Inherited Cardiomyopathies

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Inherited cardiomyopathies are a major cause of heart disease in all age groups, often with an onset in adolescence or early adult life. Not only the patients but also their families can be severely burdened by these illnesses. More than 20 years ago, the first “disease gene” for hypertrophic cardiomyopathy was identified. This finding led to the concept that hypertrophic cardiomyopathy is a disease of the sarcomere. Similar advances in the elucidation of the genetic basis of other forms of cardiomyopathy, as well as in other inherited cardiovascular diseases, soon followed.

The identification of disease genes in numerous inherited diseases has raised expectations for new forms of treatment, but experience has shown that such novel therapies rarely follow. For some inherited cardiomyopathies, however, there are realistic prospects that molecular insights will soon lead to novel treatments. This review focuses on recent findings regarding the mechanisms underlying cardiomyopathies that will inform clinical practice and guide the search for therapeutic targets.

Classification of Inherited Cardiomyopathies

The long-standing classification of inherited cardiomyopathies according to functional and morphologic features is crude yet clinically useful. Despite considerable heterogeneity within the categories of hypertrophic, dilated, restrictive, arrhythmogenic right ventricular, and other types of cardiomyopathies, these diagnostic classifications can predict major complications and delineate treatment options for each group. Finer resolution of these categories is possible with the aid of molecular genetics, which can identify clinically significant subtypes. Molecular insights, however, do not supersede the clinical classification, since different mutations within the same gene can underlie different disorders (Fig. 1). Mutations that affect adjacent amino acids in the β-myosin heavy chain, for example, cause either hypertrophic cardiomyopathy or dilated cardiomyopathy. All the inherited cardiomyopathies are genetically heterogeneous; within each category there are multiple disease genes, and many different mutations, each of which is uncommon. Nevertheless, technical advances now allow routine genetic testing of families. The degree of genetic heterogeneity varies among the cardiomyopathies and determines the extent to which a final common pathway of pathogenesis can be identified for each condition.

Hypertrophic Cardiomyopathy, a Disease of the Sarcomere

Hypertrophic cardiomyopathy is an autosomal dominant disease characterized by unexplained hypertrophy of the left ventricle (and sometimes of the right ventricle),
often with predominant involvement of the interventricular septum. Other hallmark features are myocyte disarray and fibrosis (Fig. 2). Hypertrophic cardiomyopathy was termed a “disease of the sarcomere” when the first three disease genes to be identified were found to encode components of the contractile apparatus of heart muscle. Mutations in nine genes encoding sarcomeric proteins have now been convincingly shown to cause hypertrophic cardiomyopathy. Disease-causing mutations in any one of these genes are found in up to two thirds of patients with hypertrophic cardiomyopathy. Mutations in MYH7, encoding the β-myosin heavy chain, and in MYBPC3, encoding cardiac myosin-binding protein C (cMyBP-C), are the most common, each accounting for one fourth to one third of all cases of the disease; the remaining seven genes each account for less than 1% to 5% of cases. The mutations generally cause single amino acid substitutions in proteins that become incorporated into the sarcomere. However, about half of the reported MYBPC3 mutations are truncations; these, and some MYBPC3 missense mutations, can result in haploinsufficiency, a condition in which the gene product of the wild-type allele cannot compensate for the decreased product from the mutant allele. Analyses in vitro and in mouse models of cardiomyopathy have shown increased contractility of mutant myofilaments due to altered myosin kinetics, increased thin-filament calcium sensitivity, or changes in cMyBP-C–mediated regulation. These perturbations trigger signaling pathways.
Hypertrophic cardiomyopathy

Normal myocardial tissue

Myocyte disarray
that induce cardiac hypertrophy and are likely to contribute to the diastolic dysfunction in hypertrophic cardiomyopathy. The elevated sarcoplasmic calcium concentration during diastole, as documented in mouse models of hypertrophic cardiomyopathy, is likely to promote signaling (e.g., by means of calcineurin–nuclear factor of activated T cells [NFAT] and calcium-calmodulin–dependent protein kinase II)\(^1\); the changes in calcium handling may also confer a predisposition to arrhythmias.\(^1\)

At least two mechanisms explain how sarcomeric mutations alter calcium balance. First, mutations affecting the thin-filament regulatory proteins tropomyosin, troponin T, and troponin I all enhance calcium sensitivity by increasing the affinity of troponin C for calcium\(^1\); mutations affecting myosin and cMyBP-C also increase this affinity through the formation of additional cross-bridges between thick and thin filaments. Since troponin is the principal dynamic calcium buffer in the sarcoplasm,\(^1\) the increased affinity should elevate calcium levels during diastole.\(^1\) Second, sarcomeric mutations increase the energy requirements of myosin ATPase. Since the cross-bridge cycle, which generates the contractile force of the myocyte, accounts for about 70% of the cardiomyocyte’s ATP consumption, contractile inefficiency could compromise the energetics of the myocyte.\(^1\) The energy deficiency could reduce the activity of other ATP-consuming processes such as ion pumps (in particular, the sarcoplasmonic reticulum Ca\(^{2+}\) ATPase [SERCA]), thereby reducing calcium uptake during diastole. There is evidence of increased tension-dependent ATP consumption (tension cost) in isolated myofibril preparations\(^2\) and of compromised energetics in mouse models\(^2\) and in patients with cardiomyopathy, including mutation carriers before hypertrophy has developed.\(^2\) Moreover, other diseases that limit myocardial energy production, including mitochondrial transfer RNA mutations, cause a form of cardiac hypertrophy that resembles hypertrophic cardiomyopathy.\(^1\)

Other disease genes have been implicated in hypertrophic cardiomyopathy, albeit sometimes with less than robust evidence. Co-segregation in large families with members affected by hypertrophic cardiomyopathy\(^2\) supports pathogenic roles for mutations in \(CSRP3\), which encodes muscle LIM protein, and in \(ACTN2\), which encodes alpha-actinin-2. Rare variants of \(TCAP\) (telethonin),\(^2\) \(ANKRD1\) (encoding cardiac ankyrin repeat protein, or CARP),\(^2\) \(JPH2\) (junctophilin-2),\(^2\) and \(MYOZ2\) (myozin-2)\(^2\) have been described in candidate-gene analyses and studies of small families, but their role in the disease is unclear. All these genes encode proteins that are not integral components of the contractile apparatus, which suggests the involvement of additional mechanisms. These variants potentially disrupt processes common to the downstream consequences of myofilament mutations, such as mechanosensory signaling and calcium handling. Mutations in \(PRKAG2\), which encodes the \(\gamma2\) subunit of AMP-activated protein kinase (AMPK), produce a phenocopy of hypertrophic cardiomyopathy accompanied by the Wolff–Parkinson–White syndrome and progressive heart block.\(^9\) AMPK, an important energy sensor, interacts with multiple signaling cascades.\(^3\) Although glycogen accumulation probably contributes to myocyte hypertrophy, early activation of hypertrophic signaling pathways also occurs in transgenic mice in which mutant \(PRKAG2\) is overexpressed.\(^1\)

Rodents have been used to test proposed therapeutic targets, in some cases leading to pilot studies in humans. The L-type calcium-channel inhibitor diltiazem prevented dysregulation of calcium in the sarcoplasmic reticulum and cardiac hypertrophy in mice with a myosin heavy-chain mutation.\(^3\) A phase 2 trial of diltiazem in patients in the preclinical hypertrophic phase of cardiomyopathy is in progress (ClinicalTrials.gov number, NCT00319982).

Therapies to improve cardiac energetics have also been tested. In a randomized trial of perhexilene in patients with nonobstructive hypertrophic cardiomyopathy and activity-limiting symptoms, the partial inhibition of fatty acid oxidation, in the context of the oxygen limitation due to microvascular disease in hypertrophic cardiomyopathy,\(^3\) improved cardiac ATP levels and diastolic function, reduced symptoms, and increased exercise capacity.\(^3,\) Progressive interstitial cardiac fibrosis, resulting from non–myocyte (e.g., fibroblast)-mediated activation of transforming growth factor \(\beta\) signaling, is a feature of hypertrophic cardiomyopathy.\(^3\) The finding that preemptive angiotensin II type 1–receptor inhibition prevented myocardial fibrosis in a mouse model of cardiomyopathy,\(^3\) as well as encouraging results...
Dilated Cardiomyopathy, A Final Common Phenotype with Diverse Causes

The main features of dilated cardiomyopathy are left ventricular dilatation, systolic dysfunction, myocyte death, and myocardial fibrosis (Fig. 3). Analysis of asymptomatic relatives of affected patients indicates that familial disease accounts for one third to one half of cases. More than 40 disease genes have been identified; the most common mode of inheritance is autosomal dominant transmission, although autosomal recessive and X-linked forms have been described. Dilated cardiomyopathy is sometimes inherited with other phenotypes, both cardiac (e.g., conduction disorder) and noncardiac (e.g., sensorineural hearing loss). Unlike hypertrophic cardiomyopathy, dilated cardiomyopathy is caused by mutations in genes that encode components of a wide variety of cellular compartments and pathways, including the nuclear envelope, contractile apparatus, the force transduction apparatus (e.g., Z-disk and costamere), gene transcription and splicing machinery, and calcium handling (Fig. 3).

Given the diversity of affected cellular processes, multiple proximal factors probably contribute to contractile dysfunction of cardiomyocytes before cell death and fibrotic repair occur. In dilated cardiomyopathy, mutations in the genes encoding contractile proteins result in functional changes that are the opposite of the changes caused by mutations in the same contractile genes that cause hypertrophic cardiomyopathy. Mutations in the β-myosin heavy chain gene depress motor function in dilated cardiomyopathy, and mutations in genes for thin-filament regulatory proteins reduce the calcium sensitivity of contractile regulation and the affinity of troponin for calcium; hence, these mutations depress the generation of force. Several disease genes encode components of the Z-disk (e.g., Cypher/ZASP), the structure at the boundary of each sarcomere, or the costamere (e.g., δ-sarcoglycan), the structural complex that links the contractile apparatus to the sarcolemma and extracellular matrix. These mutations may cause defective transmission of force, affect stretch-sensing mechanisms involving titin, or both. The arginine-14 deletion in phospholamban (a membrane protein of muscle cells that regulates SERCA) causes excessive inhibition of the calcium pump and thus reduces calcium reuptake during diastole. The pathogenic effects of other mutations (e.g., those in LMNA, encoding the lamin A and C nuclear envelope proteins) are less clear. Nevertheless, the diverse changes in cardiomyocyte structure and function result in autophagy, a pathway of protein and organelle degradation, and ultimately apoptosis.

The molecular complexity of dilated cardiomyopathy suggests only a limited scope for specific disease-modifying therapies. Broad-based approaches, perhaps involving regenerative medicine, may be needed.

Arrhythmogenic Right Ventricular Cardiomyopathy, A Disease of the Desmosome

The main feature of arrhythmogenic right ventricular cardiomyopathy (ARVC) is fibrofatty replacement of the myocardium, mainly in the right ventricle but also in the left ventricle. This change results in the predominant clinical feature of susceptibility to ventricular arrhythmias. The disease is familial, and typically autosomal dominant, in about half the cases. Mutations in five genes that encode desmosomal proteins (desmoplakin, plakoglobin, plakophilin 2, desmoglein 2, and desmocollin 2) have been found in ARVC and in two related autosomal recessive disorders, Naxos disease (ARVC accompanied by woolly hair and palmoplantar keratoderma) and the Carvajal syndrome (which has a similar dermatologic phenotype but in which left ventricular involvement is predominant) (Fig. 4). The majority of causative mutations are insertions or deletions or nonsense mutations that result in premature truncation of the encoded proteins. Two other, nondesmosomal genes have been implicated in ARVC: one for transforming growth factor β3 (TGF-β3) and the other for transmembrane protein 43 (TMEM43). The existence of further mapped loci indicates that additional disease genes remain to be discovered in ARVC.

Desmosomes mediate intercellular attachments and anchor cytoplasmic domains of membrane proteins to the sarcolemma, until the structural integrity is compromised, fibrotic repair occurs, and myocyte death ensues.
proteins to the intermediate desmin filaments of cardiomyocytes. Mutant desmosomes may therefore compromise cell-to-cell adhesion at intercalated disks, lessening the ability of myocytes to withstand mechanical forces during the cardiac cycle. Damage to the cell surfaces, causing cell detachment and cell death, probably ensues. Experimental data indicating that mutant desmosomes also cause remodeling of gap junctions explain how electrocardiographic changes and
ventricular arrhythmias can develop before the loss of myocytes and dysfunction of the right ventricle become apparent (the concealed phase of disease).

However, this mechanical defect does not explain the right ventricular predominance, nor the prominence of inflammation and fibrofatty change. Desmosomal proteins also modify the Wnt/β-catenin signaling pathway, which is important for myogenesis in the heart. Increased nuclear translocation of plakoglobin, which is caused by the reduced plakoglobin-sequestering capacity of mutant desmosomes, appears to suppress Wnt signaling of cardiac progenitor cells. Redistribution of plakoglobin is a central feature of ARVC and could serve as a diagnostic test for the disease in postmortem tissue and, conceivably, in endomyocardial-biopsy specimens. The predilection for involvement of the right ventricle in ARVC probably depends on properties of cardiac progenitor cells in the second heart field, the embryonic source of the right ventricle. These primitive right-ventricle precursor cells are prone to differentiate into adipocytes (because of reduced transcription mediated by T-cell factor/lymphoid enhancer factor [Tcf/Lef]), rendering them more susceptible to the reduced Wnt signaling. Adipogenic transcription factors, such as peroxisome proliferator-activated receptor gamma (PPARG) (which is known to drive TMEM43 expression), may also mediate intracellular lipid perturbations and may contribute to the fibrofatty change (Fig. 4).

Thus, although existing therapy for end-stage ARVC includes conventional therapy for heart failure, genetic insights predict that the restitution of Wnt/β-catenin myocardial signaling and modification of lipid-metabolism pathways (e.g., by PPARG modifiers) may represent more targeted, disease-modifying therapies.

**LESSONS LEARNED FROM MOLECULAR GENETIC FAMILY STUDIES**

The diversity of the cardiomyopathies results from genetic, allelic, epigenetic, and environmental heterogeneity, all of which contribute to the phenotype (Fig. 5). Here we summarize how studies of cardiomyopathies improve our understanding of “simple” monogenic conditions and their polygenic counterparts.

**INCOMPLETE AND AGE-RELATED PENETRANCE**

As in most other autosomal dominant disorders, inherited cardiomyopathies show marked phenotypic variability, even within families. Penetrance — the proportion of mutation carriers with clinically detectable disease — increases with age but remains less than 100%. In most persons with hypertrophic cardiomyopathy, the hypertrophy is manifested in adolescence, whereas the age at onset in patients with sarcomeric dilated cardiomyopathy is bimodal (with peaks during childhood and mid-adulthood). The disease is gradually progressive in patients with dilated cardiomyopathy due to LMNA. It is uncommon to find numerous persons with clinically apparent ARVC in a single pedigree, indicating a low level of penetrance.

**VARIABLE EXPRESSIVITY**

Early reports of each of the cardiomyopathies described patients with severe forms of the disease. Subsequent studies, however, have shown that most affected persons have mild, sometimes atypical disease; as a result, the number of cases in a given family, and thus the proportion of familial cases, is greater than originally suspected. Only a minority of patients with hypertrophic cardiomyopathy have the classic feature of outflow obstruction at rest, and up to half the cases of idiopathic dilated cardiomyopathy are familial.
Altered Wnt/β-catenin signaling

Impaired cell adhesion and intercellular communication

**A**

Plakophilin → Desmoplakin → Plakoglobin

Desmoglein → Desmocollin → Gap junction

N-cadherin

Intermediate filaments

Outer dense plaque

Intracellular space

Nucleus

**B**

No ARVC

ARVC

N-cadherin

Plakoglobin

**C**

Fat

Fibrosis

Muscle

**D**

Nucleus
Arrhythmogenic right ventricular cardiomyopathy (ARVC) results from perturbation of one of three groups of desmosomal proteins: transmembrane proteins (e.g., the desmosomal cadherins, desmoglein and desmocollin), proteins anchored directly to intermediate filaments (e.g., desmoplakin), and the armadillo family of proteins (e.g., plakoglobin and plakophilin), which bind the desmosomal cadherins to desmoplakin (Panel A). In addition to the disruption of desmosomal mechanical function, which can lead to the death of myocytes under physical stress, the suppression of canonical Wnt/β-catenin signaling by nuclear plakoglobin translocation appears to promote adiopogenesis in mesodermal precursors. Panel B shows immunofluorescence images of left ventricular myocardium from patients with ARVC and controls without ARVC. Although both patients with ARVC and those without show a strong junctional signal for N-cadherin, a non-desmosomal adhesion molecule, plakoglobin, is markedly reduced in patients with ARVC whether or not the section shows typical pathological changes of fibrofatty replacement (Panel B). These changes explain the progressive fibrofatty replacement of ventricular myocardium (Panel C, hematoxylin and eosin), with progressive gross effects on ventricular morphology and function, classically, but not exclusively, with right ventricular pre-dominance (arrows), as shown on cardiac magnetic resonance imaging (Panel D). (Panel B reprinted from Asimaki et al.18 with the permission of the publisher.)

has also become apparent that ARVC often goes unrecognized and is more common than was first thought.69 Left ventricular noncompaction, initially considered a rare disorder associated with very high rates of cardioembolism and heart failure,70 is now considered to be substantially more common and less severe than was previously believed.71 Incomplete penetrance requires diagnostic criteria of less than the usual stringency for first-degree relatives, in whom the prior risk is generally 50%; clinicians caring for families at risk now use complex diagnostic algorithms to interpret minor abnormalities.69 The corollary is that, in the general population, patients with subtle features of inherited cardiomyopathies are difficult to recognize. Thus, population screening is generally ineffective; instead, cascade screening (sequential identification of related family members, increasingly guided by genetic testing) is key.72

GENETIC HETEROGENEITY AND ALLELIC DISORDERS

Hypertrophic cardiomyopathy and dilated cardiomyopathy can be allelic, each caused by specific missense mutations in the same genes encoding sarcomeric proteins. Since these diseases arise from mutations with opposing biophysical consequences,48 a variant “breeds true” within each family; there has been no reliable documentation of families in which a single sarcomere mutation causes hypertrophic cardiomyopathy in some members and dilated cardiomyopathy in others. However, other aspects of the cardiomyopathy phenotype can vary within families, indicating the absence of a precise relationship between the mutation and its biophysical consequences. For example, apical hypertrophic cardiomyopathy most likely occurs in families affected primarily by typical hypertrophic cardiomyopathy; in only a minority of cases does apical hypertrophic cardiomyopathy have a consistent relationship with a specific mutation (e.g., Glu101Lys in the alpha cardiac actin gene [ACTC1]).73 Similarly, familial restrictive cardiomyopathy is part of the spectrum of sarcomeric hypertrophic cardiomyopathy, with a loose relationship between certain mutations and this variant of the phenotype.74 Left ventricular noncompaction is characterized by myocardium with a spongy appearance. The disease may reflect a failure of normal development and sometimes occurs together with cardiac and extracardiac developmental defects, but progressive dysfunction in adults indicates that left ventricular noncompaction is a newly recognized aspect of cardiac remodeling. In some families, the phenotype is consistently manifested (the genetic basis of such families is unknown), but cases of noncompaction do occur in families with otherwise typical hypertrophic or dilated cardiomyopathy attributable to sarcomeric mutations.49,75

PHENOCOPIES

The term phenocopy refers to apparently similar disorders with different causes. Distinctions among such conditions can be clinically important, because disorders with similar cardiac morphology can have different inheritance patterns, natural histories, or responses to therapy. Certain autosomal dominant cardiomyopathies (those caused by PRKAG2 mutations) and X-linked cardiomyopathies (Fabry’s disease and Danon’s disease) share clinical features with sarcomeric hypertrophic cardiomyopathy yet are distinct disorders.29,76,77 Such phenocopies may also inform our understanding of disease mechanisms. Although hypertrophy due to PRKAG2 mutations is often attrib-
uted to glycogen accumulation, the increase in cardiac mass cannot be explained by a simple bulk effect; instead, the glycogen probably initiates signaling mechanisms involved in sarcomeric hypertrophic cardiomyopathy.31,78

Genotype–Phenotype Correlations
In certain circumstances, knowledge of the gene underlying the cardiomyopathy will alter patient care. One example is phenocopies of hypertrophic cardiomyopathy with different inheritance patterns and natural histories. Another example is the susceptibility to conduction disease of patients with dilated cardiomyopathy due to LMNA mutations; when this is sufficient to warrant pacemaker insertion, use of an implantable cardioverter–defibrillator should be considered.79,80 However, for most cardiomyopathies, correlations between the disease gene and the phenotype are currently of limited usefulness for managing the care of individual patients; some quantitative differences exist, but there is substantial overlap between disease-gene groups, and exceptions are common.81–83 Allelic heterogeneity further complicates attempts to correlate genotype with phenotype, since the rarity of individual mutations usually means that sufficient clinical data are unavailable. Long-term efforts will be needed to accumulate reliable evidence on genotype–phenotype correlations. Data based on results from proband series are particularly vulnerable to ascertainment bias.84

Additional complexities include the presence of two or more variants, as either compound or double heterozygosity.85–87 The proportion of genotyped persons with more than one variant

Figure 5. Complexities of the Genotype–Phenotype Relationship in Inherited Cardiomyopathies.
The effect of the particular disease gene, and specific mutation, on the cardiomyopathy phenotype is modified extensively by genetic, epigenetic, and environmental factors. Accordingly, the phenotype can vary greatly even among relatives with the same mutation. Most such modifying factors remain unknown, although examples that illustrate the categories listed are emerging. DCM denotes dilated cardiomyopathy, and HCM hypertrophic cardiomyopathy.
is higher in diseases with low penetrance — notably, arrhythmogenic right ventricular cardiomyopathy.\textsuperscript{88} The presence of multiple variants complicates genetic testing in families (since it may be difficult to determine whether a “second” variant is itself sufficient to cause disease) and confounds genotype-phenotype correlations if only one allele is analyzed.

**NONMENDELIAN VARIANTS AND MODIFIER EFFECTS**

The widespread detailed sequencing of the genes implicated in the cardiomyopathies should culminate in identification of a spectrum of variants, ranging from alleles that clearly cause disease through variants of uncertain significance to silent polymorphisms. A well-validated example of a common susceptibility variant is an intronic deletion in \textit{MYBPC3}, which causes a partial splicing defect (as opposed to the complete defect in typical autosomal dominant hypertrophic cardiomyopathy) and confers susceptibility to various cardiomyopathies in people whose families come from the Indian subcontinent.\textsuperscript{89} It is likely that in a proportion of all cardiomyopathies, inheritance has a nonmendelian pattern, in which alleles with only modest effects converge; the likelihood of familial disease in these cases is low, and the disease may be milder. Patients with hypertrophic cardiomyopathy who do not have a family history of the disease are less likely to carry pathogenic sarcomeric mutations\textsuperscript{90} and usually have a relatively mild phenotype.\textsuperscript{91} Validation of variants, or modifier genes, with an intermediate effect is difficult because they cannot be tested by means of cosegregation. Common variants can be evaluated with the use of tests for association in large studies,\textsuperscript{89} but a statistical demonstration of an increased mutation load is needed for rare variants, which requires sequencing of both case patients and controls.\textsuperscript{92} The fact that variants occur in case patients but not in controls is not adequate to prove a pathogenic role because control subjects often bear similarly rare but different variants. This limitation is a problem with many recent candidate-gene studies in cardiomyopathy. Some patients who have hypertrophic cardiomyopathy without a sarcomere mutation may not have an inherited disease at all — the variants in these cases will be chance findings. In keeping with this point, identical variants are sometimes reported as causes of un-related phenotypes, suggesting that they may in fact be silent polymorphisms.\textsuperscript{93,94}

**FUTURE PROSPECTS**

The incomplete penetrance that complicates genetic evaluation of families with a cardiomyopathy paradoxically raises hopes that the development of novel disease-modifying therapies may be achievable. The underlying mutations cause subtle cellular perturbations\textsuperscript{11} that are tolerated by all mutation carriers for a period — and in many cases, throughout life — which suggests that compensatory mechanisms exist. The transition to overt disease can be abrupt in both hypertrophic and dilated cardiomyopathies,\textsuperscript{95,96} suggesting a tipping point that triggers decompensation. Novel therapies may need only to subtly shift cellular variables to sustain the compensated state, particularly if therapy begins in asymptomatic mutation carriers identified by cascade screening in families. Hypertrophic cardiomyopathy may be the most tractable cardiomyopathy, since specific therapeutic targets have been identified downstream of the perturbation in contractile regulation, hypertrophied cardiomyocytes can undergo remodeling, and the disease does not depend on myocyte death. ARVC also appears to have a final common pathway with sufficient specificity to be targeted, particularly if aberrant Wnt/β-catenin signaling rather than a mechanical defect is central to the disorder. The multiple primary defects underlying dilated cardiomyopathy appear to be the most difficult to target. Here, and also in other cardiomyopathies, avoidance of environmental precipitants that could trigger decompensation\textsuperscript{96-98} could be important.

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Dr. Watkins reports being listed as a patent holder on patents held by Harvard University for methods for detecting disease-associated mutations in hypertrophic cardiomyopathy; and Dr. Ashrafian reports holding a European method-of-use patent for perhexiline in systolic heart failure and having patents pending for its use in diastolic heart failure and hypertrophic cardiomyopathy and for its use in systolic heart failure in countries outside Europe.

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