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Harnessing Molecular Genetics for the Diagnosis and Management of Hypertrophic Cardiomyopathy

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Unexplained cardiac hypertrophy, the diagnostic criterion for hypertrophic cardiomyopathy (HCM), occurs in 1 in 500 adults. Insights into the genetic cause and molecular pathophysiology of HCM are reshaping clinical paradigms for diagnosis and treatment of this common myocardial disorder. Human genetic studies have established that dominant mutations in the proteins that comprise the contractile apparatus (the sarcomere) cause HCM. With the current availability of clinical gene-based diagnostics, pathogenic mutations in affected patients can be defined, which can suggest a clinical course and allow definitive preclinical identification of family members at risk for HCM. Genetic discoveries have also fostered mechanistic investigations in model organisms that are engineered to carry human HCM mutations. Novel therapeutic targets have emerged from these fundamental studies and are currently under clinical assessment in humans. The combination of contemporary gene-based diagnosis with new strategies to attenuate disease development and progression is changing the natural history of life-long cardiac symptoms, arrhythmias, and heart failure from HCM.

Hypertrophic cardiomyopathy (HCM) is a heritable disorder characterized by increased heart mass and abnormal diastolic function. The remarkable anatomic features of HCM (Figure 1) were first recognized more than 200 years ago, but the contemporary understanding of this disorder is based on integrated investigations into its histopathology, myocardial hemodynamics, and genetics (1–4).

Recognition of familial clustering for HCM allowed the application of genetic strategies that ultimately defined its molecular causes. Investigators have identified 13 genes and more than 900 unique mutations (5–7), which makes clinical genetic testing for HCM possible. Molecular diagnosis discriminates between HCM and other hypertrophic heart disorders with distinct clinical courses and thus provides information about expected disease course.

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Genetic testing also definitively identifies family members who have inherited a mutation and are at high risk for HCM. Finally, knowledge of genetic causes of HCM has fueled mechanistic insights and therapeutic targets. Translation of these into clinical trials is underway. Here, we consider how molecular genetic discoveries provide new opportunities for predictive and personalized medicine in HCM.

HCM Pathology

Left ventricular hypertrophy (8), the anatomic hallmark of HCM (Figure 1, A to C), varies considerably in extent and distribution among affected persons. The disorder usually causes asymmetric hypertrophy that particularly involves the interventricular septum, but hypertrophy can also be limited to the apex or be widespread throughout the ventricle (3,8). Histopathologic manifestations of HCM include enlarged myocytes with prominent nuclei, disorganized cell-to-cell contacts (myocyte disarray), and increased fibrosis (Figure 1, D to F) that can be interstitial and diffuse as well as focal (4). These anatomic findings contribute to diastolic dysfunction in HCM, which propels atrial remodeling and predisposes affected persons to arrhythmias (9).

Genetics causes of HCM

Most HCM is caused by a dominant gene mutation. One half of all offspring of affected persons will inherit the HCM mutation (Figure 2) and are at very high risk for the disease. Young carriers of the mutation often have no clinical manifestations, and symptoms evolve insidiously as hypertrophic remodeling occurs with aging (3). Because of the age-related penetrance of HCM, absence of disease at 1 evaluation cannot exclude subsequent development. Serial clinical evaluations or genetic testing of family members at risk for HCM are therefore important.

Mutations in 13 unique genes cause HCM (Table) (5) and account for approximately 75% of familial HCM (10). Mutations predominantly occur in genes that encode proteins within the sarcomere (7), the contractile unit of myocytes. These mutations usually affect thick and thin sarcomere filament proteins (11) and less commonly affect sarcomere-associated or Z-disc proteins that modulate or transmit sarcomere forces.

Most HCM mutations are “private,” or unique to a patient and his or her family members. Unrelated HCM families usually have different mutations (12), although a few are shared among specific populations. For example, 4% of persons with South Asian ancestry carry a common HCM mutation (13). However, defining the causal mutation in any given patient usually requires detailed sequencing of all HCM genes (14). This daunting technical challenge is met by newly developed DNA sequencing strategies, and genetic diagnosis of HCM is now clinically available at several certified molecular diagnostic laboratories, which are listed at the National Center for Biotechnology Information GeneTests website, www.genetests.org. Defining the pathogenic mutation in an affected family member allows subsequent definition and low-cost assessment of the mutation status in all relatives. Carriers of the mutation are at high risk for HCM (Figure 2), whereas mutation-negative persons are at no risk for the disease and do not need serial clinical evaluations.

Linking Genotype with Clinical Manifestations in HCM

The age at which signs and symptoms of HCM present is influenced by the causal gene mutation (5,7). Clinical manifestations of HCM caused by β -myosin heavy chain or troponin T mutations typically begin near adolescence (12,15). In contrast, myosin-binding protein C mutations, particularly those that foreshorten the protein, trigger HCM after a protracted period of clinical quiescence that may extend into middle age (16,17).

Different genetic causes of HCM do not correlate with the extent or distribution of hypertrophy, with a few notable exceptions. Troponin T mutations generally cause substantially less hypertrophy than other HCM genes, and gene-based diagnosis is particularly helpful in determining the status of persons at risk for inheriting these mutations (15). The different morphologic patterns of hypertrophy in HCM (asymmetric, concentric, or apical) do not relate to underlying genotype, with the exception of a unique actin mutation that uniformly produces apical hypertrophy (18). The factors that account for morphologic patterning remain unknown.

The natural history of HCM includes progressive dyspnea and angina. These symptoms reflect a poorly compliant myocardium, increased ventricular diastolic pressure, and impaired diastolic filling (3,8,19,20). Myocardial ischemia occurs in HCM despite normal coronary artery anatomy, due in part to intramural vascular remodeling and impaired myocardial relaxation that impedes diastolic blood flow (21). Approximately 5% of patients with HCM develop profound diastolic dysfunction that is ultimately accompanied by diminished systolic performance (22).

Patients with a defined sarcomere protein gene mutation have substantially worse cardiac outcomes than those in whom the cause of HCM remains unknown (23). In addition, particular HCM mutations (24), compound mutations (25), and a mutation that is prevalent among patients with Indian ancestry (13) have been shown to substantially increase the propensity for heart failure.

Arrhythmias in HCM

Cardiac arrhythmias are a common and potentially life-threatening complication of HCM. Supraventricular arrhythmias markedly increase with disease duration, and 25% of patients ultimately develop atrial fibrillation, which contributes to both morbidity and premature death due to thromboembolic events (3,9). Ventricular arrhythmias can cause sudden death in HCM (26,27), and the efficacy of implanted cardioverter defibrillators in terminating these life-threatening arrhythmias (28) makes proactive identification of patients with HCM who are at high risk for sudden death an important but difficult clinical issue. Traditional clinical parameters that define patients at increased risk for sudden death include syncope, substantial left ventricular outflow tract gradient (≥ 50 mm Hg), massive left ventricular hypertrophy (wall thickness ≥ 30 mm), exercise-induced hypotension, and sudden deaths in first-degree relatives (20). This last parameter is noteworthy, because all affected members of a family share an identical genetic mutation that causes HCM. The predictive value of sudden death in relatives implies that some HCM mutations convey greater risk for these events. This hypothesis is being studied by the compilation of sudden death events that occur in patients with different HCM mutations (24,29–31) and by analysis of models of HCM.

Mechanistic Insights from Models of HCM

Knowledge of the genetic causes of HCM has allowed the development of models that carry human mutations (32–36). Studies of these models demonstrate that HCM mutations produce stable proteins that are incorporated into the sarcomere along with the normal protein derived from the nonmutated allele. The biophysical properties of sarcomeres that contain mutant β -myosin heavy chains indicate that HCM mutations enhance contractile properties. Myosin mutations increase force generation, adenosine triphosphate (ATP) hydrolysis, and actin–myosin sliding velocity (37,38). Sarcomeres that contain mutant troponin T proteins, such as HCM myosin mutations, also increase these properties (39,40). Together, these data indicate that the hypertrophy that characterizes HCM is not a compensatory response to diminished contractile function. However, models of HCM also

show delayed myocardial relaxation that occurs before the onset of hypertrophy (41). Diastolic dysfunction therefore seems to be a direct consequence of HCM mutations.

Hearts from models of HCM progressively accumulate myocardial fibrosis in the same manner as human patients (32–36). These models have proven useful for determining whether reducing myocardial fibrosis improves the intrinsic relaxation deficits produced by HCM mutations. In one study (42), an angiotensin II type 1 receptor inhibitor (candesartan) significantly reduced myocardial fibrosis, collagen deposition, and hypertrophy in mice with HCM compared with placebo ($P < 0.001$). A second protocol examined *N*-acetylcysteine (mycomyst), which protects against oxidative stress, and demonstrated reduced HCM pathology (43). Assessment of these therapeutic strategies in human HCM is underway.

Altered Calcium Homeostasis in HCM

A critical mechanistic question in HCM is why mutations that increase biophysical properties of sarcomere proteins cause hypertrophy. Although we do not completely understand the process, biochemical studies hint that calcium signaling is a critical trigger of hypertrophy. Studies of mice that carry a human mutation in myosin heavy chains (44), troponin T (45), or regulatory myosin light chains (46) revealed abnormal calcium cycling in myocytes before overt histopathologic changes occurred in the myocardium. Abnormal calcium cycling is also a prominent feature of other cardiomyopathies (47,48).

Calcium cycling (Figure 3) is essential for cardiac function. During depolarization, calcium enters myocytes through the voltage-gated L-type Ca^{2+} channels on the cell membrane and triggers cardiac contraction. In response, the sarcoplasmic reticulum releases calcium through the cardiac ryanodine receptor (RyR2), a process termed calcium-induced calcium release. Increased cytosolic levels produce a shift in calcium from troponin I to troponin C, which releases the inhibition of actin–myosin ATPase activity. Hydrolysis of adenosine triphosphate (ATP) supplies energy that enables myosin to slide along actin and transmit force to the sarcolemma and extracellular matrix. With completion of contraction, calcium recycles back to the sarcoplasmic reticulum by means of an ATPase-dependent pump and is also extruded outside of myocytes by means of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger.

Myocytes from the hearts of patients with HCM have lower levels of calcium in the sarcoplasmic reticulum (Figure 3) and altered levels or activities of key calcium-binding proteins, including ryanodine receptors, calsequestrin, triadin, junctin, cardiac sarcoplasmic reticular Ca^{2+} –ATPase, and phospholamban (44–46). These biochemical changes may promote diastolic dysfunction in HCM. In addition, abnormal calcium cycling increases the probability for after-depolarization in myocytes, which is a cellular substrate for cardiac arrhythmias (49).

Because calcium abnormalities predate hypertrophic remodeling in HCM models, research has addressed whether early intervention with pharmacologic agents that normalized calcium levels might reduce the emergence of hypertrophic remodeling. To test this hypothesis, mice engineered to carry a human HCM mutation in myosin were treated with diltiazem, an L-type calcium channel blocker. With early administration of the drug, levels of calcium-binding proteins and sarcoplasmic reticulum calcium content were normalized. Continued treatment significantly attenuated the emergence of hypertrophy and development of hemodynamic abnormalities ($P < 0.001$) (50). These preclinical studies raise the potential for identifying persons at risk for HCM through gene-based diagnosis, and early pharmacologic interventions may delay or attenuate development of disease.

Arrhythmias have also been studied in mice with HCM. Electrophysiologic tests of mice with mutations associated with high risk in humans show more ventricular arrhythmias than

those in mice with low-risk HCM mutations (30,34), which implies that specific HCM mutations may increase sudden death risk. Other components of HCM pathophysiology that contribute to life-threatening arrhythmias remain incompletely understood. Because postmortem examination of victims of sudden death sometimes reveals striking amounts of myocardial fibrosis (51,52), fibrosis has been proposed as a contributor to arrhythmias (53,54). Although rigorous analysis of this hypothesis is difficult in human patients, the relevance of fibrosis, disarray, and cardiac hypertrophy to arrhythmia susceptibility has been assessed in mice that carry human HCM mutations. Only the amount of hypertrophy, not the fibrotic load or myocyte disarray, was found to correlate with inducible ventricular arrhythmia (55). This both confirms the observation that marked hypertrophy increases risk for sudden death in HCM and implies that strategies that limit hypertrophy may also reduce the risk for sudden death.

Established and Emerging Medical Strategies for HCM

Clinical management of HCM is focused on relief of symptoms. β -adrenergic inhibitors and L-type calcium channel blockers lower heart rate, prolong diastolic filling, diminish left ventricular outflow tract gradients, and improve HCM symptoms (3,8,56). In patients with substantial outflow tract obstruction, surgical septal myectomy (57–59) or percutaneous alcohol ablation (60–62) relieve symptoms and may also reduce sudden death risk. Although effective, these traditional management strategies apply to clinically overt HCM. Newer paradigms have emerged on the basis of pathophysiologic studies of models of HCM and the opportunity for disease prevention in persons with inherited HCM mutations.

Because angiotensin blockade decreased interstitial fibrosis and collagen deposition in mice with HCM, clinical studies have assessed angiotensin-1 receptor antagonists in nonobstructive HCM in humans (63,64). Reductions in hypertrophy that range from 6% to 15% have been reported, with the greatest benefit occurring in patients with myosin mutations (64). If replicated, this result may indicate that knowledge of the genetic cause of HCM may help direct treatment strategies.

Other novel strategies aim to prevent development of HCM and are predicated upon gene-based diagnosis. Within families, genetic testing typically defines mutation carriers with established HCM and other, usually younger, asymptomatic mutation carriers without hypertrophy (Figure 2). Detailed clinical investigation of preclinical carriers with different mutations (65) indicate electrocardiographic abnormalities (QRS widening and T-wave inversion), as well as substantially lower diastolic relaxation properties (assessed by Doppler-tissue-imaging) ($P < 0.001$) and substantially higher ejection fractions ($P < 0.001$) than are seen in age-matched relatives without mutations. These observations indicate that hypertrophy is not the earliest manifestation of HCM.

The identification of prehypertrophic manifestations of HCM mutations raises the question of whether early disruption of the signals triggered by these mutations might attenuate ventricular remodeling and reduce symptoms. Clinical studies aim to answer this by interventions that target sarcomere mutation carriers without hypertrophy. The first predictive human genetics and prevention trial in HCM, “Treatment of Preclinical Hypertrophic Cardiomyopathy With Diltiazem” (<http://clinicaltrials.gov/ct2/show/record/NCT00319982>), illustrates this strategy. This single-center trial, which is based on studies of models of HCM in which early restoration of calcium homeostasis limited disease development, will use diltiazem to normalize calcium cycling. A pilot cohort (50 prehypertrophic patients with any sarcomere mutation identified by gene-based diagnostics) treated with diltiazem or placebo will be analyzed for signs of the emergence of HCM

(electrocardiographic abnormalities, diastolic dysfunction, and hypertrophy). Results are expected in 2013.

With the ongoing efforts to discover signaling molecules that are activated by sarcomere gene mutations in model organisms, other targets for new HCM therapies should be anticipated. Combined with gene-based diagnosis of HCM for patients at risk, these fundamental mechanistic insights may someday allow strategies to prevent the development of this disease.

Additional Genetic Causes of Cardiac Hypertrophy

Although they are less common than sarcomere protein gene mutations, other human gene mutations can cause hypertrophy that mimics HCM (Table). Recognition of these is important because of their distinct manifestations and outcomes that affect clinical care. For example, mutations in *PRKAG2*, which encodes the $\gamma 2$ subunit of adenosine monophosphate-dependent protein kinase (66–69), produce hypertrophy and progressive electrophysiologic abnormalities (ventricular pre-excitation followed by conduction system disease) that necessitate pacemaker implantation. Mutations in the X-linked gene *LAMP2* (66), which encodes lysosome-associated membrane protein-2, cause massive hypertrophy with malignant ventricular arrhythmias and rapidly progressive heart failure, primarily in young males (70). Genetic testing distinguishes between HCM and these other conditions, allows interventions to limit adverse events, and enables family counseling.

Final Perspectives

Mutations in sarcomere genes are common causes of HCM. Discovering these molecular causes provides the basis for clinical genetic diagnostics, information that definitely establishes the risk for HCM in family members. For the subset of HCM mutations with defined clinical manifestations, genetic information can assist in management strategies. Through analyses of fundamental pathogenic mechanisms in HCM models engineered to carry human mutations, new approaches to prevent development of HCM have emerged. Translation of research into clinical trials in humans is underway. The integration of genetics to predict HCM and preemptive strategies to prevent HCM represents a new paradigm for personalized genetic medicine.

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References

1. Brock R. Functional obstruction of the left ventricle; acquired aortic subvalvar stenosis. *Guys Hosp Rep.* 1957; 106:221–238. [PMID: 13480570]. [PubMed: 13480570]
2. Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J.* 1958; 20:1–8. [PMID: 13499764]. [PubMed: 13499764]
3. Maron BJ. Hypertrophic cardiomyopathy: a systematic review. *JAMA.* 2002; 287:1308–1320. [PMID: 11886323]. [PubMed: 11886323]
4. Seidman JG, Seidman C. The genetic basis for cardiomyopathy: from mutation identification to mechanistic paradigms. *Cell.* 2001; 104:557–567. [PMID: 11239412]. [PubMed: 11239412]
5. Alcalai R, Seidman JG, Seidman CE. Genetic basis of hypertrophic cardiomyopathy: from bench to the clinics. *J Cardiovasc Electrophysiol.* 2008; 19:104–110. [PMID: 17916152]. [PubMed: 17916152]

6. Ahmad F, Seidman JG, Seidman CE. The genetic basis for cardiac remodeling. *Annu Rev Genomics Hum Genet.* 2005; 6:185–216. [PMID: 16124859]. [PubMed: 16124859]
7. Keren A, Syrris P, McKenna WJ. Hypertrophic cardiomyopathy: the genetic determinant of clinical disease expression. *Nat Clin Pract Cardiovasc Med.* 2008;5:158–5168. [PMID: 18227814].
8. Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. *Lancet.* 2004; 363:1881–1891. [PMID: 15183628]. [PubMed: 15183628]
9. Kubo T, Kitaoka H, Okawa M, Hirota T, Hayato K, Yamasaki N, et al. Clinical impact of atrial fibrillation in patients with hypertrophic cardiomyopathy. Results from Kochi RYOMA Study. *Circ J.* 2009; 73:1599–1605. [PMID: 19590139]. [PubMed: 19590139]
10. Morita H, Rehm HL, Menesses A, McDonough B, Roberts AE, Kucherlapati R, et al. Shared genetic causes of cardiac hypertrophy in children and adults. *N Engl J Med.* 2008; 358:1899–1908. [PMID: 18403758]. [PubMed: 18403758]
11. Marian AJ. Genetic determinants of cardiac hypertrophy. *Curr Opin Cardiol.* 2008; 23:199–205. [PMID: 18382207]. [PubMed: 18382207]
12. Watkins H, Ashrafian H, McKenna WJ. The genetics of hypertrophic cardiomyopathy: Teare redux. *Heart.* 2008; 94:1264–1268. [PMID: 18653576]. [PubMed: 18653576]
13. 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(2):187–191. [PubMed: 19151713]
14. Hershberger RE, Cowan J, Morales A, Siegfried JD. Progress with genetic cardiomyopathies: Screening, counseling, and testing in dilated, hypertrophic, and arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circ Heart Fail.* 2009; 2:253–261. [19808347]. [PubMed: 19808347]
15. Watkins H, McKenna WJ, Thierfelder L, Suk HJ, Anan R, O'Donoghue A, et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *N Engl J Med.* 1995; 332:1058–1064. [PMID: 7898523]. [PubMed: 7898523]
16. Niimura H, Bachinski LL, Sangwatanaroj S, Watkins H, Chudley AE, McKenna W, et al. Mutations in the gene for cardiac myosin-binding protein C and late-onset familial hypertrophic cardiomyopathy. *N Engl J Med.* 1998; 338:1248–1257. [PMID: 9562578]. [PubMed: 9562578]
17. Niimura H, Patton KK, McKenna WJ, Soultis J, Maron BJ, Seidman JG, et al. Sarcomere protein gene mutations in hypertrophic cardiomyopathy of the elderly. *Circulation.* 2002; 105:446–451. [PMID: 11815426]. [PubMed: 11815426]
18. Arad M, Penas-Lado M, Monserrat L, Maron BJ, Sherrid M, Ho CY, et al. Gene mutations in apical hypertrophic cardiomyopathy. *Circulation.* 2005; 112:2805–2811. [PMID: 16267253]. [PubMed: 16267253]
19. Spirito P, Seidman CE, McKenna WJ, Maron BJ. The management of hypertrophic cardiomyopathy. *N Engl J Med.* 1997; 336:775–785. [PMID: 9052657]. [PubMed: 9052657]
20. Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, et al. Task Force on Clinical Expert Consensus Documents. American College of Cardiology. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol.* 2003; 42:1687–1713. [PMID: 14607462]. [PubMed: 14607462]
21. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med.* 2007; 356:830–840. [PMID: 17314342]. [PubMed: 17314342]
22. Harris KM, Spirito P, Maron MS, Zenovich AG, Formisano F, Lesser JR, et al. Prevalence, clinical profile, and significance of left ventricular remodeling in the end-stage phase of hypertrophic cardiomyopathy. *Circulation.* 2006; 114:216–225. [PMID: 16831987]. [PubMed: 16831987]
23. Olivetto I, Girolami F, Ackerman MJ, Nistri S, Bos JM, Zachara E, et al. Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy. *Mayo Clin Proc.* 2008; 83:630–638. [PMID: 18533079]. [PubMed: 18533079]
24. Anan R, Greve G, Thierfelder L, Watkins H, McKenna WJ, Solomon S, et al. Prognostic implications of novel beta cardiac myosin heavy chain gene mutations that cause familial

- hypertrophic cardiomyopathy. *J Clin Invest.* 1994; 93:280–285. [PMID: 8282798]. [PubMed: 8282798]
25. 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 [Letter]. *J Med Genet.* 2005; 42:e59. [PMID: 16199542]. [PubMed: 16199542]
 26. Maron BJ. Sudden death in young athletes. *N Engl J Med.* 2003; 349:1064–1075. [PMID: 12968091]. [PubMed: 12968091]
 27. Elliott P, Spirito P. Prevention of hypertrophic cardiomyopathy-related deaths: theory and practice. *Heart.* 2008; 94:1269–1275. [PMID: 18653582]. [PubMed: 18653582]
 28. Maron BJ, Shen WK, Link MS, Epstein AE, Almquist AK, Daubert JP, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med.* 2000; 342:365–373. [PMID: 10666426]. [PubMed: 10666426]
 29. Watkins H, Rosenzweig A, Hwang DS, Levi T, McKenna W, Seidman CE, et al. Characteristics and prognostic implications of myosin missense mutations in familial hypertrophic cardiomyopathy. *N Engl J Med.* 1992; 326:1108–1114. [PMID: 1552912]. [PubMed: 1552912]
 30. Woo A, Rakowski H, Liew JC, Zhao MS, Liew CC, Parker TG, et al. Mutations of the beta myosin heavy chain gene in hypertrophic cardiomyopathy: critical functional sites determine prognosis. *Heart.* 2003; 89:1179–1185. [PMID: 12975413]. [PubMed: 12975413]
 31. Wang S, Zou Y, Fu C, Xu X, Wang J, Song L, et al. Worse prognosis with gene mutations of beta-myosin heavy chain than myosin-binding protein C in Chinese patients with hypertrophic cardiomyopathy. *Clin Cardiol.* 2008; 31:114–118. [PMID: 18383048]. [PubMed: 18383048]
 32. Geisterfer-Lowrance AA, Christe M, Conner DA, Ingwall JS, Schoen FJ, Seidman CE, et al. A mouse model of familial hypertrophic cardiomyopathy. *Science.* 1996; 272:731–734. [PMID: 8614836]. [PubMed: 8614836]
 33. Marian AJ, Wu Y, Lim DS, McCluggage M, Youker K, Yu QT, et al. A transgenic rabbit model for human hypertrophic cardiomyopathy. *J Clin Invest.* 1999; 104:1683–1692. [PMID: 10606622]. [PubMed: 10606622]
 34. McConnell BK, Fatkin D, Semsarian C, Jones KA, Georgakopoulos D, Maguire CT, et al. Comparison of two murine models of familial hypertrophic cardiomyopathy. *Circ Res.* 2001; 88:383–389. [PMID: 11230104]. [PubMed: 11230104]
 35. Tardiff JC, Hewett TE, Palmer BM, Olsson C, Factor SM, Moore RL, et al. Cardiac troponin T mutations result in allele-specific phenotypes in a mouse model for hypertrophic cardiomyopathy. *J Clin Invest.* 1999; 104:469–481. [PMID: 10449439]. [PubMed: 10449439]
 36. Yang Q, Sanbe A, Osinska H, Hewett TE, Klevitsky R, Robbins J. A mouse model of myosin binding protein C human familial hypertrophic cardiomyopathy. *J Clin Invest.* 1998; 102:1292–1300. [PMID: 9769321]. [PubMed: 9769321]
 37. Palmiter KA, Tyska MJ, Haeberle JR, Alpert NR, Fananapazir L, Warshaw DM. R403Q and L908V mutant beta-cardiac myosin from patients with familial hypertrophic cardiomyopathy exhibit enhanced mechanical performance at the single molecule level. *J Muscle Res Cell Motil.* 2000; 21:609–620. [PMID: 11227787]. [PubMed: 11227787]
 38. Debold EP, Schmitt JP, Patlak JB, Beck SE, Moore JR, Seidman JG, 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. [PMID: 17351073]. [PubMed: 17351073]
 39. Miller T, Szczesna D, Housmans PR, Zhao J, de Freitas F, Gomes AV, et al. Abnormal contractile function in transgenic mice expressing a familial hypertrophic cardiomyopathy-linked troponin T (I79N) mutation. *J Biol Chem.* 2001; 276:3743–3755. [PMID: 11060294]. [PubMed: 11060294]
 40. Chandra M, Tschirgi ML, Tardiff JC. Increase in tension-dependent ATP consumption induced by cardiac troponin T mutation. *Am J Physiol Heart Circ Physiol.* 2005; 289:H2112–H2119. [PMID: 15994854]. [PubMed: 15994854]
 41. Georgakopoulos D, Christe ME, Giewat M, Seidman CM, Seidman JG, Kass DA. The pathogenesis of familial hypertrophic cardiomyopathy: early and evolving effects from an alpha-

- cardiac myosin heavy chain missense mutation. *Nat Med.* 1999; 5:327–330. [PMID: 10086390]. [PubMed: 10086390]
42. Lim DS, Lutucuta S, Bachireddy P, Youker K, Evans A, Entman M, et al. Angiotensin II blockade reverses myocardial fibrosis in a transgenic mouse model of human hypertrophic cardiomyopathy. *Circulation.* 2001; 103:789–791. [PMID: 11171784]. [PubMed: 11171784]
 43. Lombardi R, Rodriguez G, Chen SN, Ripplinger CM, Li W, Chen J, et al. Resolution of established cardiac hypertrophy and fibrosis and prevention of systolic dysfunction in a transgenic rabbit model of human cardiomyopathy through thiol-sensitive mechanisms. *Circulation.* 2009; 119:1398–1407. [PMID: 19255346]. [PubMed: 19255346]
 44. Fatkin D, McConnell BK, Mudd JO, Semsarian C, Moskowitz IG, Schoen FJ, et al. An abnormal Ca(2+) response in mutant sarcomere protein-mediated familial hypertrophic cardiomyopathy. *J Clin Invest.* 2000; 106:1351–1359. [PMID: 11104788]. [PubMed: 11104788]
 45. Haim TE, Dowell C, Diamanti T, Scheuer J, Tardiff JC. Independent FHC-related cardiac troponin T mutations exhibit specific alterations in myocellular contractility and calcium kinetics. *J Mol Cell Cardiol.* 2007; 42:1098–1110. [PMID: 17490679]. [PubMed: 17490679]
 46. Szczesna-Cordary D, Jones M, Moore JR, Watt J, Kerrick WG, Xu Y, et al. Myosin regulatory light chain E22K mutation results in decreased cardiac intracellular calcium and force transients. *FASEB J.* 2007; 21:3974–3985. [PMID: 17606808]. [PubMed: 17606808]
 47. Minamisawa S, Sato Y, Cho MC. Calcium cycling proteins in heart failure, cardiomyopathy and arrhythmias. *Exp Mol Med.* 2004; 36:193–203. [PMID: 15272230]. [PubMed: 15272230]
 48. Yano M, Ikeda Y, Matsuzaki M. Altered intracellular Ca²⁺ handling in heart failure. *J Clin Invest.* 2005; 115:556–564. [PMID: 15765137]. [PubMed: 15765137]
 49. Baudenbacher F, Schober T, Pinto JR, Sidorov VY, Hilliard F, Solaro RJ, et al. Myofilament Ca²⁺ sensitization causes susceptibility to cardiac arrhythmia in mice. *J Clin Invest.* 2008; 118:3893–3903. [PMID: 19033660]. [PubMed: 19033660]
 50. Semsarian C, Ahmad I, Giewat M, Georgakopoulos D, Schmitt JP, McConnell BK, et al. The L-type calcium channel inhibitor diltiazem prevents cardiomyopathy in a mouse model. *J Clin Invest.* 2002; 109:1013–1020. [PMID: 11956238]. [PubMed: 11956238]
 51. Varnava AM, Elliott PM, Baboonian C, Davison F, Davies MJ, McKenna WJ. Hypertrophic cardiomyopathy: histopathological features of sudden death in cardiac troponin T disease. *Circulation.* 2001; 104:1380–1384. [PMID: 11560853]. [PubMed: 11560853]
 52. Varnava AM, Elliott PM, Mahon N, Davies MJ, McKenna WJ. Relation between myocyte disarray and outcome in hypertrophic cardiomyopathy. *Am J Cardiol.* 2001; 88:275–279. [PMID: 11472707]. [PubMed: 11472707]
 53. Oka K, Tsujino T, Nakao S, Lee-Kawabata M, Ezumi A, Masai M, et al. Symptomatic ventricular tachyarrhythmia is associated with delayed gadolinium enhancement in cardiac magnetic resonance imaging and with elevated plasma brain natriuretic peptide level in hypertrophic cardiomyopathy. *J Cardiol.* 2008; 52:146–153. [PMID: 18922389]. [PubMed: 18922389]
 54. Adabag AS, Maron BJ, Appelbaum E, Harrigan CJ, Burows JL, Gibson CM, et al. Occurrence and frequency of arrhythmias in hypertrophic cardiomyopathy in relation to delayed enhancement on cardiovascular magnetic resonance. *J Am Coll Cardiol.* 2008; 51:1369–1374. [PMID: 18387438]. [PubMed: 18387438]
 55. Wolf CM, Moskowitz IP, Arno S, Branco DM, Semsarian C, Bernstein SA, et al. Somatic events modify hypertrophic cardiomyopathy pathology and link hypertrophy to arrhythmia. *Proc Natl Acad Sci U S A.* 2005; 102:18123–18128. [PMID: 16332958]. [PubMed: 16332958]
 56. Spirito P, Autore C. Management of hypertrophic cardiomyopathy. *BMJ.* 2006; 332:1251–1255. [PMID: 16735335]. [PubMed: 16735335]
 57. Dearani JA, Danielson GK. Septal myectomy for obstructive hypertrophic cardiomyopathy. *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu.* 2005; 86–91. [PMID: 15818363]. [PubMed: 15818363]
 58. Nishimura RA, Holmes DR Jr. Clinical practice. Hypertrophic obstructive cardiomyopathy. *N Engl J Med.* 2004; 350:1320–1327. [PMID: 15044643]. [PubMed: 15044643]

59. Ommen SR, Shah PM, Tajik AJ. Left ventricular outflow tract obstruction in hypertrophic cardiomyopathy: past, present and future. *Heart*. 2008; 94:1276–1281. [PMID: 18653577]. [PubMed: 18653577]
60. Faber L, Seggewiss H, Gleichmann U. Percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy: results with respect to intraprocedural myocardial contrast echocardiography. *Circulation*. 1998; 98:2415–2421. [PMID: 9832486]. [PubMed: 9832486]
61. Fernandes VL, Nielsen C, Nagueh SF, Herrin AE, Slifka C, Franklin J, et al. Follow-up of alcohol septal ablation for symptomatic hypertrophic obstructive cardiomyopathy the Baylor and Medical University of South Carolina experience 1996 to 2007. *JACC Cardiovasc Interv*. 2008; 1:561–570. [PMID: 19463359]. [PubMed: 19463359]
62. Kwon DH, Kapadia SR, Tuzcu EM, Halley CM, Gorodeski EZ, Curtin RJ, et al. Long-term outcomes in high-risk symptomatic patients with hypertrophic cardiomyopathy undergoing alcohol septal ablation. *JACC Cardiovasc Interv*. 2008; 1:432–438. [PMID: 19463341]. [PubMed: 19463341]
63. Yamazaki T, Suzuki J, Shimamoto R, Tsuji T, Ohmoto-Sekine Y, Ohtomo K, et al. A new therapeutic strategy for hypertrophic nonobstructive cardiomyopathy in humans. A randomized and prospective study with an Angiotensin II receptor blocker. *Int Heart J*. 2007; 48:715–724. [PMID: 18160763]. [PubMed: 18160763]
64. Penicka M, Gregor P, Kerekes R, Marek D, Curila K, Krupicka J. Candesartan use in Hypertrophic And Non-obstructive Cardiomyopathy Estate (CHANCE) Study Investigators. The effects of candesartan on left ventricular hypertrophy and function in nonobstructive hypertrophic cardiomyopathy: a pilot, randomized study. *J Mol Diagn*. 2009; 11:35–41. [PMID: 19074594]. [PubMed: 19074594]
65. Ho CY, Sweitzer NK, McDonough B, Maron BJ, Casey SA, Seidman JG, et al. Assessment of diastolic function with Doppler tissue imaging to predict genotype in preclinical hypertrophic cardiomyopathy. *Circulation*. 2002; 105:2992–2997. [PMID: 12081993]. [PubMed: 12081993]
66. Arad M, Maron BJ, Gorham JM, Johnson WH Jr, Saul JP, Perez-Atayde AR, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. *N Engl J Med*. 2005; 352:362–372. [PMID: 15673802]. [PubMed: 15673802]
67. Arad M, Benson DW, Perez-Atayde AR, McKenna WJ, Sparks EA, Kanter RJ, et al. Constitutively active AMP kinase mutations cause glycogen storage disease mimicking hypertrophic cardiomyopathy. *J Clin Invest*. 2002; 109:357–362. [PMID: 11827995]. [PubMed: 11827995]
68. Blair E, Redwood C, Ashrafian H, Oliveira M, Broxholme J, Kerr B, 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; 10:1215–1220. [PMID: 11371514]. [PubMed: 11371514]
69. Gollob MH, Green MS, Tang AS, Gollob T, Karibe A, Ali Hassan AS, et al. Identification of a gene responsible for familial Wolff-Parkinson-White syndrome. *N Engl J Med*. 2001; 344:1823–1831. [PMID: 11407343]. [PubMed: 11407343]
70. Maron BJ, Roberts WC, Arad M, Haas TS, Spirito P, Wright GB, et al. Clinical outcome and phenotypic expression in LAMP2 cardiomyopathy. *JAMA*. 2009; 301:1253–1259. [PMID: 19318653]. [PubMed: 19318653]

Figure 1. Remodeling in hypertrophic cardiomyopathy (*HCM*). The mass of the normal myocardium (*A*) is increased in *HCM* because of ventricular hypertrophy, which can be asymmetric (*B*), concentric (*C*), or focal (not shown). Diastolic dysfunction in *HCM* leads to atrial enlargement and increases risk for atrial clots (*C*), an important cause of thromboembolic events in *HCM*. The normal myocyte histology (*D*) is perturbed in *HCM*, with marked enlargement and disarray of myocytes (*E*; hematoxylin and eosin staining). Masson trichrome staining (*F*) reveals increased amounts of interstitial fibrosis (blue).

Figure 2.

Pedigree analysis of a family with HCM reveals autosomal dominant inheritance and age-related penetrance. Symbols denote sex (square, male; circle, female) and clinical status (solid, HCM; open, unaffected; slashed, deceased; gray, status unknown). Analyses of the DNA of sarcomere genes (see Table) identified a causal mutation in the β -myosin heavy-chain gene in the proband (arrow), which allowed gene-based diagnosis of all family members. The same mutation was found in adults with clinical evidence of HCM (+) but was absent in unaffected adults (−). Note that 5 children have pre-clinical HCM: They carry the β -myosin heavy-chain mutation but have no evidence of disease.

Figure 3.

HCM remodeling pathways. Ca^{2+} enters myocyte through the voltage-gated L-type Ca^{2+} channel and triggers Ca^{2+} -induced Ca^{2+} release (CICR). Ca^{2+} is released from the sarcoplasmic reticulum (SR) through the RyR2 complexes that are composed of cardiac ryanodine receptor, calsequestrin, junctin, triadin, and sorcin. When one contractile protein in the sarcomere carries an HCM mutation (red star), sarcomere contractility increases and relaxation diminishes. This results in abnormal Ca^{2+} cycling with slower Ca^{2+} reuptake of the SR by the Sarco/Endoplasmic Reticulum Ca^{2+} -ATPase (SERCA) pump and reduced Ca^{2+} content in the SR (blue arrow). Abnormal Ca^{2+} cytosolic concentration and mechanical dynamics of the mutant sarcomere stimulate signaling pathways in the nucleus that promote myocyte growth, premature myocyte death, and increased myocardial fibrosis. In model organisms that carry a human HCM mutation, early normalization of Ca^{2+} handling during the preclinical phase of disease attenuated the subsequent development of hypertrophy and fibrosis.

Table 1

Genetic Causes of Cardiac Hypertrophy

Disease	Location	Protein	Gene Symbol	Clinical Features
Hypertrophic Cardiomyopathy	Sarcomere: Thick filament	β -myosin heavy chain	<i>MYH7</i>	Variable hypertrophy
		Myosin-binding protein C	<i>MYBPC3</i>	Prognosis good
		Regulatory myosin light chain	<i>MYL2</i>	Atrial arrhythmias
		Essential myosin light chain	<i>MYL3</i>	↑ with disease duration
	Thin filament	Titin	<i>TTN</i>	Ventricular arrhythmias
		Troponin T	<i>TNNT2</i>	uncommon
		Troponin I	<i>TNNT3</i>	Heart failure uncommon
		α -Tropomyosin	<i>TPM1</i>	
		Actin	<i>ACTC1</i>	
	Z-disc	Muscle LIM protein	<i>CSR3</i>	Variable Hypertrophy + Skeletal myopathy
		Telethonin	<i>TCAP</i>	Variable hypertrophy
		Myozenin 2	<i>MYOZ2</i>	Variable hypertrophy
		Vinculin	<i>VCL</i>	Variable hypertrophy
Metabolic Cardiomyopathy	Cytosol	Adenosine mono-phosphate- activated protein kinase, $\gamma 2$ subunit	<i>PRKAG2</i>	Variable hypertrophy Atrial arrhythmias; Progressive Conduction System Disease
	Lysosome	Lysosome-associated membrane protein-2	<i>LAMP2</i>	Massive hypertrophy Ventricular arrhythmias common
				Heart failure common
	Lysosome	α -Galactosidase A	<i>GLA</i>	Variable hypertrophy Renal disease common