Long-Term Outcome of 4 Korean Families With Hypertrophic Cardiomyopathy Caused by 4 Different Mutations

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ABSTRACT

Background: We sought to describe the long-term outcome of individuals in 4 Korean families with hypertrophic cardiomyopathy (HCM) with known mutations.

Hypothesis: Long-term clinical features of familial HCM might be characterized according to the mutation causing HCM.

Methods: We performed long-term (mean, 13.1 y) clinical evaluations on 46 subjects from 4 Korean families with different mutations.

Results: Myosin light chain 3 gene (*MYL3*) mutation was associated with late-onset HCM with relatively poor prognosis; 1 sudden cardiac death and 2 cases of heart failure with atrial fibrillation occurred among 12 subjects with this mutation. Myosin binding protein C gene (*MYBPC3*) mutation was associated with 2 cases of sudden cardiac death and 3 cases of heart failure among 7 affected members. Cardiac troponin I type 3 gene (*TNNI3*) mutation was associated with 5 deaths related to atrial fibrillation and stroke among 12 mutation-positive members. Myosin heavy chain 7 gene (*MYH7*) mutation was associated with 11 deaths in 15 affected members.

Conclusions: The clinical course was quite different for different HCM mutations. Even within the same family, individuals carrying the same mutation differed in disease expression and prognosis.

Introduction

Hypertrophic cardiomyopathy (HCM) is caused by genetic abnormalities with autosomal-dominant inheritance.^{1–3} Although the clinical course is highly variable, some mutations were associated with sudden cardiac death (SCD) and 10% of patients progressed to develop dilated cardiomyopathy (DCM).⁴ We previously reported clinical phenotypes in HCM families with the ventricular essential myosin light chain 3 gene (*MYL3*) or myosin heavy chain 7 gene (*MYH7*) mutation.^{5,6} In addition to these families, we performed long-term follow-up of 2 additional

families with myosin binding protein C gene (*MYBPC3*) or cardiac troponin I type 3 gene (*TNNI3*) mutation.⁷ Because there were few long-term observational studies on familial HCM associated with defined disease-causing mutations, we evaluated the clinical manifestations and long-term outcomes in 46 cases from 4 Korean HCM families carrying different disease-causing mutations.

Methods

Study Subjects and Clinical Evaluations

Out of the 116 subjects from 4 Korean HCM families who were eligible for this study, 46 who were proven to have HCM or to carry genetic mutations related to HCM were evaluated (Figure 1). In the family members who died before the enrollment of the study (n = 18), we obtained the medical history from the siblings, first-degree relatives, and/or available medical records. Otherwise, informed consent was obtained and the patients were evaluated. All available family members were initially screened by history, physical examination, electrocardiography (ECG),

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Figure 1. Pedigrees of familial hypertrophic cardiomyopathy. Circles and boxes indicate female and male individuals, respectively. Closed symbols indicate phenotype-positive members and hatched symbols indicate genotype-positive, phenotype-negative individuals. Open symbols indicate normal-phenotype individuals with negative or unknown genotype. Slashes indicate deceased individuals. The arrow indicates the proband of each family. Asterisk (*) indicates individuals whose genotypes were unknown.

echocardiography, and genetic evaluation. Blood samples were obtained from each family member for DNA extraction, and screening for mutations was performed as described previously.⁷

Left ventricular (LV) ejection fraction (LVEF) was estimated using the Quinones method and LV systolic dysfunction was defined as LVEF <50%.⁸ Left atrial (LA) dimension >40 mm on M-mode echocardiography was defined as LA enlargement. Presence of systolic anterior motion of mitral leaflet, asymmetric septal hypertrophy (ASH), and pressure gradient at the LV outflow tract were also evaluated. Without other known causes of LV hypertrophy (LVH), a maximal LV end-diastolic wall thickness ≥ 13 mm was used as a criterion for the diagnosis of HCM.

Clinical Follow-Up

After initial evaluation, all available patients with mutations were followed up clinically with echocardiography. Mean duration of clinical follow-up from initial presentation to last follow-up visit was 13.1 years (range, 5–27 y). Medical history regarding cause of death including sudden cardiac death (SCD), admission with aggravation of heart failure (HF), atrial fibrillation (AF), cerebrovascular accident (CVA), and other clinical events was obtained from available medical records or directly from first-degree relatives.

For estimation of penetrance rate, patients with positive phenotype were defined as those shown to have HCM or known to have experienced clinical events that might be related to HCM, such as death from HF, SCD, or CVA with AF before the age of 60 years. Patients younger than 18 years without clinical phenotypes at the time of evaluation were excluded from analysis of penetrance.

Results

Genetic Mutations and Characteristics of the HCM Pedigrees

Pedigrees of the 4 Korean HCM families are shown in Figure 1. The genetic mutations were as follows: *MYL3* A57G mutation in family 1, *MYBPC3* L1238P mutation in family 2, *TNNI3* R145G mutation in family 3, and *MYH7* G716R mutation in family 4. Summaries of clinical characteristics are presented in Table 1.

Clinical Characteristics of *MYL3* Mutation in Family 1

The major phenotypic characteristics of the *MYL3* A57G mutation were typical HCM with ASH. Five cases exhibited clinical phenotypes (Figure 1, Table 2); however, none of 6 family members in the third generation who carried the mutation had phenotypic expression until their second or third decade of age. There were 2 cases with AF and 2 with HF. There were 2 deaths, 1 of which (I-II-1) was due to SCD after drinking alcohol.

Table 1. Clinical Characteristics and Genetic Mutations in 4 Korean Families With Hypertrophic Cardiomyopathy

	Gene Related to HCM			
	<i>MYL3</i>	<i>MYBPC3</i>	<i>TNNI3</i>	<i>MYH7</i>
Locus of Mutation	3p, exon 3	11q11, exon 33	19p13.2, exon 7	14q1, exon 19
Mutation	A57G	L1238P	R145G	G716R
No. of mutation carriers (study subjects)	12	7	12	15
No. of positive phenotype/study subjects	5/12 (42%)	6/7 (86%)	12/12 (100%)	15/15 (100%)
Penetrance rate	63% (5/8) ^a	100% (6/6) ^a	100% (12/12)	100% (15/15)
No. of males/study subjects	9/12	5/7	6/12	9/16
No. of SCD/positive phenotype	1/5	2/6	1/12	8/15
No. of AF/available ECG data	2/11	2/5	5/8	2/6
No. of CVA/study subjects	1/12	0/7	7/12	0/15
No. of progression to DCM/study subjects	1/12	3/7	0/12	3/15
No. of ASx/study subjects (age >30 y)	8/12 (2/6)	1/7 (1/6)	4/12 (4/12)	2/15 (1/8)

Abbreviations: A57G, alanine 57 glycine mutation; AF, atrial fibrillation; ASx, asymptomatic subjects; CVA, cerebrovascular accident; DCM, dilated cardiomyopathy; G716R, glycine 716 arginine mutation; HCM, hypertrophic cardiomyopathy; L1238P, leucine 1238 proline mutation; MYBPC3, myosin binding protein C 3; MYH7, myosin heavy chain 7; MYL3, myosin essential light chain 3; No., number; R145G, arginine 145 glycine mutation; SCD, sudden cardiac death; TNNI2, troponin I 2.

^a For the evaluation of penetrance rate in families 1 and 2, patients without phenotypic expression who were age <18 years were excluded from analysis.

The proband (1-II-3) was diagnosed as typical HCM with ASH and normal LVEF at the age of 28. Echocardiographic findings at age 40 were similar to the initial study. She experienced symptoms of palpitation and dizziness intermittently after age 43. At age 45, she had syncope; ECG showed AF with rapid ventricular response and LVEF was 35%. After 2 months of digitalization and anticoagulation, LV systolic function was improved with LVEF of 53%.

The proband's sister (1-II-14) lacked clinical phenotype until age 33. However, at age 38, she presented at the hospital with pulmonary edema due to typical HCM with ASH and mid-LV cavity obstruction. Another sister of the proband (1-II-5) who carried the mutation is now 48 years old and is currently healthy with normal ECG and echocardiographic findings.

Clinical Characteristics of MYBPC3 Mutation in Family 2

The major phenotypic characteristics of the MYBPC3 L1238P mutation were typical HCM with ASH. Six patients out of 7 who had the genetic mutation exhibited clinical phenotypes (Figure 1, Table 2). Two patients died suddenly, 2 displayed AF, and 3 developed symptoms of HF with DCM phenotype during follow-up.

The proband (2-III-3) had several attacks of syncope and was diagnosed with HCM at age 27. EchoCG at age 39 revealed borderline LV function, and LVEF was 50%.

He was a heavy alcoholic. He had symptoms of dyspnea at age 41 and was admitted for pulmonary edema with an LVEF of 31% the next year. Thereafter, he began to experience paroxysmal AF and recurrent ventricular tachycardia (VT). At age 45, LV end-diastolic dimension (LVEDD) became 68 mm and LVEF was 25%. The patient was implanted with an implantable cardioverter defibrillator (ICD) at age 53. However, he died of intractable VT the next year.

The proband's older sister (2-III-2) was diagnosed with HCM at age 40. Echocardiography revealed typical HCM with ASH and normal LVEF. Interventricular septal wall thickness (IVSd) was 23 mm. She had hypertension, at 180/100 mm Hg. At age 56 she had symptoms of HF, and an ECG showed AF. IVSd was reduced to 13 mm. LVEF was also reduced, and LV apical thrombus was observed.

The proband's younger brother (2-III-5) was a heavy alcoholic. Echocardiography at age 28 revealed typical HCM with ASH and normal LVEF. IVSd was measured as 17 mm. He continued to abuse alcohol and developed a DCM phenotype at age 31. LVEDD was enlarged, and LVEF was decreased to 39%. He completely gave up alcohol and recovered from DCM. Echocardiography at age 39 showed normalized LVEDD with LVEF of 57%.

The proband's uncle (2-II-3) is now 62 years old. He had been doing well until recently, without many symptoms. Recently he experienced palpitation, and ambulatory

Table 2. Case Summary of Study Subjects

Family-Case No.		Age (y)			ECG Findings				Echocardiographic Findings						Clinical Event					
		Sex	IP	LF	Genotype	Phenotype	L VH	AF	Others	LVOTO	ASH (IVSd)	SAM	EF↓ (%)	LAE	Others	HF	SCD	CVA	Cause of Death	Comments
1-I-1	M	56	75	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	Recurrent CVA
1-II-1 ^a	M	29	34	NA	+	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	+	+	SCD	Autopsy done, alcohol ^{b,c}
1-II-3	F	32	51	+	+	+	+	+	+	30 mmHg	+	+	+	+	+	+	+	+	+	HCM at age 28, improved LVEF after rate control
1-II-5	F	37	48	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	No phenotypic expression
1-II-7	M	31	48	+	+	+	+	+	+	36 mmHg	+	+	+	+	+	+	+	+	+	
1-II-14	F	29	38	+	+	+	+	+	+	71 mmHg	+	+	+	+	+	+	+	+	+	HCM at age 38
1-III-1	M	16	25	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
1-III-2	F	14	23	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
1-III-5	M	8	17	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
1-III-6	M	9	18	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
1-III-7	M	6	16	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
1-III-11	M	4	13	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
2-II-1 ^a	M	NA	53	NA	Probable	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	+	+	SCD	
2-II-3	M	46	63	+	+	+	+	+	+	NSVT on Holter monitor	+	+	+	+	+	+	+	+	+	ICD
2-II-5 ^a	M	NA	41	NA	+	+	NA	NA	NA	+	+	+	+	+	+	+	+	+	+	No phenotypic expression
2-III-2	F	40	57	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	DCM, hypertension ^b
2-III-3	M	27	54	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	DCM, ICD, alcohol ^b
2-III-5	M	28	49	+	+	+	+	+	+	NSVT on Holter monitor	+	+	+	+	+	+	+	+	+	DCM, alcohol ^b

Table 2. (continued)

Family-Case No.	Sex	IP	LF	Genotype	Phenotype	ECG Findings				Echocardiographic Findings					Clinical Event		
						L VH	A F	Others	L VOTO	ASH (IV5d)	SAM	EF↓ (%)	LAE	Others	HF	SCD	Cause of Death
2-IV-4	F	4	17	+	—	—	—	—	—	—	—	—	—	—	—	—	—
3-I-1 ^a	M	NA	55	NA	Probable	NA	NA	NA	NA	NA	NA	NA	NA	—	—	+	SCD
3-II-1 ^a	M	NA	49	NA	Probable	NA	NA	NA	NA	NA	NA	NA	NA	—	—	+	CVA
3-II-4 ^a	F	56	70	NA	Probable	NA	NA	NA	NA	NA	NA	NA	NA	—	—	+	HF
3-II-5 ^a	F	NA	73	NA	Probable	NA	NA	NA	NA	NA	NA	NA	NA	—	—	+	CVA
3-II-9	F	53	69	+	+	+	+	—	—	—	—	—	—	None	+	—	CVA
3-II-10	M	33	49	+	+	—	+	—	—	+	—	—	—	Typical HCM	—	—	CVA
3-III-1	M	47	60	+	+	—	+	PVCs	—	—	—	—	—	Apical HCM	—	—	PAF, on warfarin
3-III-5	M	33	51	+	—	—	+	—	—	—	—	—	—	None	—	—	—
3-III-6 ^a	F	NA	33	NA	+	—	+	—	—	—	—	—	—	RCM	+	—	CVA
3-III-8 ^a	M	NA	35	NA	Probable	NA	NA	NA	NA	NA	NA	NA	NA	NA	—	—	Working, ^b good health until sudden death
3-III-9	F	22	35	+	+	+	—	-TV ₂ -V ₆	—	—	—	—	—	Apical HCM	—	—	—
3-III-10	F	19	32	+	+	+	—	-TV ₃ -V ₆	—	—	—	—	—	Apical HCM	—	—	—
4-I-1 ^a	M	NA	35	NA	Probable	NA	NA	NA	NA	NA	NA	NA	NA	NA	—	—	SCD
4-II-3 ^a	F	34	42	NA	Probable	NA	NA	NA	NA	NA	NA	NA	NA	NA	—	—	SCD
4-II-5 ^a	F	33	47	NA	+	NA	NA	NA	—	—	—	—	—	LVEDD 64 mm	+	—	HF
4-II-7 ^a	F	NA	45	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	—	—	SCD
4-II-9 ^a	M	17	25	NA	+	NA	NA	NA	NA	NA	NA	NA	NA	NA	+	—	HF
4-II-12	M	37	46	+	+	+	+	—	—	—	—	—	—	LVEDD 71 mm	+	—	Deterioration to DCM, alcohol ^b
4-III-4	F	34	50	+	+	+	+	—	—	—	—	—	—	LVEDD 60 mm LV thrombus	+	—	Deterioration to DCM, pregnancy, ^b emotional stress, ^b HTPL

Table 2. (continued)

Family-Case No.	Sex	IP	LF	Genotype	Phenotype	ECG Findings					Echocardiographic Findings					Clinical Event			
						L VH	AF	Others	LVOTO	ASH (IVSd)	SAM	EF↓ (%)	LAE	Others	HF	SCD	CVA	Cause of Death	Comments
4-III-8	M	32	43	+	+	+	—	—	—	+	(21 mm)	—	—	Typical HCM	—	—	—	—	
4-III-9 ^a	M	NA	32	NA	Probable	NA	NA	NA	NA	NA	NA	NA	NA	NA	—	+	—	SCD	Alcohol ^{b,c}
4-III-10 ^a	M	NA	12	NA	Probable	NA	NA	NA	NA	NA	NA	NA	NA	NA	—	+	—	SCD	Walking outside ^c
4-III-11 ^a	F	NA	13	NA	Probable	NA	NA	NA	NA	NA	NA	NA	NA	NA	—	+	—	SCD	Running ^c
4-III-16 ^a	M	NA	15	NA	Probable	NA	NA	NA	NA	NA	NA	NA	NA	NA	—	+	—	SCD	Running ^c
4-III-19	F	7	20	+	+	+	—	Q _{III}	—	+	(15 mm)	+	—	Typical HCM	+	—	—	—	HCM at age 10
4-IV-1	M	9	24	+	+	+	—	Q ₄ –V ₆	—	+	(23 mm)	—	—	Typical HCM	—	—	—	—	Noncompaction-like morphology of LV
4-IV-2	M	5	11	+	+	+	—	—	—	+	(25 mm)	—	—	Typical HCM	—	+	—	SCD	Playing outside ^c

Abbreviations: ASH, asymmetric septal hypertrophy; BBB, bundle branch block; CVA, cerebrovascular accident; DCM, dilated cardiomyopathy; DM, diabetes mellitus; ECG, electrocardiographic; EF↓, left ventricular ejection fraction <50%; F, female; HCM, hypertrophic cardiomyopathy; HF, heart failure; HTPL, heart transplantation; ICD, implantable cardioverter defibrillator; IP, at initial presentation; IVSd, interventricular septal wall thickness in diastole; LAE, left atrial enlargement; LF, at last follow-up; LV, left ventricle; LVOTO, left ventricular end diastolic dimension; LVH, left ventricular hypertrophy; LVOTO, left ventricular outflow tract obstruction; M, male; NA, no available data; NSVT, nonsustained ventricular tachycardia; PAF, paroxysmal atrial fibrillation; PVC, premature ventricular contraction; Q wave; RCM, restrictive cardiomyopathy; SAM, systolic anterior motion of mitral valve; SCD, sudden cardiac death; ST, ST segment; T, T wave inversion; TIA, transient ischemic attack; VT, ventricular tachycardia.

^a Consent could not be obtained from patient due to death before study enrollment; history was obtained from relatives and/or medical records.

^b Possible aggravating factor.

^c The possible precipitating factor at the time of SCD.

ECG revealed nonsustained VT (NSVT) (Figure 2A). Echocardiography revealed LVEF of 70%. Cardiac magnetic resonance imaging (CMR) revealed large area of delayed enhancement (Figure 2B and 2C). After he had an ICD implanted, several episodes of VT developed and appropriate shocks were delivered. He was doing well with amiodarone medication thereafter.

Clinical Characteristics of *TNNI3* Mutation in Family 3

The major phenotypic characteristics of the *TNNI3* R145G mutation were both typical and apical-type HCM. Among 12 patients with the mutation, 11 had clinical phenotype of HCM or clinical events related to CVA, HF, or AF (Figure 1, Table 2). There were 8 deaths, which were due to CVA ($n = 5$), SCD ($n = 2$), and aggravation of HF ($n = 1$). Seven patients developed CVA and 4 had documented AF. Three patients had the apical variant of HCM, but only 1 of these had AF at the time of evaluation. One patient (3-III-6) had restrictive cardiomyopathy and died of CVA with embolic infarction due to AF.

The proband (3-III-1) had several attacks of syncope and was diagnosed with HCM at age 27. Echocardiography at age 39 showed LVEF of 50%. Although IVSd was normal, the entire apical wall was thickened up to 18 mm. LA dimension was 48 mm. He had symptoms of paroxysmal AF at age 54 and echocardiography revealed restrictive physiology in a mitral inflow Doppler study. He started medication with warfarin and has been doing well since.

Clinical Characteristics of *MYH7* Mutation in Family 4

The major phenotypic characteristics of the *MYH7* G716R mutation were HCM with frequent deterioration to DCM or SCD at a young age. All 15 patients with the mutation exhibited clinical phenotype or clinical events such as SCD or HF with deterioration to DCM (Figure 1, Table 2).

The proband (4-II-12) was diagnosed with HCM with normal LVEF at age 23. He was a heavy alcoholic. At age 38, LVEDD was 60 mm and LVEF was 39%. He had New York Heart Association (NYHA) class II–III dyspnea. He continued to drink alcohol despite aggravation of symptoms. Clinical events of AF, LV thrombus, and renal infarction developed during follow-up. At age 45, LVEDD was further enlarged to 71 mm and LVEF was reduced to 20%. He died of HF while awaiting cardiac transplantation at age 46.

The proband's niece (4-III-4) began to experience dyspnea at age 18, and typical HCM with ASH was diagnosed. Echocardiography revealed normal LVEF and thickened IVSd (21 mm) at age 35. LVEF was reduced to 38% without significant change in IVSd at age 37. When she was 40, she lost her son to SCD, and her symptoms aggravated to NYHA class III–IV. Echocardiography at age 45 showed DCM feature with LVEF of 13%. Cardiac transplantation was performed at age 45 years.

Discussion

In this long-term observational study, we evaluated the clinical features of 46 subjects with known genetic mutations associated with HCM. There were several unique findings in HCM families of the current study.

First, family 1 with the *MYL3* mutation could be characterized by the late-onset HCM. Considering that late-onset HCM is associated with better prognosis, the fact that 3 out of 6 patients with clinical expression of HCM experienced a significant clinical event of AF, CVA, or HF is noteworthy.^{9,10} Thus, prognosis of familial HCM might not be regarded benign simply because of late expression of the clinical phenotype.

The second important observation is that there were several external factors possibly associated with the progression of LV remodeling in familial HCM. In the current study, follow-up echocardiography of 2 alcoholic patients (2-III-3 and 2-III-5) and 1 with uncontrolled hypertension (2-III-2) revealed morphological changes similar to DCM. In addition, patient 4-II-12 continued to drink alcohol and died of HF, and patient 4-III-4 displayed clinical deterioration after the death of her son. Although the causal relationship is not definite, we hypothesize that HCM might be susceptible to external factors such as excessive alcohol intake, unfavorable loading conditions, and emotional stress.

Another notable finding of this study was the high prevalence of AF and CVA in family 3 with the *TNNI3* mutation. High prevalence of SCD and CVA with AF at relatively young ages suggests that the clinical course of this family was significantly affected by development of AF. The effect of AF on disease progression was also evident in the case of the proband of family 1. These observations are consistent with previous studies showing that AF was independently associated with stroke, HF-related death, and long-term progression with HF symptoms.^{11,12}

Recently, dense delayed enhancement was reported to be related with SCD even in the HCM patients with borderline risk.^{13,14} Patient 2-II-3, who had dense fibrosis on CMR, was found to have NSVT and appropriate shock after ICD implantation. SCD is rare but important because it might occur even in reasonably good clinical status with preserved LVEF. Thus, in the case of family history of SCD and dense delayed enhancement on CMR, NSVT seems to be seen more and we need to consider prophylactic ICD implantation, such as in the case of 2-III-3.

Since we published the results of our initial analysis of families 1 and 4, further observations were conducted for 8 and 11 years, respectively.^{5,6} Notable changes during this period were as follows: In family 1, patient 1-II-14 developed severe clinical phenotype (HCM and pulmonary edema) at age 38 with mid-LV cavity obliteration. Thus, mid-LV obstruction might be considered as one of the clinical findings of the *MYL3* mutation, as previously

Figure 2. Non-sustained ventricular tachycardia (A) was found on the 24-hour ambulatory electrocardiogram in patient 2-II-3 of family 2. Magnetic resonance imaging of the left ventricle shows (B) marked hypertrophy of interventricular septum and (C) delayed hyperenhancement in anterior interventricular septum taken at 10 minutes after gadolinium injection in the same patient.

reported.¹⁵ In family 4, the proband and his niece (4-III-4) died or underwent cardiac transplantation due to further deterioration of LV function. Additionally, patient 4-IV-1 had morphologic changes similar to LV noncompaction at age 22, which might have resulted from rapid cell death and

replacement with fibrosis related to the malignant nature of the *MYH7* mutation.

Study Limitations

There were several limitations to this study. First, clinical evaluation was not available for some subjects with SCD

Table 3. Notable Findings in Each Family

Family	Involved Gene	Characteristics	Case Examples
1	MYL3	Late onset of phenotypic expression	II-5, II-14
		Old age with genotype positive, but phenotype negative	II-5
		Midventricular obliteration	II-14
		SD	II-1
2	MYBPC3	Deterioration with chronic alcohol intake	II-3, III-5
		VT	III-3, II-3
		SD	II-1, II-5
3	TNNT3	AF	II-9, II-10, III-1, III-5, III-6
		CVA	I-1, II-1, II-4, II-5, II-9, II-10, III-6
		Apical HCM	III-1, III-9, III-10
		SD	I-1, III-8
4	MYH7	Early onset of phenotype	IV-1, IV-2, III-19
		Deterioration to DCM	II-12, III-4
		LV noncompaction-like change	IV-1
		HTPL	III-4
		SD	I-1, II-3, II-7, III-9, III-10, III-11, III-16, IV-2

Abbreviations: AF, atrial fibrillation; CVA, cerebrovascular accident; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HTPL, heart transplantation; LV, left ventricle; SD, sudden death; VT, ventricular tachycardia.

who were not evaluated before their death. Second, only a small number of families was included in the current study, and only 1 family was evaluated for each mutation. Thus, the findings in our study could not be generalized to other familial HCM with the same mutations.

Conclusion

The penetrance, phenotypes, and clinical courses of familial HCM were highly variable, and a wide spectrum of clinical

features was evident even within the same family. However, within each family the clinical presentations displayed certain unique clinical characteristics, and it is worthwhile to consider these in relation to the genetic mutations (Table 3). Our results suggest a relationship between clinical deterioration and extrinsic factors such as alcohol intake.

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