REVIEW ARTICLE

MECHANISMS OF DISEASE
Robert S. Schwartz, M.D., *Editor*

Inherited Cardiomyopathies

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N Engl J Med 2011;364:1643-56.

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.[1,2] This finding led to the concept that hypertrophic cardiomyopathy is a disease of the sarcomere.[3] 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.[4] 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,[5,6] 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.[7] 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.[7] 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),

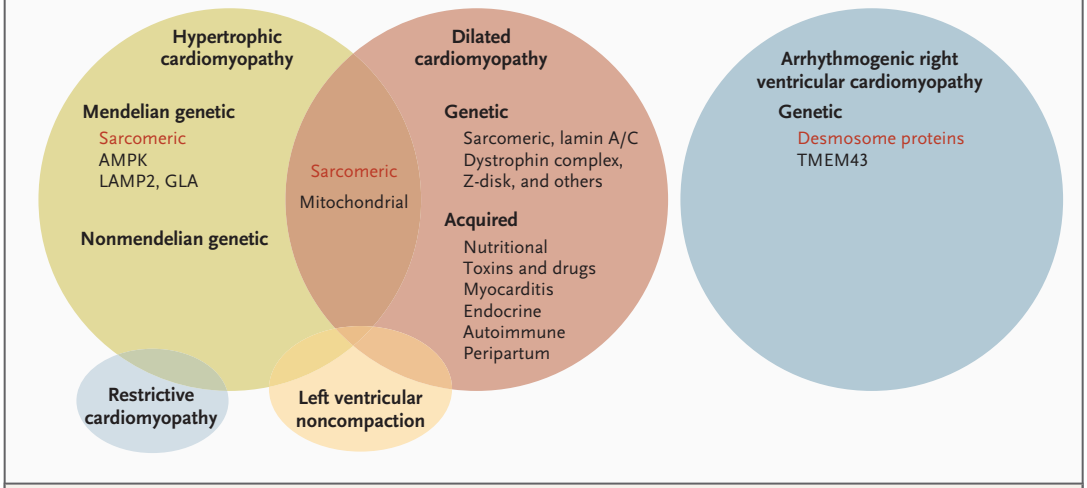


Figure 1. Clinical Categories of Inherited Cardiomyopathies and Their Genetic Basis.

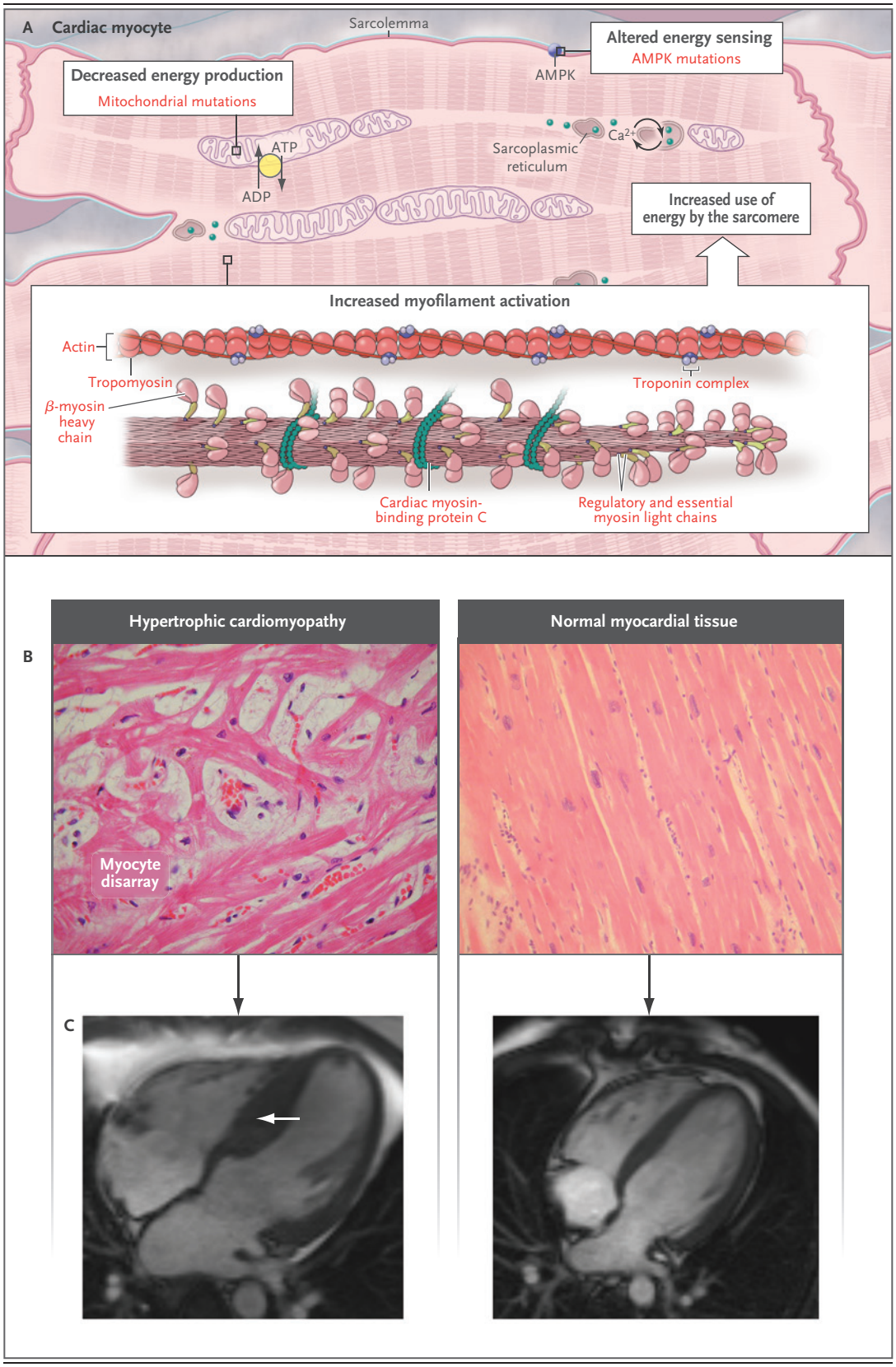
The clinical entities hypertrophic cardiomyopathy and dilated cardiomyopathy share some disease genes with each other, as well as with restrictive cardiomyopathy and left ventricular noncompaction, which are less common. Arrhythmogenic right ventricular cardiomyopathy appears to be a genetically distinct category, although its clinical phenotype cannot always be easily distinguished from that of dilated cardiomyopathy. AMPK denotes AMP-activated protein kinase, GLA α-galactosidase A, LAMP2 lysosomal-associated membrane protein 2, and TMEM43 transmembrane protein 43. Classes of genes shown in red are the overwhelmingly predominant cause of disease within the respective categories.

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.[3] 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.[8] The mutations generally cause single amino acid substitutions in proteins that become incorporated into the sarcomere. However, about half 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.[9,10]

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.[11,12] These perturbations trigger signaling pathways

Figure 2 (facing page). Pathogenesis of Hypertrophic Cardiomyopathy.

In hypertrophic cardiomyopathy, mutations in sarcomeric proteins generally increase myofilament activation and result in myocyte hypercontractility and excessive energy use (Panel A). Alterations in myocardial energy status can also result from primary mutations affecting myocardial energy generation (e.g., mitochondrial transfer RNA mutations). These mitochondrial defects and mutations in the cardiac energy-sensing apparatus (e.g., AMP-activated protein kinase [AMPK]) recapitulate a hypertrophic cardiomyopathy–like phenotype. Alterations in myocardial energetics and in calcium handling combined with stimulation of signaling pathways (e.g., the Janus-associated kinase–signal transducers and activators of transcription [JAK-STAT] signaling pathway) diminish myocyte relaxation and promote myocyte growth, with aberrant tissue architecture (i.e., myofibrillar disarray and myocardial fibrosis) (Panel B, hematoxylin and eosin). In patients with hypertrophic cardiomyopathy, these changes often result in gross hypertrophy, with especially prominent septal hypertrophy (arrow) as compared with the normal heart, as shown on the cardiac magnetic resonance images (Panel C).



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,[13] 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)[14]; the changes in calcium handling may also confer a predisposition to arrhythmias.[15]

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[16]; 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,[17] the increased affinity should elevate calcium levels during diastole.[18] 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.[19] The energy deficiency could reduce the activity of other ATP-consuming processes such as ion pumps (in particular, the sarcoendoplasmic 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[20] and of compromised energetics in mouse models[21] and in patients with cardiomyopathy, including mutation carriers before hypertrophy has developed.[22] Moreover, other diseases that limit myocardial energy production, including mitochondrial transfer RNA mutations, cause a form of cardiac hypertrophy that resembles hypertrophic cardiomyopathy.[19]

Other disease genes have been implicated in hypertrophic cardiomyopathy, albeit sometimes with less than robust evidence. Cosegregation in large families with members affected by hypertrophic cardiomyopathy[23,24] 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),[25] *ANKRD1* (encoding cardiac ankyrin repeat protein, or CARP),[26] *JPH2* (junctophilin-2),[27] and *MYOZ2* (myozenin-2)[28] 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 $\gamma 2$ subunit of AMP-activated protein kinase (AMPK), produce a phenocopy of hypertrophic cardiomyopathy accompanied by the Wolff–Parkinson–White syndrome and progressive heart block.[29] AMPK, an important energy sensor, interacts with multiple signaling cascades.[30] 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.[31]

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.[32] 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 perhexiline 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,[33] improved cardiac ATP levels and diastolic function, reduced symptoms, and increased exercise capacity.[34,35] Progressive interstitial cardiac fibrosis, resulting from non–myocyte (e.g., fibroblast)-mediated activation of transforming growth factor β signaling, is a feature of hypertrophic cardiomyopathy.[36-38] The finding that preemptive angiotensin II type 1–receptor inhibition prevented myocardial fibrosis in a mouse model of cardiomyopathy,[38] as well as encouraging results

from a small clinical study, supports further investigation of this approach.[39]

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.[40,41] 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.[42,43] Dilated cardiomyopathy is sometimes inherited with other phenotypes, both cardiac (e.g., conduction disorder)[44] and noncardiac (e.g., sensorineural hearing loss).[45] 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).[36,42,43]

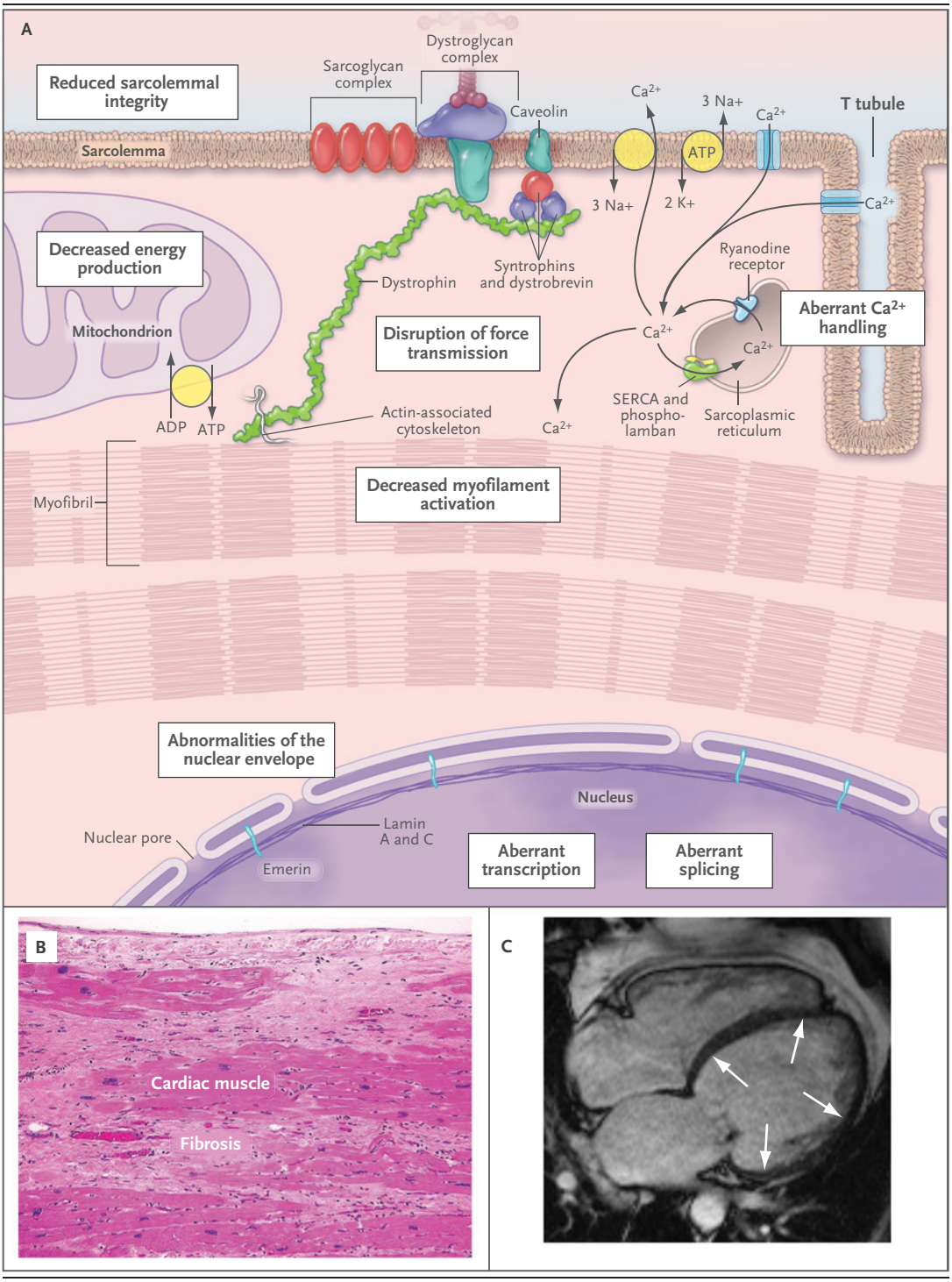
Given the diversity of affected cellular processes, multiple proximal factors probably contribute to contractile dysfunction of cardiomyocytes before cell death and fibrotic repair occur. In dilated cardiomyopathy, mutations in the genes encoding contractile proteins result in functional changes that 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,[46,47] and mutations in genes for thin-filament regulatory proteins reduce the calcium sensitivity of contractile regulation and the affinity of troponin for calcium[16,48]; hence, these mutations depress the generation of force. Several disease genes encode components of the Z-disk (e.g., Cypher/ZASP),[49] 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.[50] These mutations may cause defective transmission of force, affect stretch-sensing mechanisms involving titin, or both.[51,52] 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.[53] The pathogenic effects of other mutations (e.g., those in *LMNA*, encoding the lamin A and C nuclear envelope proteins)[54] 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.[55,56]

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.[57] 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).[59,60] The existence of further mapped loci indicates that additional disease genes remain to be discovered in ARVC.[61]

Desmosomes mediate intercellular attachments and anchor cytoplasmic domains of membrane



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.[62] Experimental data indicating that mutant desmosomes also cause remodeling of gap junctions[63] explain how electrocardiographic changes and

Figure 3 (facing page). Pathogenesis of Dilated Cardiomyopathy.

Dilated cardiomyopathy is the end phenotype of diverse mutations in heterogeneous pathways ranging from components of the membrane-scaffolding apparatus (e.g., sarcoglycan and dystrophinopathies), sarcomeric proteins (which exhibit reduced myofilament activation, unlike the case for hypertrophic cardiomyopathy), nuclear envelope proteins (e.g., lamin A and C), calcium-handling proteins (e.g., phospholamban [PLN]), transcription cofactors (e.g., eyes absent homolog 4 [EYA4]), and RNA splicing (e.g., ribonucleic acid–binding protein [RBM20]), to the cell energy-generating machinery (Panel A). Although these mutations are highly diverse in terms of the pathways affected, their common features are impaired contraction, insurmountable cellular compromise with consequent cell death and fibrotic repair (Panel B, hematoxylin and eosin), and ultimately, gross cardiac thinning and dilatation. Such biventricular dilatation and wall thinning relative to the cavity dimension (arrows) can be detected on cardiac magnetic resonance imaging (Panel C).

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 and 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.[64] 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.[58] 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.[65] 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).[66]

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).[67] The disease is gradually progressive in patients with dilated cardiomyopathy due to *LMNA*.[68] 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.[40,41] It

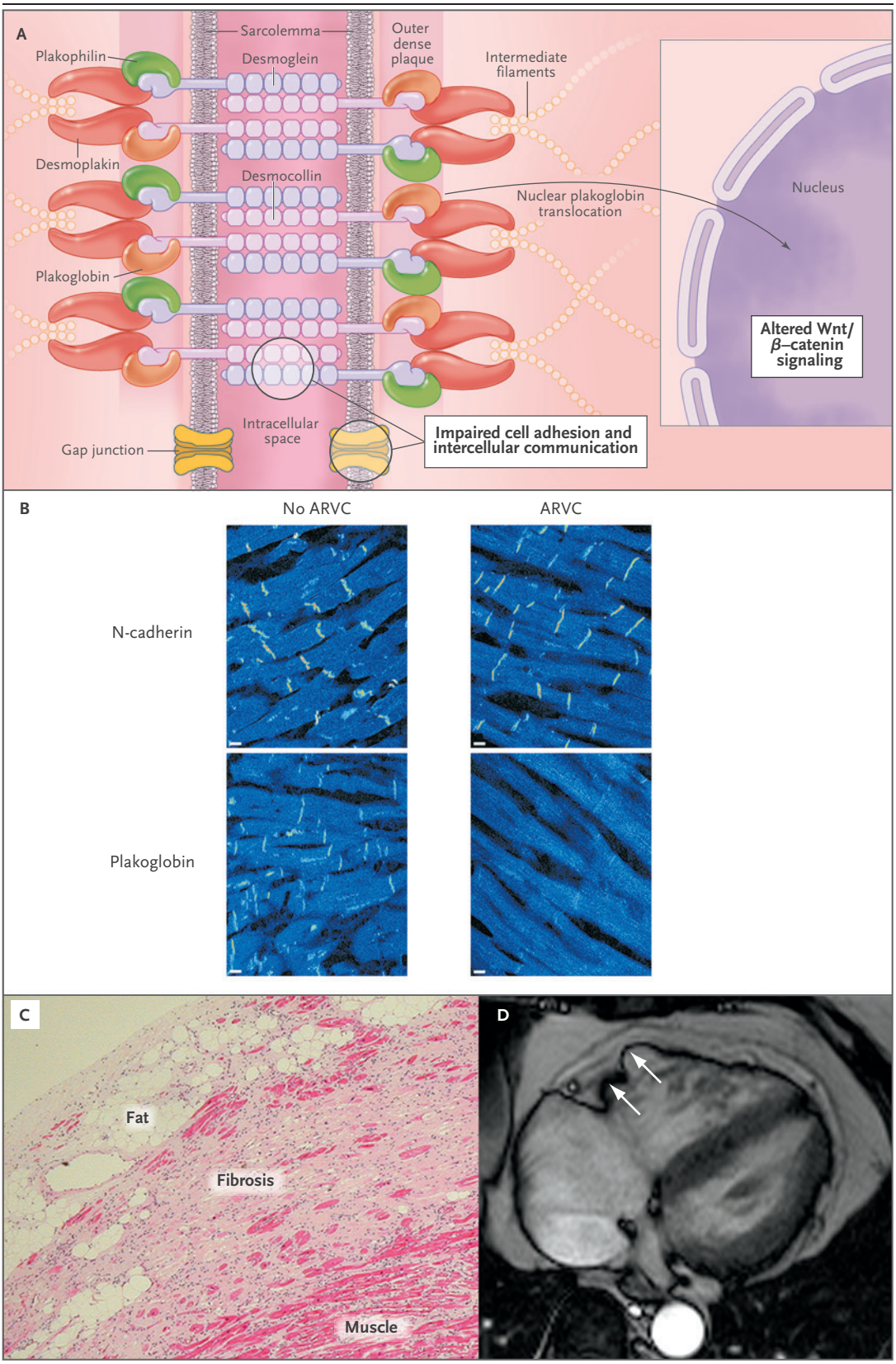


Figure 4 (facing page). Pathogenesis of Arrhythmogenic Right Ventricular Cardiomyopathy.

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 adipogenesis 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 nondesmosomal 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 predominance (arrows), as shown on cardiac magnetic resonance imaging (Panel D). (Panel B reprinted from Asimaki et al.[58] 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 mostly 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-

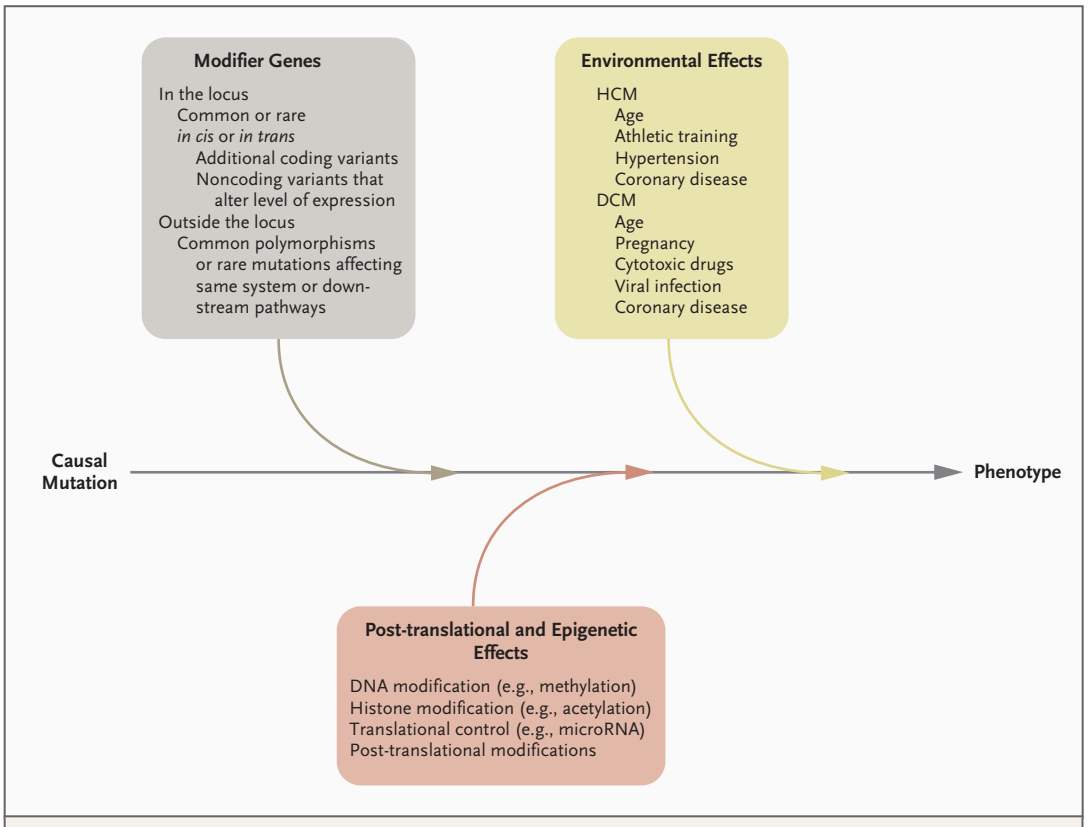


Figure 5. Complexities of the Genotype–Phenotype Relationship in Inherited Cardiomyopathies.

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.

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

is higher in diseases with low penetrance — notably, arrhythmogenic right ventricular cardiomyopathy.[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 *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.[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[90] and usually have a relatively mild phenotype.[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,[89] but a statistical demonstration of an increased mutation load is needed for rare variants, which requires sequencing of both case patients and controls.[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 unrelated phenotypes, suggesting that they may in fact be silent polymorphisms.[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[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,[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[96-98] could be important.

Supported by the British Heart Foundation Centre of Excellence at Oxford, Wellcome Trust, European Commission Framework Programme Grant (241577), and Oxford Partners National Institute for Health Research Comprehensive Biomedical Research Centre.

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.

We thank Dr. Mary Sheppard, Royal Brompton Hospital, London, for the histologic images and Dr. Theodoros Karamitsos and Professor Stefan Neubauer, University of Oxford, Oxford, United Kingdom, for the cardiac magnetic resonance images.

REFERENCES

1. Jarcho JA, McKenna W, Pare JA, et al. Mapping a gene for familial hypertrophic cardiomyopathy to chromosome 14q1. N Engl J Med 1989;321:1372-8.
2. Geisterfer-Lowrance AA, Kass S, Tanigawa G, et al. A molecular basis for familial hypertrophic cardiomyopathy: a beta cardiac myosin heavy chain gene missense mutation. Cell 1990;62:999-1006.
3. Thierfelder L, Watkins H, MacRae C, et al. Alpha-tropomyosin and cardiac troponin T mutations cause familial hypertrophic cardiomyopathy: a disease of the sarcomere. Cell 1994;77:701-12.
4. Dietz HC. New therapeutic approaches to mendelian disorders. N Engl J Med 2010;363:852-63.
5. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation 2006;113:1807-16.
6. Elliott P, Andersson B, Arbustini E, et al. Classification of the cardiomyopathies: a position statement from the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2008;29:270-6.
7. Kamisago M, Sharma SD, DePalma SR, et al. Mutations in sarcomere protein genes as a cause of dilated cardiomyopathy. N Engl J Med 2000;343:1688-96.
8. Richard P, Charron P, Carrier L, et al. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. Circulation 2003;107:2227-32. [Erratum, Circulation 2004;109:3258.]
9. Marston S, Copeland O, Jacques A, et al. Evidence from human myectomy samples that MYBPC3 mutations cause hypertrophic cardiomyopathy through haploinsufficiency. Circ Res 2009;105:219-22.
10. van Dijk SJ, Dooijes D, dos Remedios C, et al. Cardiac myosin-binding protein C mutations and hypertrophic cardiomyopathy: haploinsufficiency, deranged phosphorylation, and cardiomyocyte dysfunction. Circulation 2009;119:1473-83.
11. Redwood CS, Moolman-Smook JC, Watkins H. Properties of mutant contractile proteins that cause hypertrophic cardiomyopathy. Cardiovasc Res 1999;44:20-36.
12. Seidman JG, Seidman C. The genetic basis for cardiomyopathy: from mutation identification to mechanistic paradigms. Cell 2001;104:557-67.
13. Knollmann BC, Kirchhof P, Sirenko SG, et al. Familial hypertrophic cardiomyopathy-linked mutant troponin T causes stress-induced ventricular tachycardia and Ca2+-dependent action potential remodeling. Circ Res 2003;92:428-36.
14. Bers DM, Guo T. Calcium signaling in cardiac ventricular myocytes. Ann N Y Acad Sci 2005;1047:86-98.
15. Huke S, Knollmann BC. Increased myofilament Ca2+-sensitivity and arrhythmia susceptibility. J Mol Cell Cardiol 2010;48:824-33.
16. Robinson P, Griffiths PJ, Watkins H, Redwood CS. Dilated and hypertrophic cardiomyopathy mutations in troponin and alpha-tropomyosin have opposing effects on the calcium affinity of cardiac thin filaments. Circ Res 2007;101:1266-73.
17. Smith GA, Dixon HB, Kirschenlohr HL, Grace AA, Metcalfe JC, Vandenberg JI. Ca2+ buffering in the heart: Ca2+ binding to and activation of cardiac myofibrils. Biochem J 2000;346:393-402.
18. Kataoka A, Hemmer C, Chase PB. Computational simulation of hypertrophic cardiomyopathy mutations in troponin I: influence of increased myofilament calcium sensitivity on isometric force, ATPase and [Ca2+]i. J Biomech 2007;40:2044-52.
19. Ashrafian H, Redwood C, Blair E, Watkins H. Hypertrophic cardiomyopathy: a paradigm for myocardial energy depletion. Trends Genet 2003;19:263-8.
20. Belus A, Piroddi N, Scellini B, et al. The familial hypertrophic cardiomyopathy-associated myosin mutation R403Q accelerates tension generation and relaxation of human cardiac myofibrils. J Physiol 2008;586:3639-44.
21. Spindler M, Saupe KW, Christe ME, et al. Diastolic dysfunction and altered energetics in the alphaMHC403/+ mouse model of familial hypertrophic cardiomyopathy. J Clin Invest 1998;101:1775-83.
22. Crilley JG, Boehm EA, Blair E, et al. Hypertrophic cardiomyopathy due to sarcomeric gene mutations is characterized by impaired energy metabolism irrespective of the degree of hypertrophy. J Am Coll Cardiol 2003;41:1776-82.
23. Geier C, Gehmlich K, Ehler E, et al. Beyond the sarcomere: CSRP3 mutations cause hypertrophic cardiomyopathy. Hum Mol Genet 2008;17:2753-65.
24. Chiu C, Bagnall RD, Ingles J, et al. Mutations in alpha-actinin-2 cause hypertrophic cardiomyopathy: a genome-wide analysis. J Am Coll Cardiol 2010;55:1127-35.
25. Hayashi T, Arimura T, Itoh-Satoh M, et al. Tcap gene mutations in hypertrophic cardiomyopathy and dilated cardiomyopathy. J Am Coll Cardiol 2004;44:2192-201.
26. Arimura T, Bos JM, Sato A, et al. Cardiac ankyrin repeat protein gene (ANKRD1) mutations in hypertrophic cardiomyopathy. J Am Coll Cardiol 2009;54:334-42.
27. Landstrom AP, Weisleder N, Batalden KB, et al. Mutations in JPH2-encoded junctophilin-2 associated with hypertrophic cardiomyopathy in humans. J Mol Cell Cardiol 2007;42:1026-35.
28. Osio A, Tan L, Chen SN, et al. Myozenin 2 is a novel gene for human hypertrophic cardiomyopathy. Circ Res 2007;100:766-8.
29. Blair E, Redwood C, Ashrafian H, et al. Mutations in the gamma(2) subunit of AMP-activated protein kinase cause familial hypertrophic cardiomyopathy: evidence for the central role of energy compromise in disease pathogenesis. Hum Mol Genet 2001;10:1215-20.
30. Kim AS, Miller EJ, Young LH. AMP-activated protein kinase: a core signalling pathway in the heart. Acta Physiol (Oxf) 2009;196:37-53.
31. Banerjee SK, McGaffin KR, Huang XN, Ahmad F. Activation of cardiac hypertrophic signaling pathways in a transgenic mouse with the human PRKAG2 Thr400Asn mutation. Biochim Biophys Acta 2010;1802:284-91.
32. Semsarian C, Ahmad I, Giewat M, et al. The L-type calcium channel inhibitor diltiazem prevents cardiomyopathy in a mouse model. J Clin Invest 2002;109:1013-20.
33. Petersen SE, Jerosch-Herold M, Hudsmith LE, et al. Evidence for microvascular dysfunction in hypertrophic cardiomyopathy: new insights from multiparametric magnetic resonance imaging. Circulation 2007;115:2418-25.
34. Ashrafian H, Frenneaux MP, Opie LH. Metabolic mechanisms in heart failure. Circulation 2007;116:434-48.
35. Abozguia K, Elliott P, McKenna WJ, et al. Metabolic modulator perhexiline corrects energy deficiency and improves exercise capacity in symptomatic hypertrophic cardiomyopathy. Circulation 2010;122:1562-9.
36. O'Hanlon R, Grasso A, Roughton M et al. Prognostic significance of myocardial fibrosis in hypertrophic cardiomyopathy. J Am Coll Cardiol 2010;56:867-74.
37. Ho CY, López B, Coelho-Filho OR, et al. Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy. N Engl J Med 2010;363:552-63.
38. Teekakirikul P, Eminaga S, Toka O, et al. Cardiac fibrosis in mice with hypertrophic cardiomyopathy is mediated by non-myocyte proliferation and requires Tgf-beta. J Clin Invest 2010;120:3520-9.
39. Penicka M, Gregor P, Kerekes R, et al. The effects of candesartan on left ventricular hypertrophy and function in non-obstructive hypertrophic cardiomyopa-

thy: a pilot, randomized study. J Mol Diagn 2009;11:35-41.
40. Baig MK, Goldman JH, Caforio AL, Coonar AS, Keeling PJ, McKenna WJ. Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. J Am Coll Cardiol 1998;31:195-201.
41. DeWitt MM, MacLeod HM, Soliven B, McNally EM. Phospholamban R14 deletion results in late-onset, mild, hereditary dilated cardiomyopathy. J Am Coll Cardiol 2006;48:1396-8.
42. Jefferies JL, Towbin JA. Dilated cardiomyopathy. Lancet 2010;375:752-62.
43. Dellefave L, McNally EM. The genetics of dilated cardiomyopathy. Curr Opin Cardiol 2010 February 24 (Epub ahead of print).
44. Wolf CM, Wang L, Alcalai R, et al. Lamin A/C haploinsufficiency causes dilated cardiomyopathy and apoptosis-triggered cardiac conduction system disease. J Mol Cell Cardiol 2008;44:293-303.
45. Schönberger J, Wang L, Shin JT, et al. Mutation in the transcriptional coactivator EYA4 causes dilated cardiomyopathy and sensorineural hearing loss. Nat Genet 2005;37:418-22.
46. Schmitt JP, Debold EP, Ahmad F, et al. Cardiac myosin missense mutations cause dilated cardiomyopathy in mouse models and depress molecular motor function. Proc Natl Acad Sci U S A 2006; 103:14525-30.
47. Debold EP, Schmitt JP, Patlak JB, et al. Hypertrophic and dilated cardiomyopathy mutations differentially affect the molecular force generation of mouse alpha-cardiac myosin in the laser trap assay. Am J Physiol Heart Circ Physiol 2007;293: H284-H291.
48. Mirza M, Marston S, Willott R, et al. Dilated cardiomyopathy mutations in three thin filament regulatory proteins result in a common functional phenotype. J Biol Chem 2005;280:28498-506.
49. Vatta M, Mohapatra B, Jimenez S, et al. Mutations in Cypher/ZASP in patients with dilated cardiomyopathy and left ventricular non-compaction. J Am Coll Cardiol 2003;42:2014-27.
50. Tsubata S, Bowles KR, Vatta M, et al. Mutations in the human delta-sarcoglycan gene in familial and sporadic dilated cardiomyopathy. J Clin Invest 2000;106: 655-62.
51. Bowles NE, Bowles KR, Towbin JA. The "final common pathway" hypothesis and inherited cardiovascular disease: the role of cytoskeletal proteins in dilated cardiomyopathy. Herz 2000;25:168-75.
52. Miller MK, Granzier H, Ehler E, Gregorio CC. The sensitive giant: the role of titin-based stretch sensing complexes in the heart. Trends Cell Biol 2004;14:119-26.
53. Haghighi K, Kolokathis F, Gramolini AO, et al. A mutation in the human phospholamban gene, deleting arginine 14, results in lethal, hereditary cardiomyopathy. Proc Natl Acad Sci U S A 2006;103: 1388-93.
54. Malhotra R, Mason PK. Lamin A/C deficiency as a cause of familial dilated cardiomyopathy. Curr Opin Cardiol 2009; 24:203-8.
55. Mudd JO, Kass DA. Tackling heart failure in the twenty-first century. Nature 2008;451:919-28.
56. Foo RS, Mani K, Kitsis RN. Death begets failure in the heart. J Clin Invest 2005;115:565-71.
57. Sen-Chowdhry S, Morgan RD, Chambers JC, McKenna WJ. Arrhythmogenic cardiomyopathy: etiology, diagnosis, and treatment. Annu Rev Med 2010;61:233-53.
58. Asimaki A, Tandri H, Huang H, et al. A new diagnostic test for arrhythmogenic right ventricular cardiomyopathy. N Engl J Med 2009;360:1075-84.
59. Beffagna G, Occhi G, Nava A, et al. Regulatory mutations in transforming growth factor-beta3 gene cause arrhythmogenic right ventricular cardiomyopathy type 1. Cardiovasc Res 2005;65:366-73.
60. Merner ND, Hodgkinson KA, Haywood AF, et al. Arrhythmogenic right ventricular cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the TMEM43 gene. Am J Hum Genet 2008; 82:809-21.
61. Matolweni LO, Bardien S, Rebello G, et al. Arrhythmogenic right ventricular cardiomyopathy type 6 (ARVC6): support for the locus assignment, narrowing of the critical region and mutation screening of three candidate genes. BMC Med Genet 2006;7:29.
62. Kirchhof P, Fabritz L, Zwiener M, et al. Age- and training-dependent development of arrhythmogenic right ventricular cardiomyopathy in heterozygous plakoglobin-deficient mice. Circulation 2006; 114:1799-806.
63. Kaplan SR, Gard JJ, Protonotarios N, et al. Remodeling of myocyte gap junctions in arrhythmogenic right ventricular cardiomyopathy due to a deletion in plakoglobin (Naxos disease). Heart Rhythm 2004;1:3-11.
64. Garcia-Gras E, Lombardi R, Giocondo MJ, et al. Suppression of canonical Wnt/beta-catenin signaling by nuclear plakoglobin recapitulates phenotype of arrhythmogenic right ventricular cardiomyopathy. J Clin Invest 2006;116:2012-21.
65. Lombardi R, Dong J, Rodriguez G, et al. Genetic fate mapping identifies second heart field progenitor cells as a source of adipocytes in arrhythmogenic right ventricular cardiomyopathy. Circ Res 2009;104:1076-84.
66. Djouadi F, Lecarpentier Y, Hébert JL, Charron P, Bastin J, Coirault C. A potential link between peroxisome proliferator-activated receptor signalling and the pathogenesis of arrhythmogenic right ventricular cardiomyopathy. Cardiovasc Res 2009;84:83-90.
67. Lakdawala NK, Dellefave L, Redwood CS, et al. Familial dilated cardiomyopathy caused by an alpha-tropomyosin mutation: the distinctive natural history of sarcomeric dilated cardiomyopathy. J Am Coll Cardiol 2010;55:320-9.
68. Fatkin D, MacRae C, Sasaki T, et al. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction-system disease. N Engl J Med 1999;341:1715-24.
69. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation 2010;121:1533-41.
70. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R et al. Long-term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. J Am Coll Cardiol 2000;36:493-500.
71. Lofiego C, Biagini E, Pasquale F, et al. Wide spectrum of presentation and variable outcomes of isolated left ventricular non-compaction. Heart 2007;93:65-71.
72. Wordsworth S, Leal J, Blair E, et al. DNA testing for hypertrophic cardiomyopathy: a cost-effectiveness model. Eur Heart J 2010;31:926-35.
73. Arad M, Penas-Lado M, Monserrat L, et al. Gene mutations in apical hypertrophic cardiomyopathy. Circulation 2005; 112:2805-11.
74. Kubo T, Gimeno JR, Bahl A, et al. Prevalence, clinical significance, and genetic basis of hypertrophic cardiomyopathy with restrictive phenotype. J Am Coll Cardiol 2007;49:2419-26.
75. Klaassen S, Probst S, Oechslin E, et al. Mutations in sarcomere protein genes in left ventricular noncompaction. Circulation 2008;117:2893-901.
76. Maron BJ, Roberts WC, Arad M, et al. Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. JAMA 2009;301:1253-9.
77. Monserrat L, Gimeno-Blanes JR, Marin F, et al. Prevalence of Fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. J Am Coll Cardiol 2007;50:2399-403.
78. Watkins H, Ashrafian H, McKenna WJ. The genetics of hypertrophic cardiomyopathy: Teare redux. Heart 2008;94: 1264-8.
79. Pasotti M, Klersy C, Pilotto A, et al. Long-term outcome and risk stratification in dilated cardiolaminopathies. J Am Coll Cardiol 2008;52:1250-60.
80. Meune C, Van Berlo JH, Anselme F, Bonne G, Pinto YM, Duboc D. Primary prevention of sudden death in patients with lamin A/C gene mutations. N Engl J Med 2006;354:209-10.
81. Watkins H, McKenna WJ, Thierfelder

L, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. N Engl J Med 1995;332:1058-64.
82. Niimura H, Bachinski LL, Sangwatanaroj S, et al. Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. N Engl J Med 1998;338:1248-57.
83. Van Driest SL, Ellsworth EG, Ommen SR, Tajik AJ, Gersh BJ, Ackerman MJ. Prevalence and spectrum of thin filament mutations in an outpatient referral population with hypertrophic cardiomyopathy. Circulation 2003;108:445-51.
84. Blair E, Redwood C, Watkins H. Ascertainment strategies and genotype: phenotype correlations in hypertrophic cardiomyopathy. Circulation 2003;108(4): e24-e25.
85. Blair E, Price SJ, Baty CJ, Ostman-Smith I, Watkins H. Mutations in cis can confound genotype-phenotype correlations in hypertrophic cardiomyopathy. J Med Genet 2001;38:385-8.
86. Ingles J, Doolan A, Chiu C, Seidman J, Seidman C, Semsarian C. Compound and double mutations in patients with hypertrophic cardiomyopathy: implications for genetic testing and counselling. J Med Genet 2005;42(10):e59.
87. Girolami F, Ho CY, Semsarian C, et al. Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations. J Am Coll Cardiol 2010;55:1444-53.
88. Xu T, Yang Z, Vatta M, et al. Compound and digenic heterozygosity contributes to arrhythmogenic right ventricular cardiomyopathy. J Am Coll Cardiol 2010;55:587-97.
89. Dhandapany PS, Sadayappan S, Xue Y, et al. A common MYBPC3 (cardiac myosin binding protein C) variant associated with cardiomyopathies in South Asia. Nat Genet 2009;41:187-91.
90. Andersen PS, Havndrup O, Hougs L, et al. Diagnostic yield, interpretation, and clinical utility of mutation screening of sarcomere encoding genes in Danish hypertrophic cardiomyopathy patients and relatives. Hum Mutat 2009;30:363-70.
91. Olivotto I, Girolami F, Ackerman MJ, et al. Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. Mayo Clin Proc 2008;83:630-8.
92. Matkovich SJ, Van Booven DJ, Hindes A, et al. Cardiac signaling genes exhibit unexpected sequence diversity in sporadic cardiomyopathy, revealing HSPB7 polymorphisms associated with disease. J Clin Invest 2010;120:280-9.
93. Cinquetti R, Badi I, Campione M, et al. Transcriptional deregulation and a missense mutation define ANKRD1 as a candidate gene for total anomalous pulmonary venous return. Hum Mutat 2008; 29:468-74.
94. Duboscq-Bidot L, Charron P, Ruppert V, et al. Mutations in the ANKRD1 gene encoding CARP are responsible for human dilated cardiomyopathy. Eur Heart J 2009;30:2128-36.
95. Maron BJ, Niimura H, Casey SA, et al. Development of left ventricular hypertrophy in adults in hypertrophic cardiomyopathy caused by cardiac myosin-binding protein C gene mutations. J Am Coll Cardiol 2001;38:315-21.
96. van Spaendonck-Zwarts KY, van Tintelen JP, van Veldhuisen DJ, et al. Peripartum cardiomyopathy as a part of familial dilated cardiomyopathy. Circulation 2010; 121:2169-75.
97. Noutsias M, Fechner H, de Jonge H, et al. Human coxsackie-adenovirus receptor is colocalized with integrins alpha(v) beta(3) and alpha(v)beta(5) on the cardiomyocyte sarcolemma and upregulated in dilated cardiomyopathy: implications for cardiotropic viral infections. Circulation 2001;104:275-80.
98. Xiong D, Lee GH, Badorff C, et al. Dystrophin deficiency markedly increases enterovirus-induced cardiomyopathy: a genetic predisposition to viral heart disease. Nat Med 2002;8:872-7.

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