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A Contemporary Approach to Hypertrophic Cardiomyopathy

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A previously healthy 32-year-old female undergoes evaluation after a syncopal episode. Physical examination reveals a systolic ejection murmur. Echocardiography demonstrates a vigorous LV with marked asymmetric septal hypertrophy, systolic anterior motion of the mitral valve, and a 50–mm Hg outflow tract gradient. Family history is notable for unexpected death in 4 paternal family members. She has 2 children (Figure 1A).

The prevalence of unexplained left ventricular hypertrophy (LVH) in the general population is estimated to be 1 in 500.[1,2] Hypertrophic cardiomyopathy (HCM) caused by sarcomere mutations may account for up to 60% of unexplained LVH, making HCM the most common genetic cardiovascular disorder.[3–5] Accurate diagnosis of HCM is important for appropriate management of major HCM comorbidities, including atrial fibrillation, stroke, heart failure, and sudden cardiac death (SCD).[6,7]

Clinical Aspects

HCM typically is diagnosed by unexplained LVH on echocardiography. Age of onset of LVH ranges from early childhood to late adulthood and depends, in part, on the underlying genetic cause.[8,9] Histopathological hallmarks of HCM are myocyte hypertrophy with disarray and increased cardiac fibrosis (Figure 2). Although small amounts of myocyte disarray and fibrosis may be seen in other forms of cardiac disease, the higher degree present in HCM is distinctive. In their absence, the diagnosis of HCM should be questioned.

The spectrum of HCM is broad. Diagnosis of some individuals occurs incidentally during the investigation of asymptomatic murmurs or with family screening; others present with dyspnea, chest pain, or exercise intolerance. Clinical progression can be indolent or more rapidly result in refractory symptoms and heart failure. Medical treatment is first-line therapy, traditionally with either β-blockers or nondihydropyridine calcium channel blockers to facilitate diastolic filling and to reduce intracavitary gradients. The negative inotropic effect of disopyramide also may be beneficial in reducing obstructive physiology.[10] Intracavitary obstruction that is significant ($>$50 mm Hg at rest or $>$100 mm Hg with provocation) and associated with refractory symptoms can be addressed by ethanol septal ablation or surgical myectomy to mechanically reduce outflow tract obstruction. An end-stage phenotype with impaired systolic function and, in some, LVH regression occurs in a small subset of HCM patients. These patients require standard therapy for advanced heart failure, including consideration for cardiac transplantation.

SCD risk is increased in a small subset of patients. In the United States, HCM is the leading cause of SCD in competitive athletes.[7] Assessment of an individual's risk for SCD, although imprecise and controversial, is a critical component of management. The presence of clinical predictors (SCD in first-degree family members, identification of a malignant genotype, unexplained syncope, abnormal blood pressure response to exercise, significant ventricular ectopy on Holter monitoring, and massive [$>$30 mm] LVH) is associated with increased risk and should prompt consideration of implantable cardioverter-defibrillator placement in appropriate individuals.[11] The positive predictive value of these risk factors individually is low, but with $>$2 risk factors, the annual SCD incidence approximates 3% to

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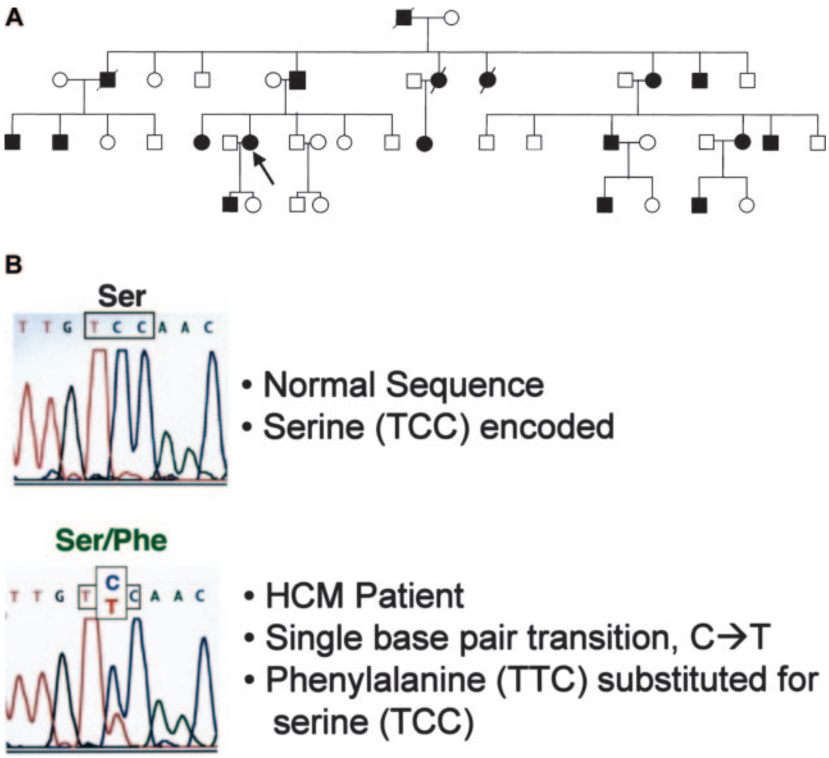

Figure 1. A, HCM is a genetic cardiovascular disease. This family shows autosomal dominant inheritance with ≈50% of the family affected and equal numbers of affected male (■) and female (●) family members. The case patient is indicated by an arrow. Deceased individuals are indicated by a diagonal slash (all died suddenly). B, DNA sequence analysis can identify sarcomere mutations that cause HCM. Top, The normal sequence of a portion of the cardiac troponin T gene is displayed with a triplet codon, TCC, encoding serine present. Bottom, DNA sequence obtained from a patient with HCM. The normal sequence is present on the allele inherited from the unaffected parent; the other allele shows a single base-pair substitution of a thymidine residue for the normal cytosine residue. This triplet codon, TTC, encodes phenylalanine and results in the substitution of a phenylalanine residue for the normal serine residue at amino acid position 179.

5%.[12,13] In contrast, in the absence of any risk factors, individuals are at low risk (annual incidence <1%) and require regular reassessment of risk profile but not intervention.[12,13]

Genetic Aspects

HCM is caused by dominant mutations in genes that encode constituents of the sarcomere (Figure 1). More than 400 individual mutations have been identified in 11 sarcomere genes summarized in Table 1 (and at http://cardiogenomics.med.harvard.edu/mutation-db.tcl),[4,14,15] including cardiac β- and α-myosin heavy chains; cardiac troponins T, I, and C; cardiac myosin binding protein C; α-tropomyosin; actin; the essential and regulatory myosin light chains; and titin. HCM mutations do not show specific racial predilections and are typically "private," ie, unique from family to family. Sarcomere mutations also account for sporadic cases of HCM. Select mutations identified in family studies have yielded some phenotypic correlates. A few families have demonstrated a high incidence of premature death or end-stage heart failure, defining their mutations as potentially "malignant." Others are associated with distinctive HCM morphology; eg, familial inheritance of apical pattern hypertrophy has been associated with mutations in cardiac actin.[16] However, there are numerous exceptions, indicating the importance of genetic modifiers and environment on ultimate phenotypic development. Integration of genotype information with comprehensive clinical evaluation and risk assessment is appropriate and necessary for optimal patient management.

Beyond LVH: Redefining the Phenotype of HCM

Although an HCM gene mutation is present at birth, it may be decades before LVH becomes clinically detectable. With gene-based diagnosis and newer imaging techniques, there is increased recognition that LVH is not the most specific nor sensitive manifestation of HCM. Studies of preclinical individuals with sarcomere gene mutations demonstrate that diastolic abnormalities, detected by Doppler tissue imaging, develop in advance of LVH.[17,18] These results indicate that altered diastolic function is not, as previously considered, a secondary consequence of increased fibrosis and hypertrophy but rather a primary and early manifestation of sarcomere dysfunction resulting from an underlying genetic mutation.

Ongoing research in animal models of HCM has illuminated disease mechanisms. Promising results have been seen with therapeutic strategies to manipulate intracellular calcium handling in prehypertrophic mice,[19] as well as with treatment targeted against myocardial fibrosis (with angiotensin II receptor blockers, aldosterone antagonists, and HMG-CoA reductase inhibitors) in animals with overt HCM.[20–22] Translation into human clinical protocols may be beneficial and presents an exciting new treatment paradigm with a goal of altering phenotype rather than merely palliating symptoms.

New Causes of Inherited Cardiac Hypertrophy

Metabolic Cardiomyopathies: Deficits of Myocardial Energetics

Genetic studies of familial and sporadic unexplained LVH accompanied

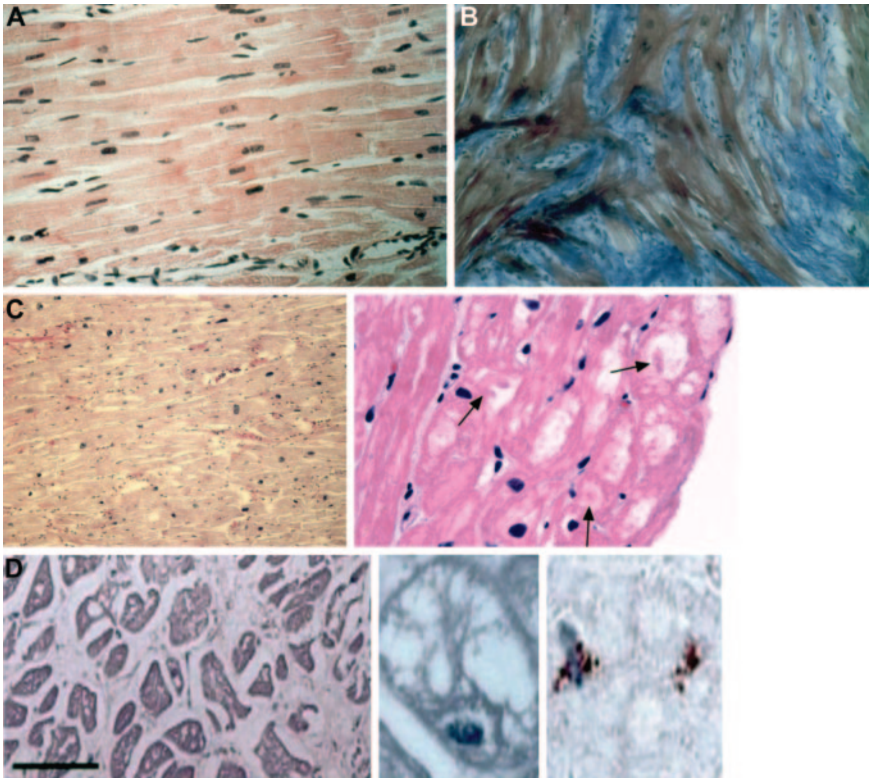

Figure 2. A, Histological section of normal myocardium stained with hematoxylin and eosin. Note the orderly arrangement of myocytes and scant interstitial fibrosis. B, In contrast, the histology from a patient with HCM stained with Masson's trichrome shows characteristic myocyte disarray, hypertrophy, and increased interstitial fibrosis (stained blue). C, Patients with mutations in *PRKAG2* show non–membrane-bound vacuoles in myocytes (arrows) that stain for glycogen and amylopectin. There is only mild fibrosis and no myocyte disarray. D, Mutations in *LAMP2* show vacuoles with large periodic acid-Schiff–positive (PAS+) inclusions. As with *PRKAG2* mutations, myocyte size is increased, not because of classic hypertrophy but rather because of the presence of glycogen-filled vacuoles.

by conduction abnormalities (progressive AV block, atrial fibrillation, ventricular pre-excitation/Wolff-Parkinson-White syndrome) have identified metabolic cardiomyopathies. These genetic forms of hypertrophy reflect mutations in the $\gamma 2$ regulatory subunit (*PRKAG2*) of AMP-activated protein kinase, an enzyme involved with glucose metabolism, or in the X-linked lysosome-associated membrane protein (*LAMP2*) gene.[5,23,24]

These clinical entities are distinct from HCM caused by sarcomere protein mutations, despite the shared feature of LVH. A high prevalence of conduction system disease (with the requirement of permanent pacing in 30% of patients in 1 series) characterizes *PRKAG2* mutations.[24] *LAMP2* mutations are X-linked, resulting in male predominance. *LAMP2* mutations are further distinguished by profound LVH seen on the ECG and echocardiogram (typically concentric) (Movie) and ventricular pre-excitation. In addition, LAMP2 mutations are associated with early-onset LVH (often in childhood) with rapid progression of heart failure and a poor prognosis.[5] The histopathology of *PRKAG2* and *LAMP2* mutations shows prominent non–membrane-bound vacuoles containing glycogen and amylopectin rather than the myocardial disarray or interstitial fibrosis characteristic of HCM (Figure 2). Although incompletely defined, the molecular signaling pathways triggered by *PRKAG2* and *LAMP2* mutations are almost certainly different from those produced by sarcomere gene mutations, suggesting that clinical approaches should not be predicated on HCM management tenets.

Contemporary Diagnosis of HCM

Genetic testing allows accurate diagnosis and precise identification of mutations in sarcomere proteins, *PRKAG2* and *LAMP2*, independently of age, family history, or clinical manifestations. As such, incorporating genotype assessment can importantly enhance the contemporary evaluation of unexplained LVH. This is currently accomplished by bidirectional DNA sequence analysis of sarcomere genes to identify potential disease-associated sequence variants (Figure 1B).

The identification of a sarcomere gene mutation provides a definitive diagnosis of HCM and establishes the precise genetic cause. Mutation confirmation in family members can be accomplished simply and identify family members at risk for disease development. Mutation carriers without clinical manifestations are at risk for developing HCM and require longitudinal clinical follow-up, as summarized in Table 2. All mutation carriers should be counseled about the 50% chance of transmission of the mutation to offspring. Family members who do not carry a mutation are not at risk for developing HCM or transmitting HCM to offspring. Longitudinal clinical follow-up is not required.

Despite the power and specificity of genetic diagnosis, there are important current limitations. Mutations in sarcomere genes account for ≈60% of cases of inherited LVH; expanding the screen to include *PRKAG2* and *LAMP2* will slightly increase diagnostic yield. Nonetheless, mutations will not be detected in all individuals with unexplained LVH, and a negative analysis does not exclude a genetic origin. Discovery of other genes that cause LVH will continue to improve gene-based diagnosis. Increasingly, efforts to determine the molecular mechanisms by which

TABLE 1. Gene Mutations That Cause Unexplained Left Ventricular Hypertrophy

	Gene	Designation	Chromosome	Frequency	No. of Mutations	Phenotypic Correlation
HCM-sarcomere proteins	β-Myosin heavy chain	β-MHC	14q1	$\approx$30% to 40%	$>$80	Typically obvious disease with significant LVH; several severe phenotypes (end-stage heart failure and sudden death).
	α-Myosin heavy chain	α-MHC	14q1	Rare	$<$5	
	Cardiac myosin binding protein C	cMYBPC	11q1	$\approx$30% to 40%	$>$50	Typically more mild disease, but severe phenotypes have been described; associated with elderly-onset HCM.
	Cardiac troponin T	cTnT	1q3	$\approx$15% to 20%	$>$20	Typically mild LVH but increased association with sudden death.
	Cardiac troponin I	cTnI	19p1	$<$5%	$>$10	
	Cardiac troponin C	CTnC	3p	Rare	1	
	α-Tropomyosin	α-TM	15q2	$<$5%	8	
	Myosin Essential Light Chain	MLC-1	3p	Rare	2	Skeletal myopathy
	Myosin regulatory light chain	MLC-2	12q	Rare	8	Skeletal myopathy
	Actin		11q	Rare	5	
	Titin		2q3	Rare	1	
Metabolic cardiomyopathies	γ-Subunit AMP kinase	PRKAG2	7q3	?	4	Ventricular preexcitation and conduction disease.
	Linked lysosome-associated membrane protein	LAMP2	X	?	6	Ventricular preexcitation, elevated liver transaminases, cognitive impairment

gene mutations produce HCM will inspire clinical trials of new strategies for disease prevention and rational treatment. Through its ability to identify preclinical individuals with gene mutations, genetic diagnosis will play a crucial role in these endeavors by targeting preventive therapy to patients at high risk for disease development.

Case Conclusion

Genetic testing was performed on this patient, and an *Arg92Trp* mutation was identified in the cardiac troponin T gene. She received an implantable cardioverter-defibrillator on the basis of her syncopal episode, her family history, and the identification of this mutation (associated with SCD in other families[25]). Family mutation confirmation testing revealed that her father (previously diagnosed with atrial fibrillation and mild LVH) and 1 of her 2 children (clinically unaffected at 14 years of age) carry the mutation.

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Disclosures

None.

TABLE 2. Approach for Family Clinical Screening for Hypertrophic Cardiomyopathy

First Degree Relatives (Offspring, Parents, and Siblings)	Screening (PE, Echocardiogram, ECG)
Under 12 years of age	Definitive findings rare; screening optional unless patient has malignant FH or is a competitive athlete or there is suspicion of early onset LVH. Consider screening every 5 years
Age 12 to 22 years	Repeat every 12 to 24 months
Age 23 years or older	Repeat every 5 years (or until genetic testing confirms diagnosis)

If genetic testing results are available, continue serial clinical evaluation as above if the genotype is positive; if negative, no further clinical evaluation is required.

PE indicates physical examination; FH, family history.

Additional Resources

CardioGenomics Home Page for sarcomere gene mutations. Available at: http://cardiogenomics.med.harvard.edu. Accessed May 31, 2006.

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