

Gene Mutations in Apical Hypertrophic Cardiomyopathy

Michael Arad, MD; Manual Penas-Lado, MD; Lorenzo Monserrat, MD; Barry J. Maron, MD; Mark Sherrid, MD; Carolyn Y. Ho, MD; Scott Barr, BSc; Ahmad Karim, MD; Timothy M. Olson, MD; Mitsuhiko Kamisago, MD; J.G. Seidman, PhD*; Christine E. Seidman, MD*

Background—Nonobstructive hypertrophy localized to the cardiac apex is an uncommon morphological variant of hypertrophic cardiomyopathy (HCM) that often is further distinguished by distinct giant negative T waves and a benign clinical course. The genetic relationship between HCM with typical hypertrophic morphology versus isolated apical hypertrophy is incompletely understood.

Methods and Results—Genetic cause was investigated in 15 probands with apical hypertrophy by DNA sequence analyses of 9 sarcomere protein genes and 3 other genes (*GLA*, *PRKAG2*, and *LAMP2*) implicated in idiopathic cardiac hypertrophy. Six sarcomere gene mutations were found in 7 samples; no samples contained mutations in *GLA*, *PRKAG2*, or *LAMP2*. Clinical evaluations demonstrated familial apical HCM in 4 probands, and in 3 probands disease-causing mutations were identified. Two families shared a cardiac actin Glu101Lys missense mutation; all members of both families with clinical manifestations of HCM (n=16) had apical hypertrophy. An essential light chain missense mutation Met149Val caused apical or midventricular segment HCM in another proband and 5 family members, but 6 other affected relatives had typical HCM morphologies. No other sarcomere gene mutations identified in the remaining probands caused apical HCM in other family members.

Conclusions—Sarcomere protein gene mutations that cause apical hypertrophy rather than more common HCM morphologies reflect interactions among genetic etiology, background modifier genes, and/or hemodynamic factors. Only a limited number of sarcomere gene defects (eg, cardiac actin Glu101Lys) consistently produce apical HCM. (*Circulation*. 2005;112:2805-2811.)

Key Words: hypertrophy ■ cardiomyopathy ■ genetics ■ remodeling

Since the first application of echocardiography to the diagnosis of hypertrophic cardiomyopathy, cardiologists have recognized that the distribution of ventricular and septal wall thickening in hypertrophic cardiomyopathy (HCM) varies widely. Ventricular hypertrophy in HCM can be focal or diffuse, asymmetrical or concentric, obstructive or nonobstructive. These different cardiac morphologies are often observed in affected individuals within the same family, all of whom share a common disease-causing mutation. One of the more unusual hypertrophic morphologies is apical HCM: nonobstructive hypertrophy that is localized to the cardiac apex. The ECG in apical HCM can also be unusual and show giant negative T waves¹⁻⁴ that can be labile and even disappear during long-term follow-up.⁵ In addition to this unique ventricular morphology, other clinical manifestations can further distinguish apical HCM. Epidemiological studies indicate that ≈18% of HCM patients in Japan but only 3% to

10% of other HCM patients worldwide have apical hypertrophy.^{1,6-8} Patients with apical hypertrophy may develop typical HCM symptoms and complications⁹ but are at additional risk for apical myocardial infarction and apical aneurysm development.^{1,10} Despite these potential complications, apical HCM is generally characterized by a benign clinical course with favorable long-term prognosis.

An apical hypertrophic morphology is sometimes encountered in the context of clinical investigations of family members with more common morphological patterns of HCM. For example, a troponin I Lys183 deletion was associated with apical morphology in 2 members of 1 Asian kindred,¹¹ but among 24 other Asian HCM patients (from 6 families) with the same mutation, only 1 individual had apical hypertrophy.¹² Cardiac troponin T missense mutations Phe110Ile¹³ and Arg102Leu¹⁴ have been found in 2 Asian apical HCM patients and 1 European apical

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From the Department of Genetics, Harvard Medical School, Boston, Mass (M.A., S.B., M.K., J.G.S., C.E.S.); Heart Institute, Sheba Medical Center, Tel Hashomer, Israel (M.A.); Cardiology Service, Hospital Juan Canalejo, La Coruña, Spain (M.P.-L., L.M.); Minneapolis Heart Institute Foundation, Minneapolis, Minn (B.J.M.); St Luke's Roosevelt University Hospital, New York, NY (M.S.); Division of Cardiology and Howard Hughes Medical Institute, Brigham and Women's Hospital, Boston, Mass (C.Y.H., C.E.S.); Division of Cardiology, Wright State University, Dayton, Ohio (A.K.); Mayo Clinic Cardiovascular Genetics Laboratory, Rochester, Minn (T.M.O.); and Department of Pediatrics, Nippon Medical School, Tokyo, Japan (M.K.).

*J.G. and C.E. Seidman contributed equally to this work.

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Correspondence to Christine E. Seidman, MD, Department of Genetics, NRB Room 256, Harvard Medical School, 77 Avenue Louis Pasteur, Boston, MA 02115. E-mail cseidman@genetics.med.harvard.edu

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HCM patient, respectively, whereas 20 other carriers of these mutations had more typical HCM morphologies. Seven different cardiac troponin I mutations¹⁵ were recently reported to cause “predominantly” apical HCM mutations in 11 European patients but not in 48 other mutation carriers.

Apical HCM has also been occasionally recognized as familial disease, implicating a primary role for genetics in the development of this morphological pattern of hypertrophy. Three clinical reports described pedigrees that are consistent with autosomal dominant inheritance of apical HCM.^{9,16,17} Genetic analyses of one small family with apical HCM identified a disease-causing cardiac actin mutation Glu101Lys.¹⁸ Another study demonstrated midcavitary hypertrophy in individuals with essential or regulatory myosin light chain mutations.¹⁹

To more completely ascertain the role of genetics in apical remodeling, we performed genetic analyses of DNA samples from a cohort of probands with apical HCM. Genes encoding 9 sarcomere proteins, which account for 60% to 70% of HCM,^{20,21} and genes encoding the γ 2 subunit of AMP-dependent protein kinase (*PRKAG2*), lysosome-associated membrane-2 (*LAMP2*), and α -galactosidase A (*GLA*), which can cause metabolite accumulation and cardiac hypertrophy,^{22,23} were studied. Clinical and molecular evaluations of family members identified 1 sarcomere gene mutation that caused apical HCM in 100% of clinically affected individuals; another mutation caused apical HCM in 50% of affected individuals. We conclude that although development of apical HCM is not typically genetically programmed, a few select sarcomere gene mutations specifically produce this unusual morphology.

Methods

Clinical Evaluation

Human studies were performed in accordance with institutional guidelines for human research. Review of medical records, clinical evaluation, ECG, and echocardiogram studies of HCM probands and family members were performed as described.^{24–26} Fifteen probands with apical hypertrophy were identified from consecutively enrolled HCM subjects. The diagnosis of apical HCM was made by 2-dimensional echocardiography on the basis of the presence of unexplained left ventricular hypertrophy (LVH) localized to cardiac apex, defined when the apex was the thickest ventricular segment and when significant hypertrophy was absent from other segments measured in the parasternal long-axis view.¹ Apical hypertrophy was quantified by measuring the thickest portion of the apical endocardium as assessed in the apical 4-chamber view.

Genetic Data

Genomic DNA was extracted from whole blood or Epstein-Barr virus transformed lymphocytes.²⁴ Sequences of β -cardiac myosin heavy chain, cardiac myosin binding protein C, cardiac troponin T, cardiac troponin I, cardiac troponin C, cardiac actin, essential myosin light chain, regulatory myosin light chain, and α -tropomyosin were determined with the use of an ABI Prism 377 or ABI 3700 automated capillary sequencer.²² Identified sequence variants that were absent in >200 normal chromosomes were confirmed by restriction digestion. *ACTC* G515A (encoding Glu101Lys) abolished an *Ava*I site. *MYL3* A445G (encoding Met149Val) abolished an *Nla*III site. *TNNI3* C61T (encoding Arg21Cys) abolished an *Hga*I site. *MYH7* G728A (encoding Arg243His) abolished an *Acl*I site. *MYH7* G1491T (encoding Glu497Asp) abolished a *Bpm*I site. To confirm *MYH7* A2717G (encoding Asp906Glu), a reverse primer 5'-CACCTTAGCCTCCAGCTGAATCTTGTTTTAAATCAGCTGA-3' was used to demonstrate disappearance of a *Bcl*I site.

Data Analysis

Group data are presented as mean \pm SD. Two-point logarithm of the odds ratio (LOD) scores were calculated with the use of MLINK computer program assuming disease allele frequency 0.1%, 95%

TABLE 1. Features of Apical HCM Probands

ID	Mutation	Age, y	Sex	Presenting Symptoms	Family History		
					HCM	Apical	SCD
MH	ACTC E101K	64	M	Angina	Yes	Yes	0
MG	ACTC E101K	62	M	Dyspnea	Yes	Yes	0
DF	MYL3 M149V	23	F	Palpitations	Yes	Yes	3
GX	β -MHC D906G	36	F	Angina, fatigue	Yes	No	1
HK	TnI R21C	40	F	Palpitations	Yes	No	5
GB	β -MHC R243H	40	M	Presyncope	No	No	0
HZ	β -MHC E497D	60	F	Palpitations	No	No	0
GC		58	M	Angina	No	No	0
GE		64	F	Angina, fatigue	No	No	0
FSG		61	F	Angina, fatigue	No	No	0
MK		49	M	None	No	No	0
HD		66	M	None	No	No	0
II		52	M	None	No	No	0
IJ		45	M	None	Yes	Yes	0
IL		55	M	Angina	No	No	1

ID indicates identification code; Age, age at diagnosis; Apical, with or without apical morphology; SCD, sudden cardiac deaths in relatives; ACTC, cardiac actin; MYL3, essential light chain; and β -MHC, β -myosin heavy chain.

TABLE 2. Clinical Manifestations of the Cardiac Actin Glu101Lys Mutation

Subject	Symptoms	Age, y/Sex	Echocardiography*								ECG				
			IVS	PW	Mid	Apex	LVED	LA	FS, %	Other	Rhythm	PR	LVH	T ↓	Other
MH-II-2	Angina, CHF	64/M	10	12	10	27	50	54	33	MR+ AR+	SB	0.34	N	Y	LAFB
MH-II-3	Angina, syncope	80/M	12	14	14	15	52	44	33	RVH	SB	NL	Y	N	ST-T Ab
MH-III-1	Asymptomatic	50/F	14	10	16	17	42	44	39	MR++	NSR	0.22	Y	N	Q V2-3
MH-III-2	Palpitations†	49/M	12	13	16	29	49	46	38		NSR	NL	N	Y	ST-T Ab
MH-III-3	Angina	43/M	10	11	16	21	52	51	27	TA	NSR	NL	N	Y	ST-T Ab
MH-III-6	Asymptomatic	40/F	11	10	13	16	47	39	26		NSR	NL	N	N	ST-T Ab
MH-III-7	Asymptomatic	35/M	12	11	14	17	47	46	36	TA	NSR	NL	N	N	ST-T Ab
MH-III-8	Asymptomatic	29/F	10	9	10	12	47	31	46		NSR	NL	N	N	
MH-III-9	Palpitations	28/F	7	9	13	14	44	35	33		NSR	NL	N	N	
MH-IV-1	Angina	19/M	10	13	NA	17	48	38	29		NSR	NL	N	Y	
MH-IV-3	Asymptomatic‡	5/M	7	8	8	13	28	NL	NL		ST	NL	N	N	
MG-I-2	CHF, CVA	78/F	10	11	14	23	60	57	38	MR++ AR+	AF	NL	N	N	
MG-II-1	Dyspnea	62/F	13	12	12	21	52	48	40		AF	NL	N	Y	RBBB
MG-II-2	Angina	48/F	12	10	16	17	55	49	36		AF	NL	N	Y	
MG-II-5	Asymptomatic	41/M	10	11	12	15	47	43	36	MR+	NSR	NL	N	N	
MG-III-1	Syncope	26/M	9	9	10	14	44	34	47		NSR	0.11	N	Y	
MG-III-2	Asymptomatic	15/F	10	9	16	22	45	29	32		NSR	NL	N	Y	
MG-III-3	Asymptomatic	10/F	8	8	10	10	39	28	49		NSR	0.10	N	N	

IVS indicates interventricular septum; PW, posterior wall; LVED, left ventricular end-diastolic diameter; LA, left atrial diameter; FS, fractional shortening; PR, PR interval (seconds); LVH, voltage criteria for LVH; T ↓, T wave inversion; CHF, congestive heart failure; MR, mitral regurgitation; Q V2-3, Q waves V₂-V₃; AR, aortic regurgitation, SB, sinus bradycardia; N, no; Y, yes; LAFB, left anterior fascicular block; RVH, right ventricular hypertrophy; NL, normal limits; ST-T Ab, ST-T wave abnormality; NSR, normal sinus rhythm; TA, trabeculated apex; NA, not available; ST, sinus tachycardia; AF, atrial fibrillation; CVA, cerebrovascular accident; and RBBB, right bundle branch block.

*Cardiac dimensions are provided in millimeters.

†Atrial septal defect repaired at age 13 mo.

‡Prominent (III-VI) systolic murmur identified during routine examination.

disease penetrance (over age 20 years), and 0% recombination fraction (θ). Statistical significance was assessed with the use of χ^2 or Fisher exact test.

Results

A cohort of 15 individuals of European descent (9 men and 6 women; mean age, 52±13 years; range, 23 to 66 years) were diagnosed with apical HCM (Table 1). Symptoms led to the evaluation of 11 individuals: 6 had angina, and cardiac catheterization revealed absent or clinically insignificant coronary artery disease; 4 had palpitations or arrhythmia; and 1 had exercise-induced dyspnea. Cardiac evaluation of 4 asymptomatic individuals was prompted by diagnosis of HCM in a family member and/or abnormal findings on screening ECGs. Seven probands had a family history of HCM, including 4 with apical HCM in another family member. Four probands had a family history of sudden cardiac death.

Echocardiographic examinations showed apical hypertrophy (left ventricular [LV] wall thickness 21±5 mm); 3 also had mild hypertrophy of the basal portion of the left ventricle. LV chamber dimensions (mean LV end-diastolic diameter 52±6 mm) and function (fractional shortening >28%) were normal in all except for individual MG-I-2 (Table 2). Six individuals had left atrial enlargement (diameter ≥40 mm), 2 had midcavitary gradients (30 and 34 mm Hg), and 1 had systolic anterior movement of the mitral valve. Mild mitral

valve regurgitation was found in 7 and was significant in 1 individual. ECGs showed voltage criteria for LVH in 7 (47%), T-wave inversion in 13 (86%), and deep T-wave inversion (≥10 mm) in 4 individuals.

DNA samples from the 15 probands were studied by nucleotide sequence determination of 9 genes encoding sarcomere proteins β -myosin heavy chain, myosin binding protein C, troponin T, troponin I, troponin C, α -tropomyosin, cardiac actin, regulatory myosin light chain, and essential myosin light chains. Heterozygous mutations (Table 1) were identified in 7 samples. In the remaining 8 probands, nucleotide sequences of *PRKAG2*, *GLA*, and *LAMP2* were analyzed because mutations in these genes produce cardiac hypertrophy that mimics HCM.^{22,23} No additional mutations were found.

Familial Apical HCM Mutations

A cardiac actin missense mutation affecting residue 101 (designated Glu101Lys; Table 1) was found in the probands of families MH and MG. This same missense mutation has been reported in another small family with apical HCM.¹⁸ (Additional information is provided in Table I in the online-only Data Supplement: <http://circ.ahajournals.org/cgi/content/full/112/18/2805/DC1>.) To determine whether these 3 families shared common ancestors, haplotype analyses (data not shown) were performed with the use of 7 poly-

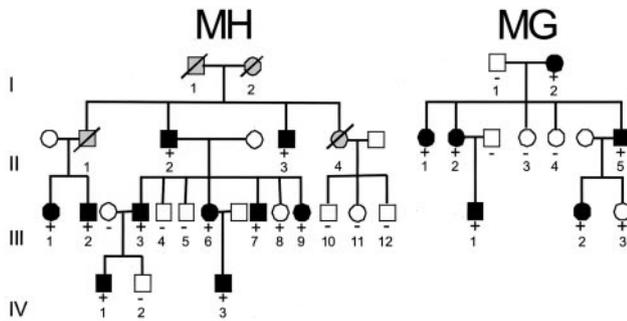


Figure 1. Pedigrees of the 2 kindreds with familial apical hypertrophy and E101K mutation in cardiac actin. Solid symbols indicate apical HCM; open symbols, normal cardiac dimensions; shaded symbols, clinical status unknown; +, mutation present; and -, mutation absent. Note dominant transmission of apical HCM.

morphic loci spanning 125 kb of the cardiac actin gene. A shared haplotype was identified in families MH and MG, providing odds >100:1 that a founding mutation caused apical HCM in both families. In contrast, haplotype data indicated that the cardiac actin Glu101Lys arose independently in the family reported by Olson and colleagues.¹⁸

Clinical phenotypes were assessed in all MH and MG family members (Figure 1). Sixteen of 18 surviving individuals with the mutation fulfilled standard criteria for HCM²⁵ and had echocardiographic and ECG findings of apical HCM (Figure 2). Two individuals (ages 10 and 29 years) with the cardiac actin Glu101Lys mutation had no clinical evidence of cardiomyopathy. The combined LOD score (4.53, $\theta=0$) provided odds <1:33 000 that chance alone accounted for coinheritance of this mutation and apical HCM in families MG and MH. We conclude that cardiac actin Glu101Lys causes familial apical HCM.

The extent of hypertrophy in families MH and MG (Table 2) ranged from 13 to 29 mm (mean, 19 ± 5 mm). Isolated apical hypertrophy was found in 5 individuals; 11 others also had mild thickening (13 to 14 mm) of the basal segments and/or involvement (13 to 16 mm) of the midventricular segment. Systolic ventricular function was preserved in all affected individuals; none had an outflow or midcavitary gradient, and 2 had significant mitral regurgitation. Progressive symptoms of exertional dyspnea prompted cardiac catheterization in individual MH-III-3; a right ventricular endomyocardial biopsy showed myocyte hypertrophy and disarray

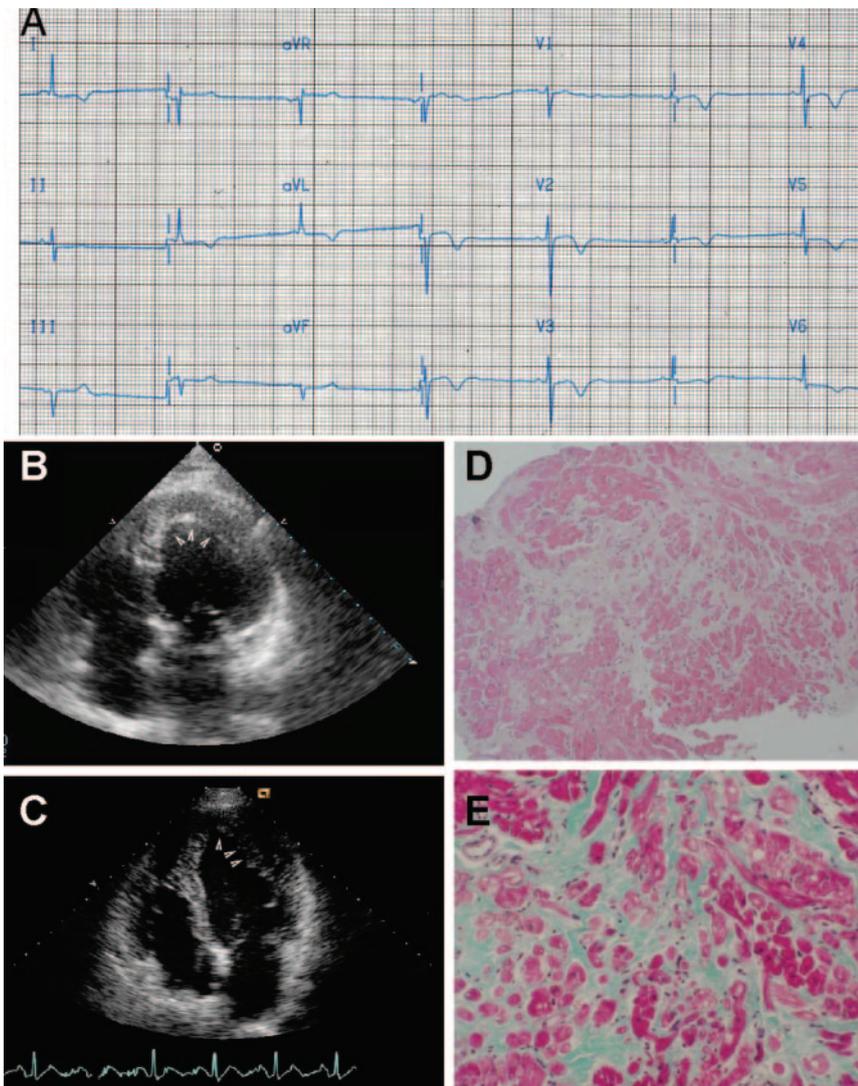


Figure 2. Cardiac features of apical HCM due to actinGlu101Lys mutation. A, ECG (obtained from subject MH III-3; Figure 1) showed left atrial enlargement, T-wave inversion, and ST-T abnormalities. Note absence of standard criteria for LVH. B, An apical 4-chamber echocardiogram (from subject MG-II-2) with marked hypertrophy localized to the apex. C, An apical 4-chamber echocardiogram (subject MH-III-7) showed apical and apicolateral hypertrophy. D and E, Endomyocardial biopsy (subject MH-III-3) showed disorganized myofibers with considerable interstitial fibrosis. D, Hematoxylin and eosin stain; E, Masson trichrome stain.

with extensive replacement fibrosis (Figure 2E) that was increased from that typically found in HCM associated with other morphological patterns of hypertrophy.

ECGs in affected members of families MH and MG showed voltage criteria for LVH in only 2 individuals; T-wave inversion and ST-T abnormalities (Figure 2) were present in 8 individuals (44%). Among 8 individuals with ECG abnormalities, 3 had atrial fibrillation, 3 had first-degree AV block or sinus bradycardia, and 2 had short PR interval without delta waves. One individual (MHIII-I) had pathological Q waves consistent with apical infarction.

The clinical course of affected members in families MH and MG (Table 2) indicated slow disease progression with increasing symptoms of angina and dyspnea. Although some elderly affected individuals developed congestive heart failure in the context of atrial fibrillation, none had a myocardial infarction, history of life-threatening arrhythmia, or sudden cardiac death.

An essential light chain missense mutation Met149Val was identified in proband DF. Previously, clinical evaluations of family members⁹ (echocardiography, left ventriculography, and/or necropsy) identified apical HCM in 5 and typical asymmetrical hypertrophy of the anterior basal septum in 6 individuals. The clinical histories of family DF, unlike those obtained in families MG and MH, indicated heart failure deaths in 2 individuals (at ages 54 and 35 years) and sudden death in 3 individuals (at ages 26, 35, and 33 years.)

Mutations Causing Apical and Other HCM Morphologies

Two of 3 β -myosin heavy chain missense mutations identified in probands with apical HCM also caused other HCM morphologies. A novel mutation (Arg243His) found in proband GB was absent from all family members. A Glu497Asp mutation produced apical HCM in proband HZ with associated ECG abnormalities of LVH and deeply inverted precordial T waves. In a family member with concurrent coronary artery disease, the Glu497Asp mutation caused massive concentric hypertrophy (interventricular septum=29 mm); after a syncope episode, an automatic implanted cardioverter/defibrillator was implanted in this patient. An Asp906Gly mutation was found in proband GX, who was evaluated after sudden death (at age 45 years) of a sibling; necropsy showed massive, asymmetrical LVH (interventricular septum >30 mm; posterior LV wall 18 mm). This same mutation was described previously²⁷ in 22 members of an HCM family with a range of maximum LV wall thickness of 13 to 29 mm; none had apical hypertrophy.

A cardiac troponin I missense mutation (Arg21Cys) was identified in proband HK, who presented with atrial fibrillation shortly after the sudden death of her child (age 18 years). Three surviving mutation carriers from the family (Figure 3) had asymmetrical septal hypertrophy (n=1), isolated left atrial enlargement (n=1), and normal cardiac dimensions (n=1). We recently also identified the Arg21Cys mutation in another HCM family (designated ES): 4 mutation carriers had subaortic asymmetrical hypertrophy; 1 mutation carrier with normal cardiac dimensions was resuscitated from sudden death.

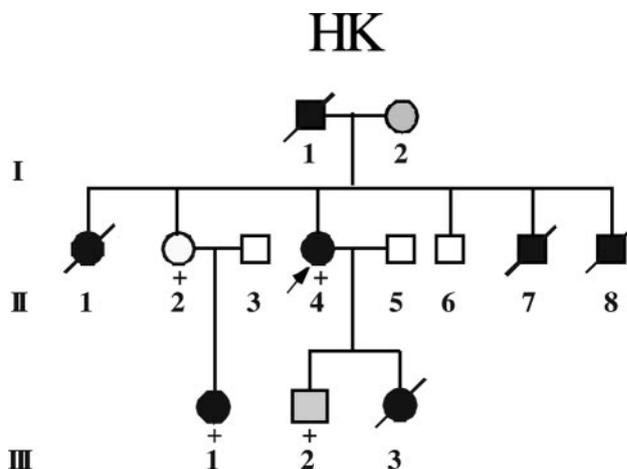


Figure 3. Morphological variations of HCM found with troponin I mutation Arg21Cys in pedigree HK. Apical HCM was identified in the proband (arrow) after onset of atrial fibrillation. Sudden cardiac death occurred in her father, 3 siblings, and her 18-year-old daughter. Clinical evaluations of III-1 showed asymmetrical septal hypertrophy and normal cardiac dimensions in III-2 despite an abnormal ECG. Solid symbols indicate HCM; open symbols, normal cardiac dimensions; shaded symbols, cardiac status unknown; and +, mutation present.

Discussion

Comprehensive genetic analyses of 15 probands with apical HCM identified 6 disease-causing mutations in genes encoding β -myosin heavy chain, troponin I, cardiac actin, and myosin essential light chain. One myosin essential light chain mutation increased the propensity for apical or midventricular segment remodeling, and 1 cardiac actin mutation consistently produced apical remodeling. Apical HCM was not caused by mutations in genes involved in cardiac glycogen metabolism. We conclude that most apical HCM caused by a sarcomere gene mutation reflects the interactions of modifying genetic background and/or local hemodynamics and other factors. Only a select few sarcomere gene defects (eg, cardiac actin Glu101Lys) specifically produce this distinctive HCM morphology.

The identification of mutations in 7 of 15 probands presenting with apical HCM provides molecular validation that hypertrophy localized to the cardiac apex is within the spectrum of morphologies triggered by sarcomere protein gene defects. Despite a shared molecular etiology, there are notable differences in the genetic and clinical profiles associated with apical and prototypic morphologies of HCM. First, among unselected HCM patients referred for genetic analyses, 80% report familial disease.²⁸ Among this cohort of apical HCM probands, less than half reported HCM in another family member. However, molecular analyses were equally likely to define a potentially heritable sarcomere protein gene mutation in patients with apical HCM as in patients with prototypic HCM morphologies, suggesting that there may be inadequate clinical screening of the family members of apical HCM patients. Second, although a substantial fraction (\approx 40%) of HCM is due to myosin binding protein C mutations,²⁸ these genetic defects were notably absent from this cohort of apical HCM patients. In contrast, myosin heavy chain mutations that collectively account for

45% of HCM cases were also commonly found (43%) in individuals who presented with apical HCM. Third, the identification of an actin mutation in this small cohort is notable, given that defects in this gene are a rare cause of all morphological forms of HCM.^{21,28}

Sequence analyses of 12 candidate genes failed to define the cause of apical HCM in 8 probands. This may reflect a mutation in a sarcomere gene that was not sequenced or in an unrelated gene. Alternatively, a single gene defect may not be the cause of apical HCM in some patients. The negative family history for HCM in 7 of 8 patients with apical HCM in whom a sarcomere mutation was not found is consistent with the model that either complex genetics and/or gene-environment interactions account for this morphology in some patients.

Many of the sarcomere mutations found in probands with apical HCM could also trigger other morphological patterns of hypertrophy. Typical HCM findings of hypertrophy involving the anterior basal septum were found in 8 individuals with the cardiac troponin I mutation Arg21Cys and in 14 individuals with β -cardiac myosin heavy chain mutation Glu497Asp (n=1) or Asp906Gly (n=13). Although we cannot exclude the possibility that one novel mutation β -myosin heavy chain mutation Arg243His identified here causes only apical hypertrophy, the ventricular morphologies associated with mutations affecting nearby residues (eg, Lys246Gln²⁹) make this unlikely. On the basis of these data, 9% of individuals with a sarcomere protein gene mutation are predicted to exhibit apical remodeling, an approximation that is consistent with clinical estimates of apical HCM (3% to 10%) in Western patients.^{1,6–8} We suggest that apical hypertrophy in patients with a sarcomere gene mutation is due to the influence of a modifying gene(s) that affects cardiac remodeling. Given the geographic differences in the incidence of apical HCM, this genetic modifier is likely to be more prevalent in certain populations, such as Japanese.

Apical remodeling is directly related to genetic cause in some HCM patients. For example, an essential myosin light chain Met149Val mutation caused apical HCM in 1 member of a family previously reported by one of us.⁹ Six of 12 family members had hypertrophy localized to the apex, and 6 had prototypic asymmetrical hypertrophy. This essential myosin light chain mutation was also reported by Epstein and colleagues¹⁹ to cause midcavitary hypertrophy. Because the morphological classification of hypertrophy as midcavitary or apical may in part reflect the evolution of diagnostic imaging techniques from angiography, by which midcavitary hypertrophy was historically recognized, to echocardiography and MRI, these may represent overlapping morphologies.¹⁰ Alternatively, midventricular hypertrophy may occur as a late manifestation of apical HCM complicated by apical ischemia, infarction, and aneurysmal dilation.³⁰

Cardiac actin mutation Glu101Lys was unique in producing apical HCM in all clinically affected members (n=16) from 2 distantly related families. Although haplotype data indicated that a single ancestral mutation accounted for disease in both families, their shared lineage could not be traced. We suspect that multiple generations that diversified background genes and perhaps influenced cardiovascular

morphology have occurred since this mutation arose. Despite this, the consistent finding of apical HCM in individuals carrying the cardiac actin mutation establishes a primary relationship (LOD score >4) between this genotype and apical hypertrophy. This conclusion is further consolidated by the finding of the identical actin mutation¹⁸ in association with apical hypertrophy or prominent trabeculation of the apex in a genetically unrelated family. Although other cardiac actin mutations cause classic HCM morphologies^{18,31,32} (also M. Arad, MD, et al, unpublished data, 2005), the phenotypes found in individuals with some mutations in this thin filament protein appear more likely than defects in other sarcomere proteins to provoke apical remodeling.³³

The mechanisms by which the actin or essential myosin light chain mutations produce apical HCM are unknown. Olson et al¹⁸ and Mogensen et al³³ suggest that mutations on the myosin-exposed surface of cardiac actin potentially disrupt important electrostatic interactions, impair force generation, and stimulate a hypertrophic response. How this model accounts for localized remodeling at the ventricular apex is unclear. Epstein and colleagues³⁴ suggest another model in which mutated residues within the essential myosin light chain distorted the stretch-activated response, an intrinsic property of muscle that results in oscillatory power and that may account for regional contraction properties of the heart, such as that found in papillary muscles. The stretch-activated response in cardiac muscle is also influenced by a gradient in the phosphorylation status of the regulatory light chain (mediated by myosin light chain kinase). In normal hearts, regulatory light chains expressed within the ventricular apex are hyperphosphorylated, resulting in diminished stretch activation.³⁴ Given that the essential myosin light chain and myosin light chain kinase each bind cardiac actin, we speculate that the sarcomere mutations that reproducibly produce apical HCM do so because they affect stretch activation within apical myocytes. Further elucidation of the relationship between changes in contractile function produced by a specific mutation and local biomechanical properties of the segment undergoing pathological remodeling may help to explain the diversity of hypertrophic morphologies found in HCM.

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