The burden of heart failure (HF) in the developed world is rivaled only by cancer, in the United States affecting 2% of the population at a treatment cost to society of $28 billion per year. Mortality rates exceed 40% at 5-year follow-up. Although definable in its simplest form as insufficient cardiac output for adequate end-organ perfusion, HF is a complex and diverse disease phenotype with variable heritability. It is also a phenotype that represents a final common pathway of diverse causes, pathophysiology, and clinical course. This complexity is mirrored in the genetic architecture of HF. This ranges from the monogenic HF syndromes caused largely by single underlying pathogenetic mutations to HF as a complex trait, for which susceptibility to environmental triggers is modified quantitatively by multiple genetic or epigenetic individually low-penetrance loci.

The focus of this review is the genetic cardiomyopathies, classically divided into dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy (AC), and restrictive cardiomyopathy (RCM), each of which may be the cause of a HF syndrome. Although this traditional

**Abstract:** Despite the striking advances in medical and surgical therapy, the morbidity, mortality, and economic burden of heart failure (HF) remain unacceptably high. There is increasing evidence that the risk and course of HF depend on genetic predisposition; however, the genetic contribution to HF is heterogeneous and complex. At one end of the spectrum are the familial monogenic HF syndromes in which causative mutations are rare but highly penetrant. At the other, HF susceptibility and course may be influenced by more common, less penetrant genetic variants. As detailed in this review, efforts to unravel the basis of the familial cardiomyopathies at the mendelian end of the spectrum already have begun to deliver on the promise of informative mechanisms, novel gene-based diagnostics, and therapies for distinct subtypes of HF. However, continued progress requires the differentiation of pathogenic mutations, disease modifiers, and rare, benign variants in the deluge of data emerging from increasingly accessible novel sequencing technologies. This represents a significant challenge and demands a sustained effort in analysis of extended family pedigrees, diligent clinical phenotyping, and systematic annotation of human genetic variation. (Circ Res. 2013;113:660-675.)

**Key Words:** cardiomyopathies ■ genetics ■ heart failure
classification based on structural and functional changes at the whole-organ level is relatively crude, it has continuing relevance for clinical diagnosis and management.\(^3\) In practice, there is extensive overlap between these phenotypes; for example, HCM, left ventricular noncompaction cardiomyopathy (LVNC), or AC may progress into a dilated ventricle with systolic dysfunction and hence the appearance of DCM. In genetic cardiomyopathy, as in other forms of HF, advanced imaging offers refinement of this structurally based classification with functional information to complement the morphological phenotype, providing insight into contractility, diastolic function, strain, synchrony, fibrosis, and energetics (Figure 1).\(^1,4\)

Painstaking linkage analysis in extended families and, less unambiguously, candidate gene sequencing have unraveled much of the genetic basis of inherited cardiomyopathy, although some remains unclear. Unexpected complexity has emerged, particularly in DCM, for which there are numerous genetic loci and mutations affecting diverse cellular pathways. This genetic landscape, combined with limited understanding of genotype–phenotype relationships, has tempered some aspects of application of genetics to the clinical setting. Nonetheless, when a pathogenic mutation can be identified, most often in HCM, this provides a powerful diagnostic test to screen family members who may carry and transmit the mutation.

Although next-generation sequencing (NGS) is likely to advance cardiomyopathy genetics, in the short term it presents a substantial challenge. Differentiating rare but benign sequence variants from disease-causing mutations is difficult and is now magnified by the increased detection of low-frequency or rare polymorphisms with NGS.\(^5\) It is clear that variants in the individual genome are far more numerous than anticipated. Moreover, existing predictive tools purporting to distinguish benign variants from causative mutations on the basis of sequence conservation or putative effects on protein structure are of limited utility. This realization has cast doubt on some findings from candidate gene sequencing, in which unclassified variants were prematurely ascribed pathogenicity on the basis of their absence in small control populations or poorly predictive in vitro data. Tight criteria for pathogenicity need to be applied to NGS to avoid a recurrence of this false dawn.

A further complication in decoding the genetic contribution to complex traits like HF is that beyond the monogenic cardiomyopathies, multiple locus interactions rather than single mutations per se contribute quantitatively to the disease

### Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>AC</td>
<td>arrhythmogenic cardiomyopathy</td>
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<tr>
<td>DCM</td>
<td>dilated cardiomyopathy</td>
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<td>HCM</td>
<td>hypertrophic cardiomyopathy</td>
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<tr>
<td>HF</td>
<td>heart failure</td>
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<tr>
<td>ICD</td>
<td>implantable cardiac defibrillator</td>
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<td>LVNC</td>
<td>left ventricular noncompaction cardiomyopathy</td>
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<tr>
<td>NGS</td>
<td>next-generation sequencing</td>
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<tr>
<td>RCM</td>
<td>restrictive cardiomyopathy</td>
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<td>SCD</td>
<td>sudden cardiac death</td>
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**Figure 1.** Cardiac magnetic resonance imaging (MRI) scan demonstrating features of phenotypic overlap across the standard cardiomyopathy classification. Horizontal long-axis (A), vertical long-axis (B), short-axis (C), and late gadolinium-enhanced (D) cardiac MRIs from a patient presenting with symptoms of heart failure. This study demonstrates a mildly dilated left ventricle with severely impaired systolic function (ejection fraction, 35%). Significant left ventricular hypertrophy is seen and is most pronounced in the septum. There was late gadolinium enhancement in the basal midseptum, also involving the inferior right ventricular–left ventricular junction (D). Additionally, the lateral wall shows prominent trabeculation, but this does not reach the current diagnostic threshold for left ventricular noncompaction. The features manifest in this scan are most consistent with hypertrophic cardiomyopathy (HCM) in a burnt-out phase, but HCM and left ventricular noncompaction cardiomyopathy are subject to phenotypic and pathogenic overlap.
phenotype. Furthermore, the cumulative effect of common variants will combine with environmental cues to influence HF susceptibility. However, when causality can be established between genetic variants and disease, then novel insights into disease mechanisms will be delineated.

**Common Features of Genetic Cardiomyopathy**

Genetic cardiomyopathies represent a small proportion of HF overall, although this varies strongly by age and population studied. In the pediatric population with HF, a familial, presumed monogenic, origin is frequently identified, eg, approximately 40% in a recent study. In younger adults with HF selected for cardiac transplantation, the prevalence of genetic disease is also high, with familial disease in one cohort confirmed in 26% and suspected in an additional 26%. Similarly, in idiopathic DCM in adults, the proportion of familial disease found on family screening is high, typically >30%. In the unselected adult HF population, precise data are lacking but the prevalence of monogenic traits will be lower. Susceptibility to HF, however, is also heritable as a complex trait; having a parent with HF who is <75 years of age was found to be a significant risk factor for development of HF in the Framingham Offspring cohort, even after adjustment for myocardial infarction, diabetes mellitus, and hypertension.

Genetic cardiomyopathies merit close study for several reasons. First, they are frequently early onset and are a major contributor to morbidity and mortality in the young. Second, if a pathogenic mutation can be identified in a family, then they allow the unique opportunity for diagnosis and intervention at a preventive stage. Once disease status has been established, patients can undergo early risk stratification (eg, for sudden cardiac death [SCD]) or begin treatment before cardiac decompensation or remodeling. Genetic testing to allow cascade screening of family members in inherited heart disease has become the standard of care.

More than 50 years ago, asymmetrical hypertrophy of the interventricular septum associated with SCD was recognized as a novel phenotype inherited within families, subsequently defined as HCM. Identification of causative mutations for HCM in genes encoding proteins of the cardiac sarcomere, initially the β-myosin heavy chain in 1990, heralded subsequent breakthroughs in the genetic basis of other cardiomyopathies.

Several common characteristics of genetic cardiomyopathies have emerged. First, different variants within a single gene can produce contrasting phenotypes. For example, mutations in the gene encoding the sarcomeric protein cardiac troponin I (TNNI3) may cause the HCM, DCM, or RCM phenotype. Importantly, in almost all instances, each specific mutation consistently produces the same qualitative phenotype; ie, a variant causes either DCM or HCM but not both. However, there is substantial quantitative variability in the given cardiomyopathy phenotype, even when the disease gene and allele are the same, which is referred to as phenotypic heterogeneity.

**Figure 2.** Opposing pathological mechanisms underlie the development of dilated (DCM) and hypertrophic cardiomyopathy (HCM) caused by sarcomeric mutations. 

A, Effect of HCM-causing and DCM-causing mutations on the calcium-binding affinity of the cardiac thin filament (left) and on the calcium sensitivity of the actin-troponymosin-activated myosin ATPase (right). Sarcomeric HCM mutations increase thin-filament calcium binding and calcium sensitivity of contraction, whereas DCM mutations cause a reduction. B, Representative example of the effect of HCM-causing and DCM-causing sarcomeric mutations on the calcium sensitivity of the ATPase, motility, and force generation by the myofilament, expressed as a percentage of the unregulated (ie, in the absence of troponin and calcium) activity. Although specific mutations cause either HCM or DCM on the basis of their biophysical consequences and thus are mechanistically distinct, HCM may progress to a hypocontractile heart failure phenotype that can be misinterpreted if clinical features are sampled at a single late time point in the disease (eg, Figure 1).
Table 1. Key Disease Genes in Dilated Cardiomyopathy

<table>
<thead>
<tr>
<th>Disease Genes</th>
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<tr>
<td>Force generation/regulation</td>
<td></td>
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<tr>
<td>Actin, α, cardiac muscle 1</td>
<td>ACTC1</td>
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<tr>
<td>Myosin, heavy chain 7, cardiac muscle, β</td>
<td>MYH7</td>
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<tr>
<td>Troponin T type 2 (cardiac)</td>
<td>TNNT2</td>
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<tr>
<td>Troponin I type 3 (cardiac)</td>
<td>TNNT3</td>
</tr>
<tr>
<td>Troponin C type 1 (slow)</td>
<td>TNRC1</td>
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<tr>
<td>Phospholamban</td>
<td>PLN</td>
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<tr>
<td>Force transduction/mechanosensing</td>
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<tr>
<td>Titin</td>
<td>TTN</td>
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<tr>
<td>Dystrophin</td>
<td>DMD</td>
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<tr>
<td>Sarcoglycan, Δ (35-kDa dystrophin-associated glycoprotein)</td>
<td>SGCD</td>
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<tr>
<td>Desmin</td>
<td>DES</td>
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<tr>
<td>Nuclear proteins/transcription</td>
<td></td>
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<tr>
<td>Lamin A/C</td>
<td>LMNA</td>
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<tr>
<td>Other</td>
<td></td>
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<tr>
<td>RNA-binding motif protein 20</td>
<td>RBM20</td>
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<tr>
<td>Implicated but not yet supported by linkage/cosegregation</td>
<td></td>
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<tr>
<td>Actinin, α 2</td>
<td>ACTN2</td>
</tr>
<tr>
<td>Vinculin</td>
<td>VCL</td>
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<tr>
<td>Thymopoietin</td>
<td>TMP2</td>
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<tr>
<td>Titin-cap</td>
<td>T-cap</td>
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<tr>
<td>BCL2-associated athanogene 3</td>
<td>BAG3</td>
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<tr>
<td>LIM domain-binding 3</td>
<td>LDB3</td>
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<tr>
<td>Ankyrin repeat domain 1 (cardiac muscle)</td>
<td>ANKRD1</td>
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Second, each of the cardiomyopathy phenotypes is caused by one of numerous genetic mutations (genetic heterogeneity). Mutations in >50 genes cause a DCM phenotype (locus heterogeneity), and within these genes numerous different pathogenic mutations are described (allelic heterogeneity). Many mutations therefore are rare and frequently private, ie, specific, to an individual family, with few hot spots or common mutations.

The consequence of this heterogeneity is that testing only for known alleles is not effective as a diagnostic test, and systematic sequencing is needed instead. Furthermore, given the high frequency of rare variants in the genome, the pathogenicity of a missense variant identified in a proband must be validated. The original HCM loci were backed-up by linkage analysis in well-phenotyped large family pedigrees, with clear tracking (cosegregation) of the putative mutation with the phenotype. Frequently this is not possible, for example, in small families, for sporadic disease, or when penetrance is low. In such cases, mutations of evolutionary-conserved residues or in vitro assays of known protein function may be supportive. Searching for known variants in genome libraries of ethnically matched control populations (eg, http://evs.gs.washington.edu/EVS/) and previously reported pathogenicity (eg, ClinVar http://www.ncbi.nlm.nih.gov/clinvar/) will become a necessary, but insufficient, approach as the number of genomes sequenced grows.

Third, genetic cardiomyopathies demonstrate variable penetrance—the proportion of individuals carrying a pathogenic mutation who display a phenotype—even within the same family. Expressivity—the severity of the phenotype that develops in a patient with a pathogenic mutation—is also highly variable, meaning the clinical presentation, disease course, and outcome can differ dramatically within an affected family. Variable expressivity and penetrance imply that factors beyond the single pathogenic mutation influence the phenotype—genetic, epigenetic, or environmental modifiers. As genetic sequencing technology advances, cardiomyopathy attributable to compound heterozygosity (≥2 mutations in the same gene) and digenic/oligogenic heterozygosity (≥2 mutations in different genes) is being identified, particularly in cardiomyopathies with low penetrance such as arrhythmogenic cardiomyopathy. Even in monogenic disease, multiple other loci are likely to act as modifiers of the disease phenotype.

The complexity of cardiomyopathy and genetic testing increasingly supports a model of clinical care involving a specialist unit with geneticists and genetic counselors. This is advantageous in that pretest counseling can be extensively supported with anticipation and management of variants of unknown significance, particularly when NGS is used. Even in referral centers, ongoing reclassification and evaluation of variants of unknown significance as new data from other probands and genome banks are published represent a major challenge.

**Dilated Cardiomyopathy**

DCM is characterized pathologically by dilatation of the left ventricle, functionally by progressive contractile failure, and histologically by cardiomyocyte hypertrophy, loss of myofibrils, and interstitial fibrosis. Patients with DCM may be initially asymptomatic but develop exertional dyspnea, orthopnea, and fatigue as the left ventricle fails. Right ventricular failure is frequently present because of concurrent involvement by cardiomyopathy or secondary to left ventricular failure. Complications of DCM such as arrhythmia, mitral regurgitation, or embolization of intracardiac thrombus may be the presenting features of the disease. Mortality is significant through progressive HF or arrhythmic sudden death.

DCM is caused by diverse insults to the heart, including ischemia, infection, autoimmune disease, collagen vascular disease, toxins and drugs (eg, alcohol, anthracyclines, trastuzumab), nutritional deficiency (eg, thiamine, selenium, carnitine), and genetic disease. In addition to these causes, idiopathic DCM has a prevalence estimated at 36 per 100000 in the United States, although this is likely to be an underestimation. In patients with idiopathic DCM, careful screening reveals that >30% have affected first-degree family members, implying an underlying genetic basis. Inheritance is typically autosomal dominant, but autosomal-recessive, X-linked, and maternal transmission have been observed.

Development of genetic DCM occurs over time, normally with a prolonged asymptomatic phase during which the heart is initially macroscopically normal both morphologically and functionally. When an individual is known to be genotype positive and phenotype negative (eg, in a family with DCM), the timing and severity of a phenotype are difficult to predict, given the variability of expressivity and penetrance. With serial follow-up, imaging by echocardiography or magnetic
resonance imaging will usually detect abnormalities of cardiac size or function before overt symptoms (ie, a subclinical phenotype). Once clear symptoms develop, there is an approximate correlation with the degree of left ventricular dysfunction, although other factors such as diastolic function, arrhythmia, mitral regurgitation, right side HF, and other comorbidities will interact.

In addition to an isolated cardiac phenotype, 3 further broad DCM categories should be distinguished on clinical grounds because the presentation, management, and complications are distinct. These include DCM with conduction disease (either atrioventricular block or arrhythmia), DCM with skeletal muscle involvement, and DCM as a component of multisystem disease.

Extensive genetic heterogeneity underlies familial DCM, with >50 causative DCM genes implicated, although not all have been robustly proven yet. Key disease genes are shown in Table 1. Mutations currently have been identified in approximately 30% to 35% of patients with familial DCM, with the following 4 genes accounting for the majority: titin (TTN), lamin A/C (LMNA), β-myosin heavy chain (MYH7), and cardiac troponin T (TNNT2). Titin mutations appear to be the most common; recently, they were reported in 25% of familial disease and 18% of sporadic DCM in a cohort of 312 patients. If conduction abnormalities are present, then a mutation in LMNA is found in up to one third of cases.

The multiplicity of genes reported represents diverse cellular pathways, all of which converge on a macroscopic DCM phenotype that is not obviously clinically distinguishable. Although there does not appear to be a unifying cellular pathophysiology, the DCM genes can be broadly grouped by pathogenetic effect on contractile force generation and regulation, force transduction and mechanosensing, and nuclear proteins and transcription factors. Beyond these categories, further candidate genes with widespread cellular effects have been proposed and will continue to emerge, for example, on ion channel function, autophagy, and mitochondrial regulation, but remain to be fully validated or replicated as mechanistic pathways leading to DCM.

**Contractile Force Generation and Regulation**

Mutations in the sarcomeric proteins responsible for the generation and regulation of cardiac contraction were identified initially as the cause of HCM and subsequently were reported in DCM. Reduced myofilament calcium sensitivity appears to be a common pathogenetic mechanism in sarcomeric DCM mutations, potentially exploitable as a therapeutic target (Figure 2).

Mutations in proteins of both the thick and thin myofilaments cause DCM. β-Myosin heavy chain (MYH7), intrinsic to contractile force generation by type II myosin, is the sarcomeric gene most commonly mutated in DCM. MYH7 mutations are found in 5% to 10% of DCM and in approximately 20% of HCM probands, and they cause LVNC and myosin storage myopathy. Allelic heterogeneity is extensive, with numerous different mutations reported. The thin-filament protein cardiac actin (ACTC1) is a rare cause of DCM, in addition to HCM and LVNC, but was the first sarcomeric DCM gene identified. Mutations at the ACTC1 dystrophin-binding site are typically associated with the development of DCM.

Regulation of sarcomeric contraction is mediated primarily by troponosin and the troponin complex, composed of T, I, and C subunits. Troponin T (TNNT2), which binds tropomyosin, regulates interaction of the troponin complex with the thin filament. Troponin I (TNNI3) modulates sarcomeric activation through an inhibitory effect on actin-myosin binding during diastole, and troponin C (TNNC1) binds calcium during systole and promotes cross-bridge formation between actin and myosin, leading to contraction. DCM-causing mutations have been identified in all 3 subunits and are associated with impaired calcium sensitivity.

Beyond the sarcomere, dysregulation of contractile force generation is clearly linked to development of DCM. Phospholamban (PLN) is a small, highly conserved phosphoprotein that modulates sarcoplasmic reticulum calcium uptake, influencing downstream force production by the myofilament. Mutations in PLN cause autosomal-dominant DCM and are rare but well characterized, with the Arg14del mutation notable for its association with ventricular arrhythmia.

**Force Transduction and Mechanosensing**

Efficient transmission of force across the sarcomere, cell cytoskeleton, and extracellular matrix is essential to normal cardiac contractile function. Multiple proteins with a primary structural function or those that act as mechanosensors that modulate the sarcomere are linked to familial DCM. Key examples such as titin, dystrophin, and desmin are discussed.

The giant protein titin, spanning half the sarcomere from the Z disk to the M line, functions as an elastic molecular spring regulating passive tension and active contraction. The titin gene (TTN) contains 363 exons and approximately 33,000 amino acids compared with 38 exons and 1935 amino acids in MYH7. It interacts with >20 other structural, signaling, and modulatory proteins, including telethonin, α-actinin, and possibly muscle LIM in a putative mechanosensor complex at the Z disk.

The size of titin has, until recently, proved to be a technical barrier to understanding its role in DCM, which appears significant; truncating variants in TTN were recently reported in 22% of idiopathic DCM by NGS. In patients >40 years of age, DCM disease penetrance was >95%, with convincing cosegregation of truncating variants with disease in some families. Pathogenicity of individual alleles is not easily established, however, because comparable mutations were identified in 3% of healthy controls. Null allele mutations appear to be clustered in the titin A band, which contains the titin kinase domain, with fewer in either the Z-band or the M-band region. Of note, RBM20, previously identified as a DCM-causing gene, has been recently demonstrated to act by splicing regulation of titin transcripts. The spectrum of titinopathies also includes skeletal muscle phenotypes, including limb-girdle muscular dystrophy, tibial muscular dystrophy, and hereditary myopathy with early respiratory failure; however, there is little evidence as yet of skeletal muscle involvement with the DCM-causing mutations.

Another example of a key protein in force transduction is dystrophin (DMD), the first DCM disease gene reported. In addition to X-linked dilated cardiomyopathy, mutations in DMD cause Duchenne and Becker muscular dystrophy,
which are characterized by progressive skeletal muscle weakness. Dystrophin is a large cytoskeletal protein which forms a transmembrane link between the sarcomere and the extracellular matrix, the dystrophin-associated glycoprotein complex, alongside other proteins such as the sarcoglycans. Mutations in δ-sarcoglycan (SGCD) also have been implicated in DCM, although typically they cause limb-girdle muscular dystrophy.

Desmin mutations are a rare cause of DCM but are significant for an association with arrhythmias alongside HF. A founder mutation in the desmin single-head domain has been reported to cause a predominantly right ventricular cardiomyopathy with conduction disease. Desmin is an intermediate filament protein, with microfilaments and microtubules, maintains the cytoskeletal infrastructure and subcellular spatial organization. In addition to DCM, desmin mutations can cause skeletal muscle disease, including myofibrillar myopathy and scapuloperoneal syndrome.

Along with structural proteins mediating force transmission, several proteins involved in mechanosensing and modulation of sarcomeric function have been linked to DCM. Cypher/ZASP (LDB3), α-actinin (ACTN2), and muscle LIM protein are found at the cardiac Z disk at the lateral borders of the sarcomere, which acts as a node for mechanosensing and mechanotransduction. All have been proposed to cause DCM, although robust support from linkage is lacking.

**Nuclear Proteins and Transcription Factors**

The laminopathies are a variable group of disorders caused by mutations in the lamin A/C gene (LMNA), which encodes the nuclear envelope proteins lamin A and lamin C by variable splicing. Mutations in lamin A/C are associated with a huge range of phenotypes, including DCM, Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy, lipodystrophy, Hutchinson-Gilford progeria syndrome, Malouf syndrome, Charcot-Marie tooth disease, and restrictive cardiomyopathy. Cardiac involvement is common.

DCM caused by LMNA mutations is clinically distinctive because it is associated with progressive conduction disease, initially atrophicventricular block, and high risk of SCD. Conduction abnormalities typically precede the development of DCM, which may be isolated or involve associated skeletal muscle disease. Other rare cardiac phenotypes also have been reported, including early atrial fibrillation, LVNC, RCM, and HCM. The risk of ventricular arrhythmia and SCD in LMNA DCM is high, with 46% of reported deaths occurring suddenly. Nonmissense mutations (insertion–deletion, truncating or mutations affecting splicing) are an independent risk factor for SCD. This has justified the early use of implantable cardiac defibrillators (ICDs), subsequently validated by high appropriate shock rates.

Additional nuclear proteins proposed to underlie DCM, although without robust linkage support, include thymopoietin (TMPO) and CARP (ANKRD1). TMPO is a nuclear membrane and nucleoplasmic protein that associates with lamin A/C, whereas CARP is a transcriptional cofactor that translocates to the nucleus when triggered by mechanical stress and is upregulated in both hypertrophy and cardiac failure. Screening of patients with familial or idiopathic DCM has revealed a number of missense heterozygous mutations, but a number of reported variants subsequently have been found at low levels in the normal population.

**Genotype-Phenotype Correlation**

So far, characterization of the genotype–phenotype relationship in genetic DCM has been limited. This is attributable primarily to the large number of causative genes, each with small numbers of probands. Additionally, almost all existing cohorts are small and to some extent biased by inclusion of probands with penetrant and more severe phenotypes. Currently, clinical use of genetic data in DCM is used primarily to guide family screening (cascade genetic testing). A clear exception to this is the identification of mutations in LMNA and DES, which are both associated with malignant arrhythmias, and justifies early use of primary prevention ICD therapy. Beyond family screening, genotype may play a future role in directing pharmacological therapy—for example, calcium-sensitizing agents in patients with sarcomeric mutations—but the efficacy of this approach remains to be demonstrated.

**Hypertrophic Cardiomyopathy**

HCM is the most common inherited cardiac disease, with a prevalence of approximately 1 in 500, and it forms a paradigm for genetics in cardiomyopathy. HCM is characterized by inappropriate myocardial hypertrophy, which develops in the absence of pressure overload (eg, hypertension, aortic stenosis) or infiltration (eg, amyloidosis). The hypertrophy in HCM classically affects the interventricular septum, causing left ventricular outflow tract obstruction, but may be apical, segmental, or concentric. The histological disease features are interstitial fibrosis, myocyte enlargement, and disarray.

The risk of SCD in HCM is rightly recognized, but the incidence and mortality from disease progression to HF syndrome are sometimes underappreciated. Up to 20% of patients with HCM develop HF at a median age of 48±19 years, and rates of HF are likely to increase as mortality from SCD reduces with ICD implantation. Three HF subtypes are clinically described. First, 30% of the HCM patients with HF have development of progressive left ventricular dilatation, thinning, and systolic dysfunction, described as “burnt-out” HCM. Another 20% have development of left ventricular systolic dysfunction attributable to pressure overload by left ventricular outflow tract obstruction. Finally, up to 50% show evidence of diastolic HF, with a normal or supranormal ejection fraction but impaired ventricular relaxation, elevated end-diastolic pressure, left atrial enlargement, and atrial fibrillation.

HCM is primarily a disease of the sarcomere, with mutations in 8 genes encoding contractile or regulatory proteins detected in approximately 60% of clinical cohorts. At a cellular level, HCM mutations lead to increased myofilament sensitivity and affinity to calcium and increased actin-activated ATPase activity (Figure 2). For a given force generation, HCM mutations have higher energy consumption (“tension cost”), with consequent energetic inefficiency.

Like DCM and AC, inheritance is autosomal dominant, with locus and allelic heterogeneity, and there is usually a silent compensatory period before emergence of a variable phenotype. The most common HCM genes—β-myosin heavy
chain (MYH7) and myosin-binding protein C (MYBPC3)—together account for approximately 50% of disease. Other key genes are shown in Table 2. The remaining sarcomeric genes are cardiac troponin T (TNNT2), cardiac troponin I (TNNI3), α-tropomyosin (TPM1), cardiac actin (ACTC1), essential myosin light chain 3 (MYL3), and regulatory myosin light chain (MYL2). In 40% of HCM patients, no causative mutation can be identified in the known disease genes. This may imply that further genes remain to be defined, but more likely, this is consistent with non mendelian inheritance or nongenetic factors.

The model of HCM as a monogenic disease following mendelian patterns of inheritance is increasingly recognized as an oversimplification. Both compound heterozygosity and oligogenic disease have been identified in HCM, although in a small minority, with >1 sarcomeric mutation identified in approximately 2.5% to 5%. In general, there is a gene-dose effect, with ≥2 mutations conferring a more severe phenotype. Such patients are younger, with more severe hypertrophy and higher rates of myectomy and ICD insertion.

Beyond pathogenic mutations, genetic, epigenetic, and environmental modifiers of the HCM phenotype are important but not yet well understood. These factors underlie the great phenotypic variability, in both the pattern of hypertrophy and the clinical course, in patients with the same genotype. For example, unrelated gene polymorphisms (eg, in the ACE gene) have been demonstrated to contribute a small proportion of the variability in hypertrophy in HCM. Although the precise mechanisms are poorly defined, sex is a disease modifier. Presentation with SCD during competitive sports is the precise mechanisms are poorly defined, sex is a disease modifier. Presentation with SCD during competitive sports is consistent with non mendelian inheritance or nongenetic factors.

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Sarcomeric Genes

Pathogenic mutations in proteins of the cardiac sarcomere have successively emerged since β-myosin heavy chain (MYH7) was identified as the first HCM gene in 1990. This followed a 1961 report of a large kindred in the rural Quebec town of Coaticook with features of unexplained myocardial hypertrophy and sudden death. Intensive phenotyping followed up by linkage, fine mapping, candidate sequencing, and avoidance of near disaster (attributable to a case of nonpaternity in the pedigree) led to the identification of MYH7 R403Q on chromosome 14.

Approximately 200 mutations in MYH7 have since been described, almost all missense, leading to gain-of-function effects with subsequent energetic inefficiency. Mutations in MYH7 account for approximately 20% of HCM, and although many mutations are private, some genotype-phenotype correlations between discrete mutations and outcome have become possible. In general, MYH7 mutations are associated with classic, relatively early-onset disease with marked hypertrophy. The MYH7 phenotype is not restricted to HCM, and mutations also cause DCM, LVNC, and skeletal myopathies (Laing distal myopathy, myosin storage myopathy, scapuloperoneal myopathy).

Mutations in myosin-binding protein C (MYBPC3) were first identified in 2 families with HCM in 1995 and have since been shown to be the most frequent cause of HCM. The function of MYBPC3 in the sarcomere remains incompletely defined, with roles in stabilization and control of myosin-mediated contraction. Unusually, the majority of MYBPC3 mutations are nonsense or frameshift, leading to truncated protein (and most probably haploinsufficiency), in contrast to the poise peptides produced by missense mutations that characterize other HCM genes. Cohort analysis indicates that mutations in MYBPC3 often have lower penetrance and later-onset disease; this leads to better overall survival, but once the phenotype is manifest, the risk profile appears similar. Mutations in the thin-filament troponin complex proteins cardiac troponin T (TNNT2) and troponin I (TNNI3) demonstrate significant phenotypic heterogeneity and can give rise to HCM, DCM, RC, or LVNC. Mutations in troponin T sometimes show relatively mild hypertrophy but disproportionately high risk of SCD. Functionally, troponin mutations causing HCM and DCM have opposing effects on the calcium-binding affinity of the thin filament, being increased by HCM and decreased by DCM (Figure 2).

HCM mutations in 4 other sarcomeric genes—TPM1, ACTC1, MYL2, MYL3—are well established, with all being rare. Like many other sarcomeric proteins, different mutations in α-tropomyosin (TPM1) cause either DCM or HCM phenotypes. Almost all HCM mutations cluster at the N-terminal domain or the troponin T binding site and increase calcium sensitivity of the thin filament. Mutations in TPM1 have been suggested to be associated with the progression of the HCM phenotype to DCM, although the reported numbers are small. Nonsarcomeric Genes and HCM Phenocopies

The finding that 40% of families with HCM test negative for myofilament mutations has triggered a hunt for further loci “beyond the sarcomere.” Candidate gene screening has led to reports of mutations in several Z-disk and calcium-handling proteins, for example, muscle LIM protein (CSRP3), telethonin (TCAP), ANKRDL, and myozin 2 (MYOZ2). However, other than for CSRP3, genome-wide linkage supporting pathogenicity has

<table>
<thead>
<tr>
<th>Errors</th>
<th>Official Symbol</th>
</tr>
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<tbody>
<tr>
<td>MYH7</td>
<td></td>
</tr>
<tr>
<td>MYBPC3</td>
<td></td>
</tr>
<tr>
<td>TNNT2</td>
<td></td>
</tr>
<tr>
<td>TNNI3</td>
<td></td>
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<tr>
<td>TPM1</td>
<td></td>
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<tr>
<td>MYL2</td>
<td></td>
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<tr>
<td>MYL3</td>
<td></td>
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<tr>
<td>ACTC1</td>
<td></td>
</tr>
<tr>
<td>CSRP3</td>
<td></td>
</tr>
<tr>
<td>PRKAG2</td>
<td></td>
</tr>
<tr>
<td>LAMP2</td>
<td></td>
</tr>
<tr>
<td>GLA</td>
<td></td>
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<tr>
<td>FHL1</td>
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</tbody>
</table>

Table 2. Key Disease Genes in Hypertrophic Cardiomyopathy

The following table shows the key disease genes in hypertrophic cardiomyopathy, including their official symbols and the number of mutations each gene contributes to HCM.

<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYH7</td>
<td></td>
<td>β-myosin heavy chain</td>
</tr>
<tr>
<td>MYBPC3</td>
<td></td>
<td>myosin-binding protein C</td>
</tr>
<tr>
<td>TNNT2</td>
<td></td>
<td>cardiac troponin T</td>
</tr>
<tr>
<td>TNNI3</td>
<td></td>
<td>cardiac troponin I</td>
</tr>
<tr>
<td>TPM1</td>
<td></td>
<td>α-tropomyosin</td>
</tr>
<tr>
<td>MYL2</td>
<td></td>
<td>light chain 2, regulatory, cardiac, slow</td>
</tr>
<tr>
<td>MYL3</td>
<td></td>
<td>light chain 3, alkal; ventricular, skeletal, slow</td>
</tr>
<tr>
<td>ACTC1</td>
<td></td>
<td>cardiac muscle 1</td>
</tr>
<tr>
<td>CSRP3</td>
<td></td>
<td>Cysteine and glycine-rich protein 3</td>
</tr>
<tr>
<td>PRKAG2</td>
<td></td>
<td>Protein kinase, AMP-activated, γ 2 noncatalytic subunit</td>
</tr>
<tr>
<td>LAMP2</td>
<td></td>
<td>Lyssosomal-associated membrane protein 2</td>
</tr>
<tr>
<td>GLA</td>
<td></td>
<td>Galactosidase, α</td>
</tr>
<tr>
<td>FHL1</td>
<td></td>
<td>Four-and-a-half LIM domains 1</td>
</tr>
</tbody>
</table>
### Table 3. Inborn Errors of Metabolism Associated With Cardiomyopathy

<table>
<thead>
<tr>
<th>Infiltrative disorders</th>
<th>Glycogen storage disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glycogen storage disease type II (Pompe disease: acid maltase deficiency)</td>
</tr>
<tr>
<td></td>
<td>Mucopolysaccharide degradation disorders</td>
</tr>
<tr>
<td></td>
<td>Mucopolysaccharidosis type I (Hurler syndrome)</td>
</tr>
<tr>
<td></td>
<td>Others</td>
</tr>
<tr>
<td></td>
<td>Fabry disease</td>
</tr>
<tr>
<td></td>
<td>Gaucher disease</td>
</tr>
<tr>
<td>Disorders with cardiotropic intermediaries</td>
<td>Proionic acidemia</td>
</tr>
<tr>
<td></td>
<td>Methylmalonic academia</td>
</tr>
<tr>
<td>Disorders of impaired energy metabolism</td>
<td>Disorder of pyruvate metabolism</td>
</tr>
<tr>
<td></td>
<td>Pyruvate dehydrogenase complex deficiency (Leigh disease)</td>
</tr>
<tr>
<td></td>
<td>Disorders of oxidative phosphorylation</td>
</tr>
<tr>
<td></td>
<td>Combined respiratory chain deficiencies</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial IRNA mutations (MELAS, MERRF, others)</td>
</tr>
<tr>
<td></td>
<td>Mitochondrial DNA deletions/duplications (Kearns-Sayre, others)</td>
</tr>
<tr>
<td></td>
<td>Barth syndrome (3-methylglutaconic aciduria type II)</td>
</tr>
<tr>
<td></td>
<td>Sengers syndrome</td>
</tr>
<tr>
<td></td>
<td>Disorders of fatty acid metabolism</td>
</tr>
<tr>
<td></td>
<td>Primary or systemic carnitine deficiency (carnitine uptake deficiency)</td>
</tr>
<tr>
<td></td>
<td>Muscle carnitine deficiency</td>
</tr>
<tr>
<td></td>
<td>Very-long-chain acyl-CoA dehydrogenase deficiency</td>
</tr>
<tr>
<td></td>
<td>Long-chain acyl-CoA dehydrogenase deficiency</td>
</tr>
<tr>
<td></td>
<td>Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency</td>
</tr>
</tbody>
</table>

**MELAS** indicates mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes; and **MERRF**, myoclonic epilepsy with ragged red fibers. Adapted from Schwartz et al. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

not been demonstrated, and many of the reported variants are now known to be in the normal population. It is, in fact, likely that many HCM cases with no sarcomeric mutation do not have a single underlying causal allele but rather reflect non mendelian genetic susceptibility or nongenetic factors.

Sarcomeric HCM is also mimicked by several phenocopies that do have a nonsarcomeric basis. Accurate identification is important because disease management, risk stratification, and inheritance patterns differ. For example, mutations in the γ2 subunit of AMP kinase (PRKAG2), which functions as an intrinsic cellular energy sensor, cause a dominant, penetrant, familial HCM phenotype characterized by glycogen accumulation and a lack of myocyte disarray.

Characteristically, mutations in PRKAG2 also cause Wolff-Parkinson-White syndrome, with ventricular pre-excitation on ECG and propensity to bradycardia and progressive conduction disease.

Danon disease is an X-linked dominant disease with features of HCM, skeletal myopathy, and intellectual impairment. It is caused by mutations in **LAMP2** (lyosome-associated membrane protein type 2), which is a lysosomal membrane receptor mediating autophagy. Danon disease is also associated with ventricular pre-excitation, arrhythmia, and massive hypertrophy with progression to DCM, and it has a more severe prognosis than HCM, with transplantation often required early in adulthood as the only definitive therapy. Unexpectedly, cardiac disease also can be severe in female patients, although without the cognitive impairment seen in male patients.

Mutations in **GLA** cause Fabry disease, a multisystem X-linked lysosomal storage disorder associated with cardiomyopathy, arrhythmia, renal impairment, acroparesthesia, cutaneous manifestations (angiokeratoma, telangiectasia), hypohidrosis, corneal opacities, and cerebrovascular disease. Fabry disease develops as a result of deficiency or absence of the lysosomal hydrolase α-galactosidase A, with subsequent accumulation of glycosphingolipid. Although classically affecting males, affected females are increasingly recognized. Multiple mutations have been reported in all 7 exons of the gene, with mutations usually private. When systematically screened, GLA mutations were identified in 3 of 90 (3%) HCM families. Importantly, cardiomyopathy may be the only manifestation of the disease, which is treatable by enzyme replacement therapy.

Mutations in four-and-a-half LIM domains (FHL1), which cause an X-linked skeletal myopathy, have recently been identified as a cause of isolated HCM in males without obvious skeletal muscle involvement. FHL proteins shuttle between the nucleus and the cytoskeleton and are proposed to contribute to sarcomere synthesis and stress sensing. Either HCM or DCM has been reported alongside reducing body myopathy, scapuloperoneal myopathy, X-linked myopathy with postural muscle atrophy, rigid spine syndrome, or Emery-Dreifuss muscular dystrophy.

#### Mitochondrial Disease

Cardiomyopathy commonly occurs as a component of mitochondrial genetic disease. The mitochondrial phenotype is heterogeneous and usually affects multiple organ systems, most commonly those with high ATP requirements such as the heart, skeletal muscle, and the nervous system. Disease manifestation occurs early, typically in infancy or even in utero, without the compensation seen in sarcomeric cardiomyopathy. Mitochondrial cardiomyopathy does not fit easily into an HCM/DCM paradigm, with increased wall thickness often occurring along with or progressing to ventricular dilatation, but an HCM-like phenotype is more commonly described. Several multisystem mitochondrial syndromes are described (eg, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes [MELAS], myoclonic epilepsy with ragged red fibers [MERRF], Kearns-Sayre syndrome, Leigh disease), and cardiomyopathy may be a feature, along with mitochondrial features such as skeletal myopathy, encephalopathy, epilepsy, ophthalmoplegia, ataxia, and deafness.

Mitochondrial dysfunction may be caused by mutations in either the mitochondrial or, more commonly, the nuclear genome. Mitochondrial DNA mutations are characterized by heteroplasmhy, when wild-type mtDNA and mutated mtDNA are found together within the same cell, requiring a threshold level of mutation for a disease phenotype to manifest. Inheritance is matrilineal, and demonstration of pathogenicity is often based on phylogenetic conservation and recurrence in
other patients with a similar phenotype. Nuclear-encoded mitochondrial disorders show marked genetic heterogeneity and may be autosomal (typically recessive) or X-linked. All mutations are rare, and genotype-phenotype correlation is limited.

The frequency of cardiomyopathy in patients with mitochondrial disease is variable, ranging from 17% to 40%, with HCM being the most commonly described phenotype. Cardiomyopathy is associated with adverse outcome in at least 1 series. In an adult population with confirmed respiratory chain disease, cardiomyopathy was present in 25% (HCM, 19%; RCM, 3%; LVNC, 3%). Although none had DCM initially, progression to impaired systolic function was seen during the follow-up period.

Mutations in the nuclear protein SCO2 are the most commonly described cause of mitochondrial cardiomyopathy in infants. SCO2 encodes an assembly factor required for the assembly of cytochrome c oxidase, complex IV of the respiratory chain. The disease phenotype is HCM combined with encephalopathy and muscular hypotonia, presenting in the neonatal period. In a cohort of 180 children with cytochrome c oxidase deficiency presenting with cardiomyopathy or encephalopathy, 9 had the p.E140K missense mutation.

Other nuclear proteins causing a mitochondrial cardiomyopathy include assembly proteins for mitochondrial respiratory chain components (eg, NDUFS2, NDUFV2, SDHA, SCO2, COX15, TMEM70), proteins with roles in mtDNA translation (MRPS22), ATP synthesis (SLC25A3), and phospholipid remodeling (TAZ). Mutations in TMEM70, for example, cause mitochondrial complex V deficiency and a generalized reduction in the ATP synthase complex associated with HCM, hypotonia, lactic acidosis, and 3-methylaciduria. TMEM70 mutations also cause X-linked endocardial fibroelastosis, X-linked fatal infantile DCM, and familial isolated LVNC. Ventricular arrhythmias are a prominent feature, with a lower threshold for ICD implantation advised.

Friedreich ataxia is an autosomal-recessive neurodegenerative disease, usually manifesting before adolescence, with features of ataxia, limb weakness, cardiomyopathy, and diabetes mellitus. Most patients carry homozygous guanine-adenine-adenine repeats in the frataxin gene (FXN), leading to deficiency of frataxin and subsequent mitochondrial iron accumulation, oxidative stress, and dysfunction. Although the progression of cardiomyopathy with Friedreich ataxia is not well characterized, the majority initially develop a concentric hypertrophic cardiomyopathy with progression to contractile dysfunction and HF, which remains the most common cause of death.

In the 16.6-kb mitochondrial genome, >250 pathogenic mtDNA mutations have been reported, with many causing multisystem diseases with cardiac dysfunction or cardiomyopathy. The m.3243A>G (MTTL1) mutation was first identified in patients with MELAS and causes encephalomyopathy, short stature, stroke-like episodes, seizures, lactic acidosis, and hemiplegia. Cardiomyopathy is found in 40%, usually symmetrical hypertrophy with hypokinesia. The phenotype is variable, and the m.3243A>G mutation can cause an isolated cardiomyopathy. These patients have abnormal cardiac energetics as assessed by magnetic resonance spectroscopy. Patients with MERRF, caused by m.8344A>G (MTTK) in 80% to 90% of cases, may also develop a HCM or DCM phenotype.

Fatal infantile cardiomyopathy with both hypertrophy and dilatation was first described in association with m.4317A>G mutation in the mitochondrial tRNA-Ile gene (MTT1). Further mutations in MTT1 have been associated with both HCM and DCM phenotypes. Four children presenting with HCM associated with congestive cardiac failure in infancy were found to carry a m.8528T>C mutation, resulting in alterations in ATPase 6 and ATPase 8. One child had a tentative diagnosis of coexistent Wolff-Parkinson-White. HCM phenotypes also are reported for MTTG.

Other

Metabolic Disease

Numerous inborn errors of metabolism cause a cardiomyopathy phenotype, usually presenting in infants or children (Table 3). These can be broadly divided into those disorders causing infiltration or cardiac storage disease, disorders of energy metabolism, and those that produce cardiotoxic intermediates. Infantile HCM is often attributable to glyocogen storage disease, for example, Pompe disease, in which mutations in the α-galactosidase gene lead to glyocogen deposition, resulting in cardiomyopathy, muscle weakness, and respiratory failure. Disorders of fatty acid metabolism (eg, very-long-chain acyl-CoA dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency) also cause HCM phenotype, with hypertrophy responsive to treatment with medium-chain triglycerides. Disorders of mucopolysaccharide degradation can cause HCM-type or DCM-type phenotype.

Synrdromic Disease

HCM is rarely a feature of multisystem genetic disease, but it is well-described in association with Noonan syndrome, cardio-facio-cutaneous syndrome, LEOPARD syndrome, neurofibromatosis, Costello syndrome, and Beckwith-Wiedemann syndrome. Cardiomyopathy has been reported as a feature of multiple other congenital syndromes but is generally less well characterized and established. In addition to mitochondrial and metabolic disorders, a skeletal muscle phenotype along with HCM is seen with some systemic gene mutations, for example, in four-and-a-half LIM domains (FHL1).

Arrhythmogenic Cardiomyopathy

AC is characterized by progressive fibrofatty replacement of the ventricular myocardium, leading to arrhythmia, HF, and SCD.

<table>
<thead>
<tr>
<th>Table 4. Key Disease Genes in Arrhythmogenic Cardiomyopathy</th>
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<tbody>
<tr>
<td><strong>Genes</strong></td>
</tr>
<tr>
<td>Desmosomal</td>
</tr>
<tr>
<td>Plakophilin 2</td>
</tr>
<tr>
<td>Desmocollin 2</td>
</tr>
<tr>
<td>Desmoglein 2</td>
</tr>
<tr>
<td>Desmplakin</td>
</tr>
<tr>
<td>Junction plakoglobin</td>
</tr>
<tr>
<td>Extradesmosomal</td>
</tr>
<tr>
<td>Transmembrane protein 43</td>
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</table>
It is classically described as a disease of the right ventricle—arrhythmogenic right ventricular cardiomyopathy—but left ventricular involvement is increasingly recognized. Left ventricular AC is distinguished from DCM by its patchy involvement and a disproportionate propensity to arrhythmia for a given degree of systolic dysfunction. Because there may be right, left, or biventricular involvement, the phenotype has been more accurately renamed AC. Characteristic histological findings are patchy fibrosis, inflammation, myocyte death, wall thinning, and aneurysm formation.

AC classically presents in a proband with malignant arrhythmia, which may cause SCD as the first manifestation of disease in adolescence or young adulthood. A “concealed” phase, with arrhythmic features, typically precedes overt cardiomyopathy. Between 10% and 20% of patients will develop HF, with right or left (or both) ventricular systolic dysfunction, which may rarely be the presenting feature of the disease.

AC is a familial disease in >50% of cases, with an estimated prevalence of 1 in 1000 to 1 in 5000. Like DCM and HCM, AC is heterogeneous in phenotype, genotype, and allele. It is classically described as autosomal-dominantly inherited, but this is likely to be an oversimplification, with many patients carrying mutations in >1 disease gene (double or compound heterozygosity). Penetration, which is age dependent as in other cardiomyopathies, is low; it is uncommon to find large extended families, and the yield of clinically affected cases through family cascade screening is often low. Two autosomal-recessive forms also have been described—the cardiocutaneous disorders Naxos disease and Carvajal syndrome—that comprise AC, palmoplantar keratoderma, and woolly hair.

Genetic characterization of AC has been slow compared with HCM for several reasons. Definitive identification of the disease phenotype is more difficult because penetrance is low; the clinical features, ECG changes, imaging appearances, and biopsy results may be subtle or nonspecific, especially in relatives of probands. Diagnosis now relies on a set of task force criteria that integrate abnormalities to try to define a clear population with the AC phenotype. Evaluation of genetic results in AC families is also problematic because a mutation currently can be identified in only 50% of patients and the lack of large families makes cosegregation difficult. Second, there is a larger degree of polymorphism in the AC disease genes, with “mutations” identified in up to 16% of controls compared with strict conservation in ACTC. Finally, it is increasingly clear that AC is not a straightforward monogenic disease, with evidence of multiple gene hits or susceptibility loci required for a clear disease phenotype.

Nevertheless, over the past 15 years, AC has emerged genetically as a “disease of the desmosome,” with pathogenic mutations identified in 5 genes encoding the desmosomal complex (Table 4). Desmosomes are symmetrical linkage complexes that span the intercellular membrane and fulfill strengthening and signaling roles, contributing to the intercalated disk. They consist of the desmosomal cadherins (desmocollin 2 [DSC2] and desmoglein 2 [DSG2]), the armadillo proteins (including junctional plakoglobin [JUP] and plakophilin 2 [PKP2]), and the plakins (desmoplakin [DSP]).

DSC2 and DSC2 form the transmembrane component of the desmosome and are anchored within the cell by plakoglobin and plakophilin 2, which bind the N-terminal domain of desmoplakin. Desmoplakin is, in turn, linked to desmin intermediate filaments at its C-terminal. In addition to structural roles, the desmosome is linked to the Wnt/b-catenin signaling pathway by plakophilin 2, which translocates to the nucleus to modify gene expression. Pathogenic mutations in AC cause mislocalization and reduction in desmosome number, remodeling of the intercalated disk with associated abnormal formation of gap junctions, and misincorporation of desmoplakin/plakoglobin.

**Desmosomal Genes**

The first AC locus identified was plakoglobin (JUP), mapped initially by linkage analysis of autosomal-recessive families with Naxos disease and named after the Greek island where the highly penetrant cardiocutaneous syndrome of AC, palmoplantar keratoderma, and woolly hair are prevalent. These clear cutaneous features facilitated identification of a homozygous JUP mutation, which was shown to cosegregate with the phenotype. Dominant mutations in JUP have since been described in familial AC without cutaneous manifestations and are associated with reduced localization of plakoglobin, desmoplakin, and connexin-43 at the cardiomyocyte intercalated disk. Across AC, reduced plakoglobin incorporation into the intercalated disk has value as a unifying diagnostic feature of the disease.

Soon after the identification of the JUP mutation in Naxos syndrome, a homozygous mutation in the desmoplakin gene DSP was reported in Carvajal syndrome, a similar autosomal-recessive cardiocutaneous syndrome with left ventricular AC. DSP was the first desmosomal gene implicated in autosomal-dominant AC, with downstream effects on plakoglobin and desmin binding and impaired cellular localization. DSP mutations also are associated with skin fragility disorders without cardiac involvement, for example, lethal acantholytic epidermolysis bullosa.

Candidate gene studies have identified mutations in PKP2 in 9% to 43% across series, making PKP2 the most common genetic cause of AC. Disease penetrance in PKP2 AC has been studied, with 49% of PKP2 mutation carriers demonstrating task force–defined disease but wide variation between families and with generally higher penetrance in males. The pathogenicity of some reported PKP2 missense mutations has been cast into doubt by the finding that several “mutations” exist at low frequency in control populations. Additionally, 9 of 38 AC probands carried >1 variant in PKP2 (compound heterozygosity), and a second variant was found in another desmosomal gene in 16 of 38 (42%; double heterozygosity). Taken together, these findings imply that a “multiple hit” of >1 pathogenic variant may be required for the development of a full (ie, task force criteria) disease phenotype. The knock-on results for family cascade screening are significant; even if a family member does not carry a presumed pathogenic PKP2 variant identified in the proband, that family member still may carry another coexisting mutation, which may be sufficient to cause disease.

The desmosomal cadherins DSG2 and DSC2 span the intercellular membrane component of the desmosome, and mutations in both genes are established causes of AC.
Although the pathogenicity of truncation alleles is generally accepted, the effects of some DSG2 missense mutations are now doubtful, given the finding that a number of previously reported missense mutations are in fact variants found in control population.119 Although not necessarily pathogenic, they may lead to disease susceptibility in the presence of other mutations or environmental triggers.

**Extradesmosomal Genes**

Several extradesmosomal genes are reported to cause AC, including TMEM43 and TGFβ3.120 Further candidate genes for AC also have been proposed, including TTN and PLN, although these are not supported by linkage, and there is blurring of phenotypic boundaries between classic arrhythmogenic right ventricular cardiomyopathy, left-dominant AC, and DCM with arrhythmia.121,122 Mutations in LMNA recently have been reported to mimic the AC phenotype.123

The TMEM43 locus was first mapped by linkage in a genetically isolated island population in Newfoundland. The TMEM43 S358L missense mutation was subsequently identified as occurring by founder effect in multiple affected individuals on the island, where there is amplification of a mutation in a population derived from a small number of common founders. Survival was significantly worse in males.124 Further instances of mutation in TMEM43 now have been identified outside this population, with pathogenicity supported by a common founder haplotype, albeit with an absence of functional analysis.125 TMEM43 encodes a nuclear envelope protein, LUMA, that interacts with both lamins and emerins. The pathogenetic mechanism underlying AC is unclear.

**Genotype Phenotype Correlation in AC**

Understanding the genotype-phenotype relationship in AC is challenging. Phenotypically, AC is subtle and heterogeneous, and its diagnosis even in family members is difficult. Within families, only one third show anatomic concordance, and the majority have disparate patterns of disease. This is compounded by the complex genetic background, with a significant proportion of patients appearing to carry >1 pathogenic variant.117,118,126 As-yet undefined modifier loci, epigenetic phenomena, or environmental influences/triggers must underlie other dramatic differences seen in the phenotype, for example, the sex-related difference in survival in carriers of TMEM43 mutations. Mutations in DSP are said to be associated with left-dominant disease.127

In AC, clear identification of causal pathogenic mutations is now key. Functional data are required to support candidate genetic variants identified in screening, ideally through effects on a final common cellular pathway. Current difficulties with evaluation of candidate mutations affect family cascade screening and genetic counseling. A genetics database for AC variants has been established (http://www.arvcdatabase.info/).

**Left Ventricular Noncompaction Cardiomyopathy**

LVNC is an uncommon but increasingly recognized cardiomyopathy, either sporadic or familial, in which deep trabeculation of the myocardium is associated with progressive contractile dysfunction. The LVNC phenotype overlaps extensively with HCM and DCM and frequently occurs alongside structural heart disease, for example, Ebstein anomaly, pulmonary atresia, atrial/ventricular septal defects, and patent ductus arteriosus. It is also a feature of multisystem disorders involving the heart, including Barth and Noonan syndromes.

There is ongoing debate regarding whether LVNC is a distinct cardiomyopathy or phenotypic variant or overlap of HCM and DCM. Its diagnostic criteria, disease origin, and genetic basis are also disputed. The pathognomonic feature of LVNC is a noncompacted, 2-layer myocardium. Persisting noncompaction from the embryological developing heart has been proposed to underlie the pathogenesis, although a normal myocardial appearance before the development of LVNC has been reported. Although diagnostic criteria based on echocardiographic appearance define the disease phenotype,128,129 there is suboptimal intertest correlation, and the false-positive rate in the control population is high.130 Furthermore, diagnostic sensitivity for LVNC is significantly higher with cardiac magnetic resonance imaging than with echocardiography.

LVNC manifests clinically with HF, thromboembolism, arrhythmia, or SCD. Systolic dysfunction and diastolic dysfunction are common, with HF reported at presentation in 53%.131 The precise mechanism behind the development of HF is unclear, but microvascular ischemia and fibrosis are both likely contributory factors. An undulating progression with intermittent periods of relative recovery is common. Presentation may occur in utero, in infancy, in childhood, or in adulthood, and this varies extensively even within families.132 The disease-related outcomes are highly variable across series, with 3% to 35% mortality reported over 44 to 46 months of follow-up.131,133

Isolated LVNC was first recognized as a familial disease in 1990, with family involvement now recognized in 25%. When an LVNC phenotype is seen consistently in family members (as opposed to occurring in individuals in a family with otherwise typical HCM or DCM), mutations in sarcomeric, cytoskeletal, and nuclear membrane genes have been found. Inheritance may be autosomal dominant, recessive, or X-linked, and penetrance is variable. Even in defined cohorts with LVNC, the yield of mutations from screening known disease genes remains low.

**Sarcomeric Genes**

In addition to DCM, HCM, and RCM, mutations in the cardiac sarcomere genes cause LVNC. The MYH7 R281T mutation was reported in a 24-member German family, some with structural heart disease, for example, atrial septal defect and Ebstein anomaly. No family members displayed a HCM phenotype or pure DCM phenotype.134 However, subsequent LVNC sarcomeric mutations (eg, in MYH7, ACTC, TNNT2, MYBPC3, and TPM1) include variants that otherwise cause either HCM or DCM.135,136 For example, the ACTC E101K mutation within the same family caused either LVNC or apical HCM phenotype.137 At present, there are no sarcomeric mutations known with a specific reproducible association with LVNC alone (ie, not also seen with either HCM or DCM).

**Nonsarcomeric Genes**

TAZ was the first gene implicated in LVNC, in patients with Barth syndrome, an X-linked disease causing DCM or LVNC,
skeletal myopathy, cyclic neutropenia, and growth restriction. Death results from either opportunistic infection or HF.\textsuperscript{137} TAZ was subsequently implicated in X-linked LVNC in a 4-generation family in Utah without many of the systemic features of Barth syndrome and in endocardial fibroelastosis.\textsuperscript{138} TAZ encodes a family of proteins called the tafazzins, which have an acyltransferase function necessary for remodeling of mitochondrial cardiolipin, in turn required for normal mitochondrial morphology and OXPHOS.\textsuperscript{15}

LVNC phenotypes also have been reported along with congenital heart defects, primarily ventricular septal defect, caused by mutations in \(\alpha\)-dystrobrevin (\(DTNA\)).\textsuperscript{139} \(\alpha\)-Dystrobrevin contributes to the dystrophin-associated glycoprotein complex, which is required for normal linkage of the extracellular matrix to the dystrophin-based cytoskeleton. Mutations in \(\alpha\)-dystrobrevin also cause a muscular dystrophy phenotype. In addition to DCM, mutations in \(LDB3\) (Cypher/ZASP) are reported in LVNC.\textsuperscript{50}

There are reports of sporadic or familial disease associated with mutations in several other genes, including \(LMNA\).\textsuperscript{44} \(MIB1\),\textsuperscript{140} mitochondrial genes, and chromosomal imbalance/deletions. Variants in \(SCN5a\) have been proposed to modify arrhythmia risk.

**LVNC Conclusions**

LVNC is the most recent cardiomyopathy phenotype to be described, and its position as a distinct genetic disease remains unclear. Defining a clear disease population is key to probing the underlying genetics and clinical course. The increased diagnostic sensitivity of magnetic resonance imaging has clarified the phenotype, with some apical HCM now reclassified as LVNC, but the finding of subclinical LVNC in the control population requires longitudinal follow-up to ascertain whether this is of long-term significance. Contractile dysfunction during a critical stage of development has been proposed as a unifying mechanism, which might explain the extensive overlap with HCM and DCM genetics.\textsuperscript{136}

**Restrictive Cardiomyopathy**

RCM is a rare cardiomyopathy characterized by impaired ventricular filling and diastolic function with relatively normal ventricular wall thickness and systolic function. The etiology of RCM is broad, including genetic disease (sporadic or familial), infiltration (eg, amyloidosis, sarcoidosis), connective tissue disease (eg, systemic sclerosis), glycosogen storage disease, drugs, and radiation. A proportion remains idiopathic, which is likely to be genetic, with no clear causative mutation known. Restrictive physiology is a feature of several other cardiomyopathies, particularly HCM, and there is clearly overlap in these 2 phenotypes. Quite commonly, individuals with classic RCM features are identified in families in which most affected members have typical HCM.

The prognosis of RCM, particularly in children, is poor, with worse outcomes than either HCM or DCM and with 5-year transplantation-free survival of only 22%.\textsuperscript{141} Elevated end-diastolic left ventricular pressure leading to atrial enlargement, atrial fibrillation, and risk of thromboembolism is common. There is progression from diastolic dysfunction to refractory systolic HF, frequently necessitating heart transplantation.

RCM was first recognized to be another of the protein manifestations of sarcomeric mutations in 2003, when causal mutations in \(TNNI3\) were identified in a family with members demonstrating a mixed HCM or RCM phenotype (D190H).\textsuperscript{142} Six other RCM individuals were found to carry mutations in \(TNNI3\).\textsuperscript{143} Mutations in several sarcomeric genes have subsequently been reported in patients with RCM, but in the majority of cases, there is no convincing association between the allele reported and a specific phenotype of RCM. Nonsarcomeric RCM mutations also have been reported. In addition to DCM, mutations in the intermediate filament protein desmin (\(DES\)) can cause a RCM phenotype with conduction disease.\textsuperscript{146}

Although not a primary cardiomyopathy, genetic forms of amyloidosis can cause a heritable HF syndrome with RCM. Amyloidosis is caused by widespread deposition of insoluble protein fibrils, which are organized in an insoluble \(\beta\)-pleated sheet structure. More than 30 proteins are amyloidogenic and accumulate in the heart, skin, and kidneys.\textsuperscript{147} Primary amyloidosis is genetically heterogeneous, with mutations in the transthyretin gene (\(TTR\)) being most common. More than 100 \(TTR\) variants are reported, with variable degrees of cardiac involvement. In Afro-Caribbeans with \(TTR\) cardiac amyloidoid, the \(Val122Ile\) mutation has been most frequently identified, causing a late-onset low-penetration cardiomyopathy.\textsuperscript{148} Up to 3% to 4% of Afro-Caribbeans are heterozygous for the mutation.\textsuperscript{149}

**Conclusions**

The genetic cardiomyopathies provide a window to cardiac pathophysiology when discrete cellular pathways are disrupted. Over the past 20 years, the role of numerous proteins in triggering cardiomyopathy and hence HF has become clear. Despite the genetic complexity, direct application of genetic testing is now a mainstay in managing affected families, and scientifically and clinically useful themes are emerging that should lead to improved treatment.

First, the genetic diversity of cardiomyopathy and its protein and overlapping manifestations have highlighted the current limitations of the conventional morphological classification. This variability in expressivity and phenotype can be exploited, however, to understand modifiers of disease. In particular, NGS will lead to identification of additional genetic variants that modify the cardiomyopathy phenotype, as well as further causative mutations in families in which no genotype has been identified.

Second, despite genetic heterogeneity, homogeneity of cellular mechanisms may be exploited as a route to common therapy. For example, reduced sensitivity of the thin filament to calcium in DCM might be specifically targeted by calcium-sensitizing agents. Reversal of energy deficiency in HCM by augmentation of cardiac energetics is an attractive common target that may modify underlying disease biology.

Third, despite the challenges of private mutations and genetic heterogeneity, genetic cascade screening is a cost-effective way of identifying the family members who need clinical assessment and surveillance.\textsuperscript{150} In the cardiomyopathies as a group, genotype-phenotype correlations remain difficult to use clinically, but some findings affect practice. For example, risk of SCD in patients with mutations in \(LMNA\) and \(DES\) is...
a clear example of when ICD therapy can be justified on the basis of genotype, along with traditional risk stratification. Larger cohorts combining genotyping with clinical and cellular phenotype and longitudinal follow-up of patients with common mutations will lead to further insights.

Difficulties clearly remain. The evaluation of pathogenicity remains problematic and, in the short term, is likely to become worse as multiple rare variants emerge in cardiomyopathy genes from NGS. In the longer term, large databases with results from NGS will help evaluate the significance of rare variants in an given disease (eg, ClinVar, http://www.ncbi.nlm.nih.gov/clinvar/). The morphological classification faces challenges from overlapping patterns, and the role of LVNC in the classification of cardiomyopathies is unclear. Compound and double heterozygosity, especially in arrhythmogenic cardiomyopathy, provides challenges for genetic counseling and risk stratification.

With each step forward in genetic technology, there have been giant leaps in understanding the genetic basis of cardiomyopathy. As NGS takes off, combined with refined clinical and cellular phenotyping, there is good reason for optimism for future insights into the genetic causes of HF, cellular mechanisms, and clinical management.

Disclosures

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References


2) gene mutation associated with dilated cardiomyopathy. 

McCabe ER, Swift M. X-linked dilated cardiomyopathy: molecular genet-


Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, McKney-Bojecky SM, Manning WI, Udell JE, Maron BJ. Prevalence, clini-
cal profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. Circulation. 2006;114:216–225.


Van Driest SL, Vasile VC, Omens SR, Will ML, Tajik AJ, Gersh BJ, Ackerman MJ. Myosin binding protein C mutations and compound heterozygosity in hyper-

Ingles J, Doolan A, Chiu C, Seidman J, Seidman C, Sensarnian C. Compound and double mutations in patients with hypertrophic cardiomyopathy: impli-

Fananapazir L, Epstein ND. Genotype-phenotype correlations in hyper-

Lechin M, Quiñones MA, Omran A, Hill R, Yu QT, Rakowski H, Wigg D, Liew CC, Sole M, Roberts R. Angiotensin-I converting enzyme genotypes and left ventricular hypertrophy in patients with hypertrophic cardiomy-


Geiferster-Loaree AA, Kass S, Tanigawa G, Vosberg HP, McKenna W, Seidman CE, Seidman JG. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense muta-

Seidman CE, Seidman JG. Identifying sarcomere gene mutations in hyper-


Regitz-Zagrosek V, Erdmann J, Wellhofer E, Rabille F, Fleck E. Novel muta-
tion in the alpha-tropomyosin gene and transition from hypertrophic to hy-


Geier C, Gehmlich K, Ehler E, et al. Be-


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