

Hypertrophic Cardiomyopathy**Lifelong Left Ventricular Remodeling of Hypertrophic Cardiomyopathy Caused by a Founder Frameshift Deletion Mutation in the Cardiac Myosin-Binding Protein C Gene Among Japanese**

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OBJECTIVES	We studied the longitudinal evolution of hypertrophic cardiomyopathy (HCM) caused by a founder frameshift mutation in the cardiac myosin-binding protein C (MyBPC) gene.
BACKGROUND	Mutations in the MyBPC gene have been associated with delayed expression of HCM and a good prognosis. Few studies, however, demonstrated the phenotype-genotype correlations in the longitudinal study.
METHODS	We studied long-term evolution of clinical features of 15 unrelated families who were found to have an identical frameshift mutation in the MyBPC gene: a one-base deletion of a thymidine at nucleotide 11645 (V592fs/8).
RESULTS	Thirty-nine individuals in 15 families were genotype-positive. Thirty of the 39 individuals with the mutation were phenotype-positive. The disease penetrance was 100% in subjects ≥ 50 years and 65% in those < 50 years. "End-stage" HCM (ejection fraction $< 50\%$) was observed in 7 (18%) of the 39 genotype-positive individuals (7 [23%] of the 30 phenotype-positive patients); 6 of them were 60 years or older. Seven patients were hospitalized for treatment of repeated congestive heart failure, and four patients died or had implantable cardioverter-defibrillator discharge (13%; incidence, 1.4%/year) during a mean follow-up period of 9.2 ± 5.5 years.
CONCLUSIONS	Elderly patients with a V592fs/8 mutation in the MyBPC gene may evolve into the "end-stage" HCM, characterized by left ventricular systolic dysfunction, cavity dilation, and irreversible heart failure. The clinical course in patients with this mutation is not benign in the long run, with progressive left ventricular remodeling with advancing age. (J Am Coll Cardiol 2005;46:1737-43) © 2005 by the American College of Cardiology Foundation

Hypertrophic cardiomyopathy (HCM) is a primary myocardial disorder with heterogeneous morphologic, functional, and clinical features (1-4). Recent molecular genetic studies have revealed that HCM is caused by mutations in 10 genes that encode sarcomeric contractile proteins (5-9).

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Cardiac myosin-binding protein C (MyBPC) is one of these sarcomeric proteins, and mutations in the MyBPC gene have been reported to be associated with delayed expression of hypertrophy and a relatively good prognosis (10-14). On the other hand, a recent report showed that patients with muta-

tions in the MyBPC gene did not differ significantly from patients with thick-filament HCM or thin-filament HCM with respect to age at diagnosis or severity of phenotype (15).

Few studies, however, have demonstrated longitudinal evolution of phenotype in relation to genotype, although the HCM phenotype itself is recognized to be a slowly progressive disorder that manifests remarkable evolution of clinical features throughout life (16).

We analyzed the MyBPC gene in probands from families with HCM and had the opportunity to study 15 unrelated families living in Kochi prefecture, Japan, who were found to have an identical frameshift mutation in the MyBPC gene: a one-base deletion of a thymidine at nucleotide 11645 (V592fs/8) (17). The results of clinical and genetic investigations in these 15 families during a long period of time are presented herein.

METHODS

Subjects. The subjects were 94 probands with familial or sporadic HCM. Twenty-two subjects were familial HCM,

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Abbreviations and Acronyms

AF	= atrial fibrillation
ECG	= electrocardiogram/electrocardiographic
EF	= ejection fraction
HCM	= hypertrophic cardiomyopathy
ICD	= implantable cardioverter-defibrillator
LVEDD	= left ventricular end-diastolic diameter
LVH	= left ventricular hypertrophy
MLVWT	= maximum left ventricular wall thickness
MyBPC	= cardiac myosin-binding protein C

whereas the other 72 subjects were not confirmed to have relatives with HCM. All probands were evaluated at the Kochi Medical School Hospital for confirmation of diagnosis, risk assessment, and symptom management between 1982 and 2004. The diagnosis of HCM was based on echocardiographic demonstration of an unexplained left ventricular hypertrophy (LVH) (i.e., maximum left ventricular wall thickness [MLVWT] ≥ 15 mm). Relatives of probands were contacted by probands themselves and visited our clinic of their own free will. After the identification of a V592fs/8 mutation, pedigree analysis, including both clinical evaluation and genotyping, was performed. Informed consent was obtained from all subjects or their parents in accordance with the guidelines of the Ethics Committee on Medical Research of Kochi Medical School. **Clinical evaluation.** The evaluation of probands and relatives included medical history, clinical examination, 12-lead electrocardiography, M-mode, two-dimensional and Doppler echocardiography, and ambulatory 24-h Holter electrocardiographic (ECG) analysis. The severity and distribution of LVH were assessed in the parasternal short-axis plane at mitral valve and papillary muscle levels (18,19). Maximum left ventricular wall thickness was defined as the greatest thickness in any single segment. Left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter were measured from M-mode and two-dimensional images obtained from parasternal long-axis views. Ejection fraction (EF) was determined from apical two- and four-chamber views because the left ventricle is of heterogeneous shape and the septum itself is usually hypokinetic in HCM. Left ventricular outflow tract gradient was calculated from continuous-wave Doppler using the simplified Bernoulli equation.

Disease penetrance was determined by the following criteria for relatives: 1) MLVWT ≥ 13 mm; 2) presence of major abnormalities on the ECG (i.e., Q-wave ≥ 0.04 s in duration or one-fourth of the ensuing R-wave in depth in at least two leads, significant ST-T changes, and Romhilt-Estes score >4); or 3) a combination of criteria 1 and 2.

Data regarding survival and clinical status of patients were collected during serial clinic visits. Evaluation of the phenotype was completed before determination of the genotype. Three modes of HCM-related death were defined: 1) sudden and unexpected death (including resuscitated cardiac arrest), in which the collapse occurred in the absence or <1 h from the

onset of symptoms in patients who previously experienced a relatively stable or uneventful course; 2) heart failure-related death, which was in the context of progressive cardiac decompensation ≥ 1 year before death, particularly if complicated by pulmonary edema or evolution to the end-stage phase (including patients with heart transplantation); and 3) stroke-related death, which occurred in patients who died as a result of embolic stroke.

Genetic analysis. Peripheral blood samples were taken at the time of clinical evaluation, and they were frozen and stored at -20°C . We extracted DNA using a DNA purification kit from QIAGEN Inc. (no.51104; Hilden, Germany). In vitro amplification of genomic DNA was performed using polymerase chain reaction. Oligonucleotide primers were used to amplify exon 18 of the MyBPC gene. Information on primer sequences and polymerase chain reaction conditions is available upon request. Sequencing was performed using a BigDye Terminator Cycle Sequencing Kit from Applied Biosystems Inc. (no.4336774; Foster City, California). The sequences were analyzed on an ABI PRISM 3100-Avant Genetic Analyzer in accordance with the manual of the manufacturer.

In patients in whom the mutation was identified, confirmation was obtained by reanalysis with direct sequencing from a second blood sample. The presence of a V592fs/8 mutation, which abolishes a *Bsm*FI restriction site, was confirmed by digestion of genomic DNA with this enzyme.

To investigate if families carrying the identical mutation were related, haplotype analysis was performed using microsatellite markers defining the MyBPC gene locus. Markers MyBPC3-CA, D11S4109, D11S1784, and D11S1326, flanking the MyBPC gene, were used. To describe haplotype results, the length (base pair) of allele was put in parentheses after each marker.

RESULTS

Genetic results. A V592fs/8 mutation, a frameshift mutation that causes truncation of cardiac MyBPC protein, was identified in 15 of 94 probands. Relatives of 15 probands were studied further, totaling 64 members, including 15 probands, of the various families (Figs. 1A to 1G). Of the 64 individuals, 39 had a V592fs/8 mutation in the MyBPC gene. This mutation was thought to be disease-causing based on presence of the mutation in all affected individuals and absence of the sequence variation in at least 200 chromosomes from healthy individuals.

Haplotype analysis with highly polymorphic markers was performed in these families to investigate whether a V592fs/8 mutation was likely to have arisen from a common ancestor (founder effect). We found that a unique haplotype, MyBPC3-CA(282)-D11S4109(151)-D11S1784(138)-D11S1326(249), was linked to the V592fs/8 mutation in all 15 families, indicating that a common founder of the mutation was likely in these families.

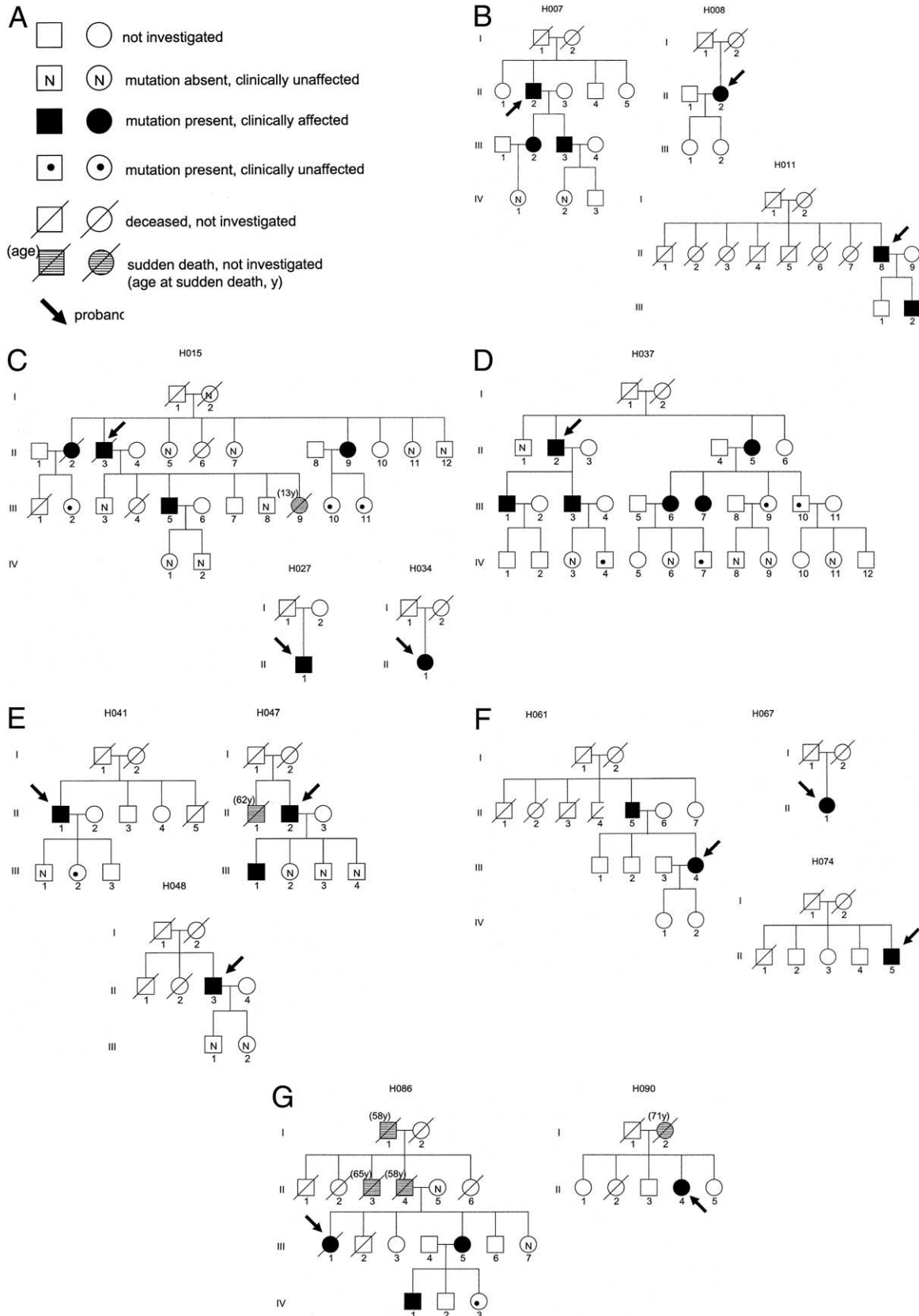


Figure 1. (A to G) Pedigree of families H007, H008, H011, H015, H027, H034, H037, H041, H047, H048, H061, H067, H074, H086, and H090. The genotypic status and phenotypic status of subjects are indicated.

Table 1. Clinical Characteristics of 30 Phenotype-Positive Patients at Presentation

Age at presentation, yrs (range)	48 ± 14 (16-83)
Gender: male, n (%)	17 (57)
Age at diagnosis, yrs (range)	47 ± 15 (14-76)
Reason for diagnosis, n (%)	
Symptoms	16 (53)
Incidental findings	4 (13)
Family or gene screening	10 (33)
Presence of symptoms, n (%)	19 (63)
Dyspnea, n (%)	14 (47)
Palpitation, n (%)	11 (37)
Syncope, n (%)	3 (10)
Chest pain, n (%)	7 (23)
NYHA functional class	
I	16 (53)
II	10 (33)
III and IV	4 (13)
History of AF (chronic or paroxysmal)	4 (13)

Data shown as mean value ± SD or number (%).

AF = atrial fibrillation; NYHA = New York Heart Association.

Clinical manifestation. Clinical evaluation was performed in the 64 individuals from the 15 proband families studied. The mean follow-up period in the all 39 genotype-positive individuals was 8.0 ± 5.4 years (range, 0.2 to 19.3 years). Thirty patients were phenotype-positive, all with echocardiographic evidence of LVH. Two adults developed hypertrophy (MLVWT ≥ 13 mm) after the age of 40. Nine of the 39 individuals were not affected phenotypically (average age at last evaluation: 33 ± 11 years; range, 12 to 43 years). The disease penetrance was 100% in subjects ≥ 50 years and 65% in those < 50 years of age.

The clinical characteristics of the 30 phenotype-positive patients at presentation were summarized in Table 1. The age at diagnosis was 47 ± 15 years. Most patients (86%) were evaluated because of symptoms or family screening of HCM. A total of 19 patients (63%) reported cardiac symptoms. Table 2 shows the echocardiographic characteristics of the 30 phenotype-positive patients at presentation and at last follow-up. At presentation, MLVWT was 21 ± 5.3 mm. Six (20%) of those 30 patients had systolic anterior movement of the mitral valve, and three (10%) showed a significant LV outflow tract gradient (pressure gradient at rest ≥ 30 mm Hg).

Sudden death occurred in six individuals from four families (Fig. 1; families H015, H047, H086, and H090). Three individuals were from one family. Five of them were older than 50 years of age.

Clinical course. During a mean follow-up period of 9.2 ± 5.5 years after the first clinical evaluation, paroxysmal or chronic atrial fibrillation (AF) was detected in 10 (33%; incidence, 3.6%/year) of the 30 phenotype-positive patients, eight of whom were 60 years of age or older. Two of those patients experienced severe embolic stroke, which was the cause of their death at the ages of 61 and 68 years, respectively. One patient (H015-II-2) was on oral anticoagulation with warfarin. In the other patient (H086-III-1), AF was detected at the time of the stroke for the first time.

Figure 2 shows longitudinal changes in LVEDD, ejection fraction (EF), and MLVWT in each of the 39 genotype-positive individuals. Figure 2A shows that LVEDD gradually became larger with advancing age. On the other hand, LV systolic function was preserved until middle age. After middle age, reduction of EF occurred in some patients (Fig. 2B). “End-stage” HCM (EF < 50%) was observed in seven (18%) of the 39 individuals; six of them were 60 years or older. Five of them showed LVEDD ≥ 55 mm. Figure 2C shows that MLVWT was thinner in elderly patients than in young patients with HCM and that it was within normal limits in the phenotype-negative individuals.

Table 3 shows the clinical characteristics of seven patients with “end-stage” HCM. More specifically, the average age when they were first identified as in the end-stage phase was 60 years (range, 46 to 70 years). Three patients (H011-II-8, H015-II-3, and H086-III-1) were already in the end-stage phase at presentation. The other four patients progressed to “end-stage” HCM during follow-up. Regarding the cause of LV systolic dysfunction, none of them was considered to have atherosclerotic coronary artery disease because three of them (H007-II-2, H011-II-8 and H086-III-1) had normal coronary angiography, and the remaining four patients had normal thallium-201 myocardial scintigraphy. No one suffered from myocardial infarction. All patients with “end-stage” HCM showed deterioration of New York Heart Association functional class together with a development of paroxysmal or chronic AF at last follow-up. All of them were treated for heart failure and/or arrhythmias: diuretics (n = 6), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (n = 5), beta-blockers (n = 3), and amiodarone (n = 2). One patient (H007-II-2), who was on amiodarone (maintenance dose 100 to 200 mg/day) for sustained ventricular tachycardia for 10 months, received an implantable cardioverter-

Table 2. Echocardiographic Characteristics of 30 Phenotype-Positive Patients

	At Presentation	At Last Follow-Up
Age, yrs	48 ± 14 (16-83)	56 ± 15 (28-83)
MLVWT, mm	21 ± 5.3 (13-38)	21 ± 6.0 (13-39)
IVST, mm	19 ± 4.7 (11-28)	18 ± 4.9 (10-32)
PWT, mm	11 ± 1.7 (7-14)	11 ± 2.3 (7-19)
Left atrial diameter, mm	40 ± 8.3 (27-60)	46 ± 9.0 (30-69)
LV end-diastolic diameter, mm	44 ± 7.4 (29-64)	47 ± 8.1 (37-67)
LV end-systolic diameter, mm	27 ± 7.8 (12-48)	31 ± 9.2 (21-55)
Ejection fraction, %	66 ± 9.9 (36-85)	61 ± 13.9 (22-81)
Gradient >30 mm Hg, n (%)	3 (10)	2 (7)
SAM, n (%)	6 (20)	6 (20)
Pattern of LVH, n		
Asymmetric	27	27
Diffuse	2	1
Apical	0	0
Others	1	2

Data shown as mean value ± SD (range) or number (%).

IVST = interventricular septal wall; LV = left ventricular; LVH = left ventricular hypertrophy; MLVWT = maximum left ventricular wall thickness; PWT = left ventricular posterior wall thickness; SAM = systolic anterior movement.

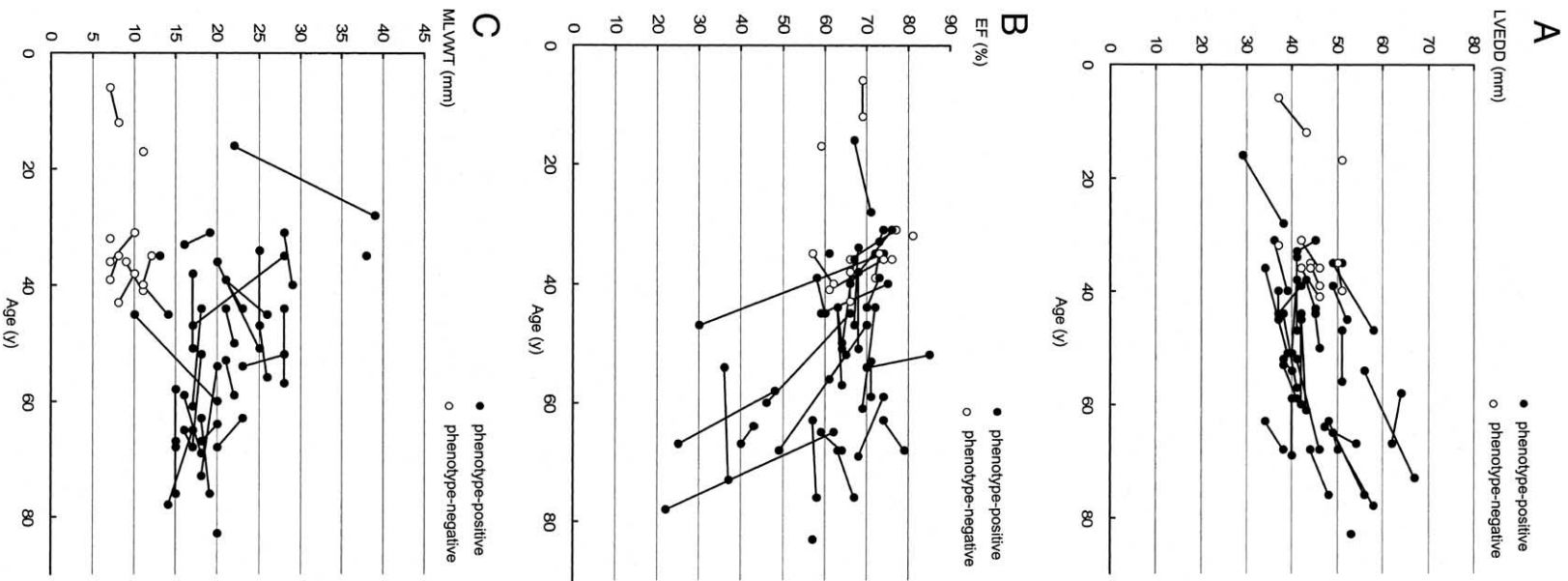


Figure 2. Longitudinal echocardiographic changes in 39 genotype-positive individuals during the follow-up period. **(A)** Changes in left ventricular end-diastolic diameter (LVEDD). **(B)** Changes in ejection fraction (EF). **(C)** Changes in maximum left ventricular wall thickness (MLVWT).

Table 3. Clinical Characteristics of Seven Patients With “End-Stage” HCM

Patient	Gender	Age (yrs) at Diagnosis	Age (yrs) at End-Stage	Echocardiography at Initial Evaluation/ at Last Evaluation				NYHA Functional Class, Initial to Last	Rhythm, Initial to Last	Hospitalization for CHF (Age, yrs)	Status (Event Age, yrs)
				Age (yrs)	LVEDD (mm)	EF (%)	MLVWT (mm)				
H007-II-2	M	65	70	65/78	49/58	62/22	17/14	I to III	SR to AF	+ (69)	ICD discharge (76)
H007-III-2	F	14	46	35/47	49/58	74/30	28/17	I to III	SR and PAF	+ (46)	Alive
H011-II-8	M	40	58	58/68	64/62	48/25	15/17	II to III	SR to AF	+ (63)	Alive, CRT, MVR
H015-II-3	M	54	54	54/73	56/67	36/37	20/18	II to IV	AF to AF	+ (54)	CHF death (73)
H015-II-2	F	45	60	45/60	42/42	66/46	10/20	II to III	SR to AF	+ (60)	Stroke death (61)
H034-II-1	F	46	68	52/68	41/46	65/49	18/17	I to III	SR to AF	—	Alive
H086-III-1	F	64	64	64/67	47/55	43/40	20/18	II to III	SR to AF	+ (64)	Stroke death (68)

AF = atrial fibrillation; CHF = congestive heart failure; CRT = cardiac resynchronization therapy; EF = ejection fraction; LVEDD = left ventricular end-diastolic diameter; MLVWT = maximum left ventricular wall thickness; MVR = mitral valve replacement; NYHA = New York Heart Association; PAF = paroxysmal AF; SR = sinus rhythm.

defibrillator (ICD) because of amiodarone-induced pulmonary fibrosis. One patient (H011-II-8) underwent mitral valve replacement and cardiac resynchronization therapy for medically-refractory heart failure.

During follow-up (9.2 ± 5.5 years), seven (23%) of the 30 patients (mean age: 62 ± 10 years; range, 46 years to 76 years) were hospitalized for treatment of heart failure, and four patients died or had ICD discharge (one heart failure-death, two stroke-deaths, one ICD discharge; 13%; incidence, 1.4%/year) (Table 3).

DISCUSSION

Hypertrophic cardiomyopathy is a heterogeneous myocardial disorder and the phenotype is not a static manifestation; LVH can appear at virtually any age and increase or decrease dynamically throughout life (16,20). However, there have been few studies on the phenotype-genotype correlation in terms of longitudinal clinical evaluation. In this study, we examined the clinical courses of patients with a founder mutation (V592fs/8) in the MyBPC gene from 15 unrelated proband families. We observed the longitudinal evolution of phenotype caused by this mutation and concluded that the patients with this mutation were likely to progress to “end-stage” HCM, characterized by LV systolic dysfunction and cavity dilation, with advancing age. To the best of our knowledge this is the first report demonstrating direct longitudinal evolution of phenotype in relation to genotype.

Disease penetrance and clinical manifestation. In the present study, the mean age of patients at diagnosis was 47 ± 15 years. During follow-up, two adults showed development of LVH in mid-life, appearing for the first time after 40 years of age. We found that disease penetrance was 100% in subjects ≥ 50 years and 65% in those < 50 years of age. Our data are in accordance with previously reported data for MyBPC mutations (12,14,21-24). Onset of the disease seems to be late in life, although two patients are diagnosed as having the disease at teenagers (H007-III-2 and H047-III-1). These findings indicate that relatives of the patients, even if they are old, should be screened for this mutation. If genetic diagnosis is not available, middle-aged or older relatives of the patients should be evaluated at least every five years for family-screening strategies (2-4,14,25). From a morphologic point of view, the degree of MLVWT varied significantly (13 to 38 mm). None of the subjects showed apical hypertrophy. Sudden death occurred in six individuals from four families in the present study. It is notable that most of sudden deaths occurred in subjects > 50 years of age (83%; five of the six individuals) because sudden death occurs most commonly in children and young adults, although the risk extends across a wide age range through mid-life and beyond (3,26,27).

Clinical course and prognosis. It was previously suggested that LV remodeling involving some degree of LV cavity enlargement and wall thinning could occur slowly over the course of decades (28-32), although direct

longitudinal evidence in relation to gene abnormality was insufficient. In the present study, we were able to demonstrate longitudinal LV remodeling in those with a V592fs/8 mutation and also evolution to “end-stage” HCM in the elderly (Fig. 2). HCM generally has been associated with only mild disability and normal life expectancy if sudden death can be avoided (27,33-35). In this study, the clinical manifestation caused by this mutation was late onset and prognosis was not poor in terms of survival (4 [13%] of the 30 patients died or had ICD discharge; incidence, 1.4%/year). However, a significant subset of the patients is likely to suffer from HCM-related cardiovascular events (repeated heart failure, stroke, and sudden death) later in their lives. The clinical course in patients with this mutation is therefore not benign in the long run, and careful management is needed, particularly in middle-aged and older patients.

Genotype/phenotype relations. A V592fs/8 mutation in the MyBPC gene is predicted to result in a truncation of the protein, including loss of C-terminal myosin and titin binding sites (36). Konno et al. (21) recently reported that a missense mutation (Arg820Gln) in the MyBPC gene is responsible for HCM with LV systolic dysfunction and dilation in elderly patients. The function of MyBPC protein has been elucidated by two recent studies using knockout mouse models (37,38). Homozygous-null mice in which full-length MyBPC protein was absent were viable and had significant cardiac hypertrophy with decreased fractional shortening. Furthermore, heterozygous MyBPC-null mice presented a slight-but-significant decrease in MyBPC amount and developed asymmetric septal hypertrophy (38). Thus, we speculate that a collapse of sarcomere stability compensated by residual MyBPC in heterozygous patients may occur with advancing age and may lead to impaired contractile function in the elderly.

Kokado et al. (39) reported that a Lys183 deletion mutation in the troponin I gene in HCM patients was associated with LV systolic impairment and dilation in those older than 40 years of age. Moolman et al. (22) presented that none of the subjects with a single-base insertion in exon 25 of the MyBPC gene showed LV systolic dysfunction and cavity enlargement, although the subjects included several elderly patients. Thus, underlying mutations may relate to the progress to the stage of LV dysfunction and dilation. However, the fact that not all elderly patients with the identical mutation develop “end-stage” disease suggests that other genetic and/or environmental factors are involved and underscores the genetic/phenotypic heterogeneity of HCM. Further investigations are needed to clarify these modifying factors.

Study limitations. Whether this particular mutation is more related to the progression to “end-stage” HCM than the other mutations in MyBPC gene or abnormal MyBPC itself is more prone to this phenotype than the other sarcomeric abnormalities is unknown. Further studies on the phenotype-genotype correlation in terms of longitudinal evolution are needed.

Conclusions. A founder V592fs/8 mutation in the MyBPC gene was identified in 15 of 94 Japanese families with HCM. Elderly patients in particular may evolve to the “end-stage” HCM, characterized by LV systolic dysfunction, cavity dilation, and irreversible heart failure. Although the manifestation is late in onset, the clinical course in patients with this mutation is not benign in the long run with progressive LV remodeling with advancing age.

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