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【 CASE REPORT 】

End-stage Hypertrophic Cardiomyopathy with Advanced Heart Failure in Patients Carrying *MYH7* R453 Variants: A Case Series

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Abstract:
The *MYH7* R453 variant has been identified in inherited hypertrophic cardiomyopathy (HCM) and is associated with sudden death and a poor prognosis. The detailed clinical course of HCM with the *MYH7* R453 variant, from a preserved to a reduced left ventricular ejection fraction, has not been reported. We identified the *MYH7* R453C and R453H variants in three patients who progressively developed advanced heart failure requiring circulatory support and summarized the clinical course and echocardiographic parameters of these patients over the years. Because of the rapid disease progression, we consider genetic screening for patients with HCM imperative for future prognosis stratification.

Key words: hypertrophic cardiomyopathy, advanced heart failure, *MYH7* variant

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Introduction

Hypertrophic cardiomyopathy (HCM) is a genetic disease characterized by left ventricular hypertrophy with a preserved left ventricular (LV) ejection fraction (LVEF), and its prevalence is estimated to be 1:344-1:625 in the general adult population (1). A cohort study of 1,259 consecutive patients with HCM demonstrated that 3.5% of patients developed LV systolic dysfunction (LVSD), defined as LVEF <50% (2). More recently, an international registry study of 6,793 patients with HCM demonstrated that 7.5% of patients developed LVSD over 15 years (3). *MYH7*, which encodes the β-myosin heavy chain, is one of the most common genes that causes HCM; pathogenic variants of *MYH7* have been identified in 20-30% of patients with HCM (4, 5). *MYH7* variants have also been identified in 4-10% of patients with dilated cardiomyopathy (DCM) (5), suggesting that the clinical course and phenotypic impact of *MYH7* variants are variable in individual patients. Recently, a clinical study examining the clinical course of 147 individuals established that *MYH7*-related DCM is characterized by an early age of onset, low LV reverse remodeling, and frequent progression to end-stage heart failure (6). Among the pathogenic variants identified in *MYH7*, the R453C and R453H mutations are associated with sudden death, a poor prognosis, and progressive heart failure (7, 8). Despite the accumulating evidence concerning *MYH7*-related cardiomyopathy, the detailed clinical course of HCM with an *MYH7* R453 variant from a preserved LVEF to LVSD over time has not yet been reported.

We herein report three cases of end-stage HCM with the *MYH7* R453 variants that required circulatory support due to advanced heart failure.

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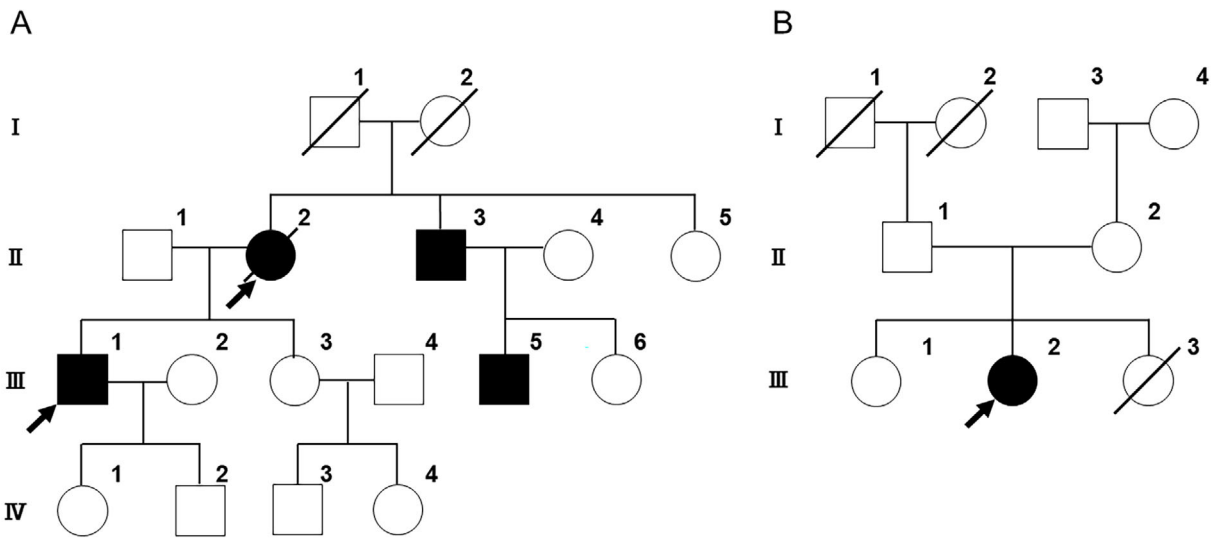

Figure 1. **Family pedigree charts of patients with HCM carrying the *MYH7* R453C variant. Black arrows indicate Patients 1 (A-III-1), 2 (A-II-2), and 3 (B-III-2). Genetic testing was performed in A-III-1, A-II-2, and B-III-2. Patients who developed HCM with LVSD are shown as black circles (females) or black boxes (males). According to the available medical records and medical interviews, the other family members were not diagnosed with HCM.**

Table 1. **Baseline Clinical Characteristics of the Patients at the Initial Visits.**

Characteristic	Patient 1	Patient 2	Patient 3
Age (years)	27	37	12
Sex	Male	Female	Female
Onset	HF	HF	HF
Initial diagnosis	HCM	HCM	HCM
Family history			
HCM	+	+	-
Symptoms			
DOE	+	+	+
Arrhythmia	AF	-	-
Edema	+	-	-
NYHA class	II	I	II
Echocardiogram			
LVDd/LVDs (mm)	42/28	44/28	35/23
IVST/PWT (mm)	15/14	21/12	10/7
LVEF (%)	62	50	64

HF: heart failure, HCM: hypertrophic cardiomyopathy, DOE: dyspnea on exertion, AF: atrial fibrillation, LVDd: left ventricular end-diastolic dimension, LVDs: left ventricular end-systolic dimension, IVST: interventricular septum thickness, PWT: posterior wall thickness, LVEF: left ventricular ejection fraction

Case Report

We encountered three patients with HCM and LVSD in two families who developed advanced heart failure and required circulatory support. Family pedigree charts of the patients are shown in Fig. 1. Patients 1 (A-III-1) and 2 (A-II-2) were a man and his mother with family histories of HCM with LVSD. Patient 3 (B-III-2) did not have any family history of cardiomyopathy or cardiovascular disease, as confirmed by the available medical records. At the initial visit, all patients had developed dyspnea of varying degrees due to heart failure. Patient 1 presented with dyspnea on exertion (DOE) and palpitations due to atrial fibrillation. Patient 2 presented with persistent coughing and an enlarged cardiothoracic ratio (CTR) on chest radiography. Patient 3 was first taken to a nearby hospital because of a fever, productive cough with an enlarged CTR, pulmonary congestion, and a provisional diagnosis of acute myocarditis. An echocardiogram revealed an increased intraventricular septal (IVS) thickness and a normal LV diastolic and systolic diameter (LVDd/LVDs) in Patients 1 and 2. Although Patient 3 was initially managed for acute myocarditis, an echocardiogram at follow-up after recovery showed asymmetric septal hypertrophy (ASH).

The baseline patient characteristics at the initial visit are shown in Table 1. At the initial visit, the LVEF of all patients was preserved at >50%. Patients 1 and 2 were definitively diagnosed with HCM based on echocardiographic findings, including ASH (9, 10). Patient 3 was initially suspected of having restrictive cardiomyopathy because of the left atrial enlargement with a preserved LVEF and LV diastolic dysfunction; eventually, a diagnosis of HCM was made based on echocardiogram findings (9, 10). Given their diagnosis, all patients were administered guideline-based standard medical treatment.

An overview of the clinical courses of the three patients is illustrated in Fig. 2, with the changes in echocardiogram parameters over time shown in Fig. 3. Patient 1 first developed heart failure symptoms of edema of the lower extremities at 31 years old, 4 years after the HCM diagnosis. Patient 2 first complained of palpitations and fatigue due to

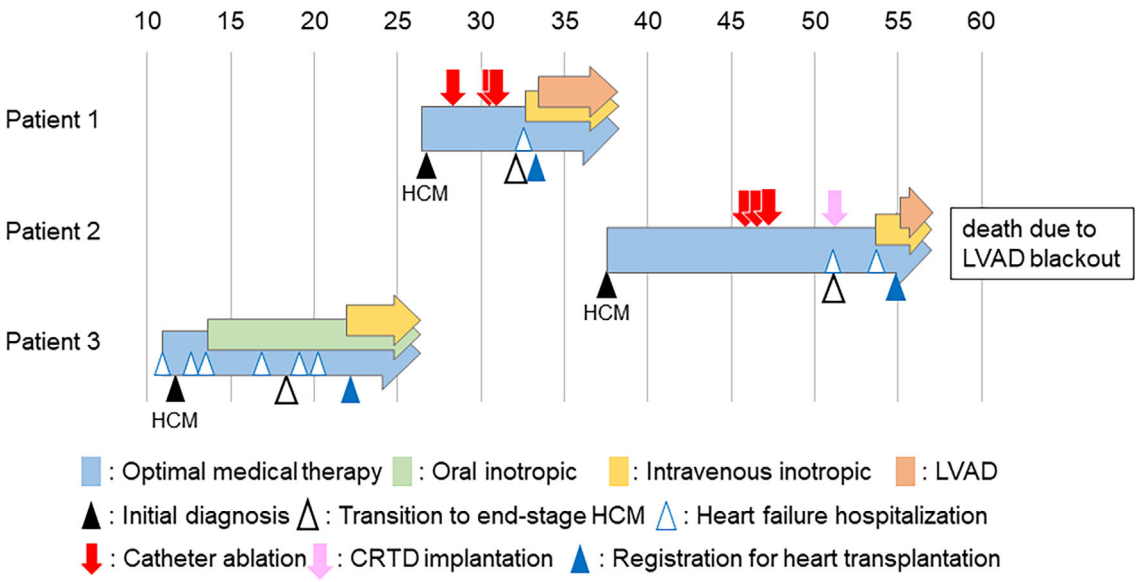

Figure 2. **Clinical courses of the three patients. All patients were diagnosed based on echocardiogram findings. The transition to end-stage HCM was defined as the first detection of a left ventricular ejection fraction of <50%. HCM: hypertrophic cardiomyopathy, RCM: restrictive cardiomyopathy, CRTD: cardiac resynchronization therapy defibrillator, LVAD: left ventricular assist device**

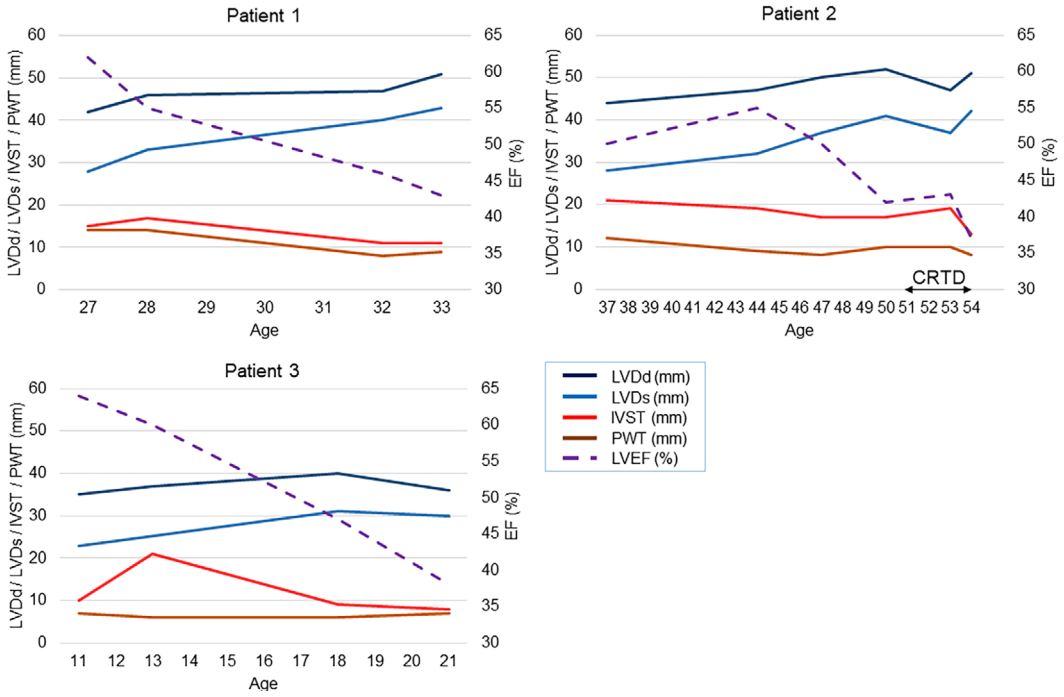

Figure 3. **Echocardiographic parameters during the clinical course. Echocardiographic parameters from HCM onset to registration for heart transplantation. LVDd: left ventricular end-diastolic dimension, LVDs: left ventricular end-systolic dimension, IVST: interventricular septum thickness, PWT: posterior wall thickness, LVEF: left ventricular ejection fraction, CRTD: cardiac resynchronization therapy defibrillator**

atrial arrhythmia at 46 years old, 9 years after the HCM diagnosis, which progressively developed to edema and DOE at 50 years old. Patients 1 and 2 developed atrial arrhythmias (atrial tachycardia and fibrillation) and underwent repeated catheter ablations. Although cardiac resynchronization therapy defibrillator (CRTD) was implanted in Patient 2 at 51 years old due to the progression of heart failure, she developed DOE that was resistant to medical treatment and required repeated hospitalization. Patient 3 complained of DOE 2 years after the initial visit at 12 years old and progressively developed New York Heart Association (NYHA) III/IV heart failure symptoms requiring the administration of

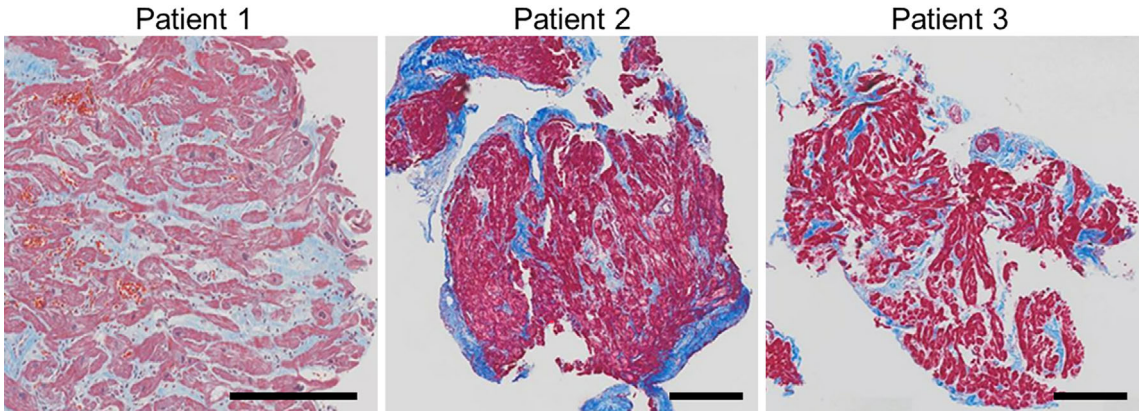

Figure 4. **Histopathological findings of myocardial biopsy samples. All specimens of the right ventricular myocardial biopsy were stained with Masson's trichrome stain. Hypertrophic cardiomyocytes with distorted shapes and pleiotropic nuclei were observed in all patients. The myocardial sections of all patients showed a disorganized myocardial architecture, including cardiomyocyte disarray and interstitial fibrosis, stained in blue. Scale bar: 200 μm.**

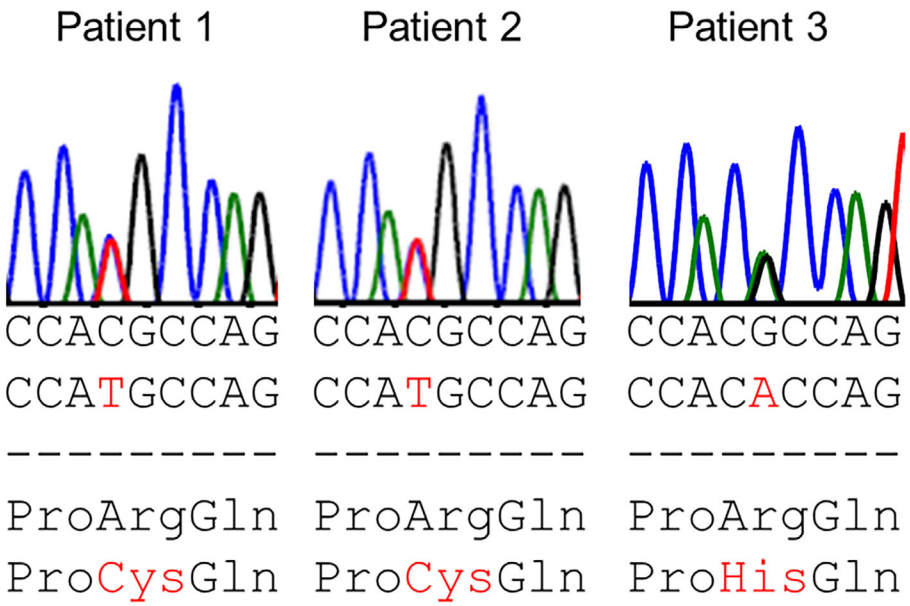

Figure 5. **Sanger sequence analyses. The results of direct Sanger sequencing using genomic DNA extracted from the peripheral blood of the patients. Genomic DNA and amino acid sequences are shown. The identified variants and substituted amino acids are highlighted in red.**

pimobendane, an oral inotropic agent. Refractory heart failure symptoms restricted her daily activity during adolescence. All patients exhibited similar echocardiographic changes from HCM with a preserved LVEF to HCM with LVSD; LV enlargement over the clinical course was modest in all patients (Fig. 3). IVS thinning and LVEF decline were detected at 32 years old in Patient 1, 51 years old in Patient 2, and 18 years old in Patient 3. The time from the diagnosis of HCM to that of HCM with LVSD was 5, 14, and 6 years in Patients 1, 2, and 3, respectively (Fig. 2).

All patients underwent a right ventricular myocardial biopsy; a histopathological analysis revealed myocardial hypertrophy and disarray, consistent with the diagnosis of HCM (Fig. 4). A genetic analysis identified a heterozygous *MYH7* R453C variant in Patients 1 and 2 and a heterozygous *MYH7* R453H variant in Patient 3 (Fig. 5).

After the transition to end-stage HCM with LVSD, all patients developed NYHA III/IV heart failure symptoms that could not be controlled with standard medical therapy alone. Thus, the patients were administered intravenous inotropic agents and were registered for heart transplantation. The patient characteristics and echocardiogram and cardiac catheterization findings during this period are shown in Table 2.

Right-heart cardiac catheterization demonstrated a decreased cardiac index (CI) and increased mean pulmonary artery pressure (mPAP) and pulmonary artery wedge pressure (PAWP) in Patients 1, 2, and 3. LV assist device (LVAD) implantation was considered because of the severely

Table 2. Clinical Characteristics of the Patient at the Time of Registration for Heart Transplantation.

Characteristic	Patient 1	Patient 2	Patient 3
Age (years)	33	54	22
Duration from the onset	6	17	11
Definitive diagnosis	End-stage HCM	End-stage HCM	End-stage HCM
Symptoms			
DOE	+	+	+
Arrhythmia	PAC, PVC, NSVT	PVC	PAC, PVC
Edema	+	-	-
NYHA	IV	IV	III
Echocardiogram			
LVDd/LVDs (mm)	51/43	51/42	37/24
IVST/PWT (mm)	11/9	13/8	10/8
LVEF (%)	43	33	47
E/A	2.00	1.88	1.52
E/e'	13.1	11.0	11.7
LVMI (g/m^2)	94.5	122.4	76.2
TAPSE (mm)	23	19.5	24.3
RHC			
CO (L/min)	4.2	3.2	2.0
CI (L/min/m^2)	2.1	1.9	1.5
mPAP (mmHg)	35	32	23
PAWP (mmHg)	35	32	18

RHC was performed under circulatory control using intravenous inotropic agents in all patients. Arrhythmia observed on Holter electrocardiography is shown. PAC: premature atrial contraction, PVC: premature ventricular contraction, NSVT: non-sustained ventricular tachycardia, LVMI: left ventricular mass index, TAPSE: tricuspid annular plane systolic excursion, RHC: right heart catheterization, CO: cardiac output, CI: cardiac index, mPAP: mean pulmonary artery pressure, PAWP: pulmonary artery wedge pressure

advanced heart failure in these patients. However, the relatively small LV diameter identified on echocardiography hindered the clinical decision concerning LVAD implantation because an insufficient LV volume might limit efficient mechanical suction via the inflow conduit. Eventually, an LVAD was implanted in Patients 1 and 2 within three months of being registered for heart transplantation; Patient 3 was deemed unsuitable for LVAD implantation because of the insufficient LV volume. Currently, Patient 1 is receiving standard medical therapy at the outpatient department, and Patient 3 is hospitalized for the continuous intravenous infusion of inotropic agents. Patient 2 died of cardiac arrest 2 years after LVAD implantation at 57 years old due to LVAD blackout during self-management.

Discussion

MYH7 variants (R453C and R453H) are leading pathogenic variants of HCM (7, 8). However, the detailed clinical course of HCM with the *MYH7* variants, including the transition from preserved LVEF to LVSD requiring intensive circulatory support, remains unclear. In this report, we summarized the detailed clinical courses of three patients with HCM carrying the *MYH7* R453C and R453H variants who exhibited advanced heart failure symptoms.

HCM in patients carrying the *MYH7* R453C and R453H variants has been reported as an inherited familial disorder worldwide (7, 8, 11, 12). In this case series, Patients 1 and 2 were a man and his mother with family histories of HCM. The mother of Patient 3 and the mother's parents did not have any cardiovascular diseases, and we were unable to obtain detailed clinical or genomic data from the father of Patient 3. Because *MYH7* R453 variants have been detected in familial HCM cases (7, 11, 12), we speculated that the father of Patient 3 might carry the *MYH7* R453H variant. However, *de novo* variants are identified more frequently in nonfamilial pediatric HCM patients than in adult patients (13, 14) and are associated with an earlier onset and higher frequency of adverse outcomes in pediatric HCM patients (15). Therefore, we also speculated that the *MYH7* R453H variant in Patient 3 diagnosed with HCM in her early teens was a *de novo* mutation.

A cohort study of 1,259 consecutively enrolled patients with HCM demonstrated that LVSD developed over a wide age range (14-74 years old), with 45% of patients <40 years old. The duration from the onset of HCM symptoms to LVSD identification was 14±10 years, while that from LVSD onset to death/transplantation was 2.7±2 years (2). A more recent international registry examining 6,793 patients with HCM demonstrated that the prevalence of LVSD was 7.5% over 15 years, and 23.8% of the patients had NYHA III/IV heart failure when LVSD was confirmed (3). Patients

with LVSD received the initial diagnosis of HCM at the mean age of 35.6±19.2 years old; LVSD was first recognized at the mean age of 50.3±17.9 years old. The median duration from LVSD confirmation to composite outcome, including cardiac death, heart transplantation, and LVAD implantation, was 8.4 years in that cohort (3). The patients in the present case series were diagnosed at 27 (Patient 1), 37 (Patient 2), and 12 (Patient 3) years old, and the duration from HCM diagnosis to LVSD confirmation was 5, 14, and 6 years, respectively. All three patients in this series developed NYHA III/IV heart failure when diagnosed with LVSD. An LVAD was implanted 1 year (Patient 1) and 4 years (Patient 2) after the LVSD diagnosis. Patient 3 was registered on the waiting list for heart transplantation four years after the LVSD diagnosis and has been receiving intravenous inotropic agents.

The entire clinical course of the patients in this report was consistent with previous findings. However, the duration from the diagnosis of HCM to LVSD detection was shorter than that described in the previous studies, suggesting that these three patients exhibited an earlier disease progression than others. Furthermore, the duration from the LVSD diagnosis to intensive circulatory support was shorter in this case series than in the general HCM population, suggesting that patients with HCM carrying the *MYH7* R453 variants progressed to a state requiring circulatory support, such as LVAD implantation. Among our three patients, Patient 3 exhibited an earlier disease onset than the others, was initially diagnosed with RCM because of restrictive phenotypes, and showed a more rapid HF progression than the others. *MYH7* R453H variants were identified in teenage HCM patients in cohort studies in Italy and Portugal (16, 17). A previous case report demonstrated that a 23-year-old man with HCM carrying both *MYH7* R403W and R453H variants exhibited progressive heart failure (8). We therefore speculated that the R453H variant might affect the disease phenotype more severely than the R453C variant. However, genetic variants, social factors, and one's lifestyle reportedly affect the clinical phenotypes of cardiomyopathy (18, 19). Therefore, we also speculated that the genetic background or environmental factors might have affected the clinical course of Patient 3.

Although the efficacy of genetic screening in predicting the prognosis in HCM has been controversial (20, 21), a recent large cohort study examining 4,591 patients with HCM, with 2,763 genotyped data points, demonstrated that pathogenic/likely pathogenic sarcomere mutations significantly increased the risk of adverse outcomes (22). Furthermore, a recently developed small-molecule myosin ATPase inhibitor (MYK-461) reduced cardiac contractility and ameliorated cardiac hypertrophy in mice carrying the R453C mutation (23). *MYH7* encodes a β-myosin heavy chain, a component of myosin that consists of a head and tail region. The head region, called the motor domain, acts as the ATPase and is involved in hydrolysis and interaction with actin, which leads to an intrinsic contractile force. R453 is located in the myosin motor domain and lies between the nucleotide-binding pocket and the actin-binding site (24). *In vitro* biomechanical analyses revealed that the β-myosin heavy chain with the R453C mutation has a 50% increased intrinsic force in the motor domain compared to the wild type, with no appreciable change in stroke size; thus, the R453C mutation causes hypercontractility of the heart muscles (25). In clinical settings, MYK-461 improves the exercise capacity, LV outflow obstruction, and NYHA functional class in patients with obstructive HCM (26). Although pharmacological therapies that improve the prognosis of patients with HCM have not yet been established (10), MYK-461 may potentially be useful for precision medicine based on biochemical evidence.

In conclusion, we summarized the clinical courses of patients with HCM carrying the *MYH7* R453 variants who exhibited advanced heart failure. We recommend genetic screening for patients with HCM and their families for the stratification of the prognosis and future development of precision medicine.

Genetic analyses

The performance of genetic analyses was approved by the Ethics Committee of Osaka University Hospital. The study protocol conformed to the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. Informed consent was obtained from all patients. We extracted genomic DNA from the peripheral blood, analyzed it by whole-exome sequencing, and searched the sequencing results for rare pathogenic variants in 57 cardiomyopathy-related genes, as previously described (27). After variant filtering, no pathogenic variants other than *MYH7* variants were identified.

The authors state that they have no Conflict of Interest (COI).

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