, Dubourg O, Burban M, Gueffet JP, Millaire A, Desnos M, Schwartz K, Hainque B, Komajda M. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. *Circulation*. 2003;107: 2227–2232.
27. Van Driest SL, Ommen SR, Tajik AJ, Gersh BJ, Ackerman MJ. Yield of genetic testing in hypertrophic cardiomyopathy. *Mayo Clin Proc*. 2005; 80:739–744.
28. Marian AJ. Genetic determinants of cardiac hypertrophy. *Curr Opin Cardiol*. 2008;23:199–205.
29. http://genetics.med.harvard.edu/~seidman/cg3/index.html. Accessed March 15, 2008.
30. Van Driest SL, Vasile VC, Ommen SR, Will ML, Tajik AJ, Gersh BJ, Ackerman MJ. Myosin binding protein C mutations and compound heterozygosity in hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2004; 44:1903–1910.
31. Ingles J, Doolan A, Chiu C, Seidman J, Seidman C, Semsarian C. Compound and double mutations in patients with hypertrophic cardiomyopathy: implications for genetic testing and counselling. *J Med Genet*. 2005;42:e59.
32. Marian AJ. Clinical and molecular genetic aspects of hypertrophic cardiomyopathy. *Curr Cardiol Rev*. 2005;1:53–63.
33. Bos JM, Ommen SR, Ackerman MJ. Genetics of hypertrophic cardiomyopathy: one, two, or more diseases? *Curr Opin Cardiol*. 2007;22:193–199.
34. Arbustini E, Diegoli M, Fasani R, Grasso M, Morbini P, Banchieri N, Bellini O, Dal Bello B, Pilotto A, Magrini G, Campana C, Fortina P, Gavazzi A, Narula J, Vigano M. Mitochondrial DNA mutations and mitochondrial abnormalities in dilated cardiomyopathy. *Am J Pathol*. 1998;153:1501–1510.
35. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, Camerini F. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology. *Br Heart J*. 1994;71:215–218.

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36. Hamid MS, Norman M, Quraishi A, Firoozi S, Thaman R, Gimeno JR, Sachdev B, Rowland E, Elliott PM, McKenna WJ. Prospective evaluation of relatives for familial arrhythmogenic right ventricular cardiomyopathy/dysplasia reveals a need to broaden diagnostic criteria. *J Am Coll Cardiol*. 2002;40:1445–1450.
37. Sen-Chowdhry S, Syrris P, Ward D, Asimaki A, Sevdalis E, McKenna WJ. Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. *Circulation*. 2007;115:1710–1720.
38. Kies P, Bootsma M, Bax J, Schalij MJ, van der Wall EE. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: screening, diagnosis, and treatment. *Heart Rhythm*. 2006;3:225–234.
39. Sen-Chowdhry S, Lowe MD, Sporton SC, McKenna WJ. Arrhythmogenic right ventricular cardiomyopathy: clinical presentation, diagnosis, and management. *Am J Med*. 2004;117:685–695.
40. *Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy, Autosomal Dominant*. Seattle, Wash: University of Washington; 1997–2008. Available at: http://www.genetests.org. Accessed November 2, 2008.
41. Sen-Chowdhry S, Syrris P, McKenna WJ. Role of genetic analysis in the management of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. *J Am Coll Cardiol*. 2007;50:1813–1821.
42. Sen-Chowdhry S, Syrris P, McKenna WJ. Genetics of right ventricular cardiomyopathy. *J Cardiovasc Electrophysiol*. 2005;16:927–935.
43. Awad MM, Calkins H, Judge DP. Mechanisms of disease: molecular genetics of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Nat Clin Pract Cardiovasc Med*. 2008;5:258–267.
44. Semsarian C. Guidelines for the diagnosis and management of hypertrophic cardiomyopathy. *Heart Lung Circ*. 2007;16:16–18.
45. Hershberger RE, Lindenfeld J, Mestroni L, Seidman CE, Taylor MR, Towbin JA. Genetic evaluation of cardiomyopathy: a Heart Failure Society of America Practice Guideline. *J Cardiac Failure*. 2009;15:83–97.
46. Fatkin D. Guidelines for the diagnosis and management of familial dilated cardiomyopathy. *Heart Lung Circ*. 2007;16:19–21.
47. Hershberger RE. Cardiovascular genetic medicine: evolving concepts, rationale and implementation. *J Cardiovasc Trans Res*. 2008;1:137–143.
48. Yu B, French JA, Jeremy RW, French P, McTaggart DR, Nicholson MR, Semsarian C, Richmond DR, Trent RJ. Counselling issues in familial hypertrophic cardiomyopathy. *J Med Genet*. 1998;35:183–188.
49. Hanson E, Hershberger RE. Genetic counseling and screening issues in familial dilated cardiomyopathy. *J Genet Counsel*. 2001;10:397–415.
50. Cowan J, Morales A, Dagua J, Hershberger RE. Genetic testing and genetic counseling in cardiovascular genetic medicine: overview and preliminary recommendations. *Congest Heart Fail*. 2008;14:97–105.
51. Robin NH, Tabereaux PB, Benza R, Korf BR. Genetic testing in cardiovascular disease. *J Am Coll Cardiol*. 2007;50:727–737.

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