Hypertrophic cardiomyopathy (HCM) is a primary cardiac disorder with a heterogeneous clinical and morphological expression. Disease-causing mutations have been described in 9 different genes encoding sarcomeric polypeptides, and the clinical characteristics of patients with familial HCM differ depending on the particular genetic mutation. In general, mutations in the \( \alpha \)-cardiac myosin heavy chain gene are associated with substantial cardiac hypertrophy, whereas patients with mutations in cardiac troponin T have mild cardiac hypertrophy. As these reports have not been follow-up studies, it is unclear whether the morphological characteristics of the patients with these mutations remain constant or change throughout life. We describe a patient with a deletion mutation in cardiac myosin binding protein C (MYBPC) gene whom we were able to follow for 17 years.

**Case Report**

A 60-year-old man with obstructive HCM has been followed by us since 1983. He experienced chest pain on effort when he was 43 years old and was administered 30 mg of propranolol per day, which improved his symptoms. The first electrocardiogram (ECG) (Fig 1A), showed normal sinus rhythm, Q waves in leads II and V4–6, tall T waves in V3–6 leads and prolonged QTc. There were no abnormal findings on the chest X-ray (Fig 2A). A mechanocardiogram (MCG) (Fig 3A) disclosed an abrupt upstroke of the carotid pulse tracing with a mild mid-systolic dip, an increased atrial wave (14.8%) and a normal interval between the aortic second heart sound and O point (IIa–O time, 128 ms, normal value = 119±9). An echocardiogram (UCG) (Fig 4A) revealed mild hypertrophy of both the interventricular septum (IVS thickness: 15 mm) and left ventricular posterior wall (LVPW thickness: 12 mm), a narrow region of the outflow tract, and incomplete systolic anterior motion of the mitral valve. Left ventricular end-diastolic and end-systolic dimensions (LVDd and LVDs) were 46 mm and 26 mm, respectively. The fractional shortening (FS) was 43.4%. No overt valvular heart disease was found. Elevations of serum cardiac enzymes were found in 1989; lactate dehydrogenase (LDH) and creatine kinase (CK) were 130 IU/L (normal value = 49–123) and 96 IU/L (12–70), respectively, and LDH1 and CK-MB were 40.0% (19–32) and 2.5% (not detected), respectively.

Until 1990, the patient’s ECGs (Fig 1A–C) showed a gradual progression of the RV5+SV1 voltages. In addition, carotid pulse tracing in 1990 and 1992 (Fig 3B,C) demonstrated a typical spike and dome shape, indicative of subaortic obstruction. Simultaneously, an increase in the atrial wave, a prolongation of the IIa–O time, disappearance of a rapid-filling wave, and an increased systolic anterior motion of the mitral valve were observed. UCGs in 1992 (Fig 4B) revealed complete systolic anterior motion of the anterior leaflet, marked progression of hypertrophy, and partial systolic semi-closure of aortic valve (not shown). The LVDd, LVDs, and FS were 42 mm, 24 mm, and 42.8%, respectively, and the thickness of the IVS and the LVPW were 20 mm and 15 mm, respectively. This gradual progression of hypertrophy caused a significant pressure gradient in the left ventricular outflow tract, the maximal pressure gradient of which was estimated by Doppler flow velocity to be 82 mm Hg (not shown) in 1992. Paroxysmal atrial fibrillation occurred in 1992 and changed to chronic atrial fibrilla-
tion by 1993, necessitating the addition of warfarin and verapamil therapy.

Since 1994, the severity of the wall thickness gradually decreased and the left ventricle tended to dilate (Fig 2B) and in 1998, congestive heart failure occurred (Fig 2C) and he was began 0.2 mg of digoxin and 12.5 mg of alacepril per day, which controlled the symptoms. The RV5+SV1 voltage gradually decreased (Fig 1C–E), and the spike and dome shape of the carotid pulse tracing and the systolic murmur on the phonogram disappeared in 2000 (Fig 3D). The IIa–O time in 2000 (132 ms, Fig 3D) was shortened in comparison with that in 1992 (Fig 3C). Fig 4C shows the thinning of the IVS and the LVPW, and dilation of the left ventricular cavity.

A blood sample for genetic analysis was obtained after the patient gave written and informed consent. We analyzed the cardiac MYBPC gene by polymerase chain reaction single strand conformation polymorphism analysis (PCR-SSCP analysis), according to methods reported previously, and exon 18 revealed an abnormal band in 8% polyacrylamide gels with 10% of glycerol (Fig 5).

To confirm this abnormality, exon 18 was amplified from DNA derived from the patient and subcloned. Ten independent plasmid clones were isolated and sequenced: 4 contained the normal sequence derived from the normal allele and 6 contained a deletion of a thymidine residue at nucleotide 11645 derived from the affected allele. The single base deletion in exon 18 caused a frameshift mutation and a truncated cardiac MYBPC protein. Because both normal and mutant sequences were identified, the patient was heterozygous for the mutation.

Fig 1. Changes in the patient’s ECG. (A–C) Gradual progression of the RV5+SV1 voltages. Note the decreased voltages in the limb and precordial leads (C–E). ST-T changes in (E) were caused by digoxin. Atrial fibrillation can be seen in (D) and (E). (A) 1983, (B) 1986, (C) 1990, (D) 1996, and (E) 2000.

Fig 2. Changes in the patient’s chest X-ray. The cardiothoracic ratio was 46.6% in 1983 (A), 61.5% in 1994 (B), and 62.3% in 1998 (C). Arrows indicate the double convex contour of the enlarged left atrium. The arrowhead shows left pleural effusion.

Fig 3. Changes in the patient’s mechanocardiogram. PCG, phonocardiogram; CPT, carotid pulse tracing; ACG, apexcardiogram. (1) Atrial wave in ACG. The ratios of the atrial wave in (A), (B), and (C) were 14.8, 27.4, and 30.2%, respectively. A gradual increase in the atrial overload led to atrial fibrillation (D). (2) Mid-systolic dip in CPT. (3) Spike and dome shape in CPT. (4) Disappearance of spike and dome shape in CPT. (5) IIa–O times in (A), (B), (C), and (D) were 128, 330, 350, and 132 ms, respectively. (A) 1983, (B) 1990, (C) 1992, and (D) 2000.
There was nothing remarkable in the patient’s family history except for the sudden death of his father at the age of 63. Unfortunately, we could not confirm the co-segregation of cardiac MYBPC mutation with HCM in his family because he had no other relatives with symptoms and both his parents had died.

Discussion

HCM has a broad spectrum of pathological findings and clinical manifestations. Molecular genetic studies of familial HCM have demonstrated that this autosomal dominant condition is caused by mutations in the genes encoding sarcomere proteins and more than 120 different disease-causing mutations have been identified in components of the thick filaments (eg, cardiac β-myosin heavy chain and ventricular essential and regulatory myosin light chains), components of the thin filaments (cardiac troponin T, troponin I, and α-tropomyosin) and cardiac MYBPC. The present patient has a mutation in the cardiac MYBPC gene: a single base deletion in exon 18. Cardiac MYBPC is an abundant myofibrillar protein that does not directly participate in force generation, but has unique functions within the sarcomere. Cardiac MYBPC gene mutations are expressed in the myocardium and exert their effect by altering the multimeric complex assembly of the cardiac sarcomere via at least one of several mechanisms.

1) They act as ‘poison polypeptides’ through a dominant negative effect. The altered proteins are incorporated in the sarcomere and alter the assembly of the sarcomeric filaments. However, Rottbauer et al showed that truncated cardiac MYBPC did not act in this way.

2) They act as ‘null alleles,’ potentially leading to haploinsufficiency; the production of insufficient quantities of normal cardiac MYBPC produces an imbalance in stoichiometry of the thick-filament components that is sufficient to alter the sarcomeric structure and function.

3) Mutated cardiac MYBPC mRNAs disturb the translation of the other sarcomeric components, which interferes with the proper assembly of sarcomeric structures.

Other mutations in sarcomere-protein genes are often silent during childhood but produce clinically significant disease early in adult life. In contrast, the effects of mutations in the cardiac MYBPC gene are often subclinical until middle age or later and patients can have a delayed expression of cardiac hypertrophy and a favorable clinical course. On the other hand, Doi et al reported that 4 of 14 patients with this mutation gradually progressed to left ventricular dilation and dysfunction during a follow-up period of 54.5±57.1 months.

Several reports have reported that the incidence of transition from typical HCM to the dilated and hypokinetic left ventricle in patients with HCM is 2.4–14%. The mechanism of the transition to the dilated phase of HCM remains...
unclear. We have reported that cardiac enzymes in serum persistently increased in more than 60% of the patients with HCM, but in the present patient, despite the elevation of cardiac enzymes in 1989, it was several years before there was significant thinning of the left ventricular wall and left ventricular dilation. Tanaka et al reported that massive myocardial fibrosis, disarray of the salvaged myocardial fibers and regional ischemia because of marked stenosis in the intramyocardial small arteries may be related to the transition. The present patient had a marked prolongation of the IIa–O time (Fig 3B, C), which we have noted previously in HCM, together with prolongation of the interval from mitral valve opening to the O point (MVO–O). Both these changes are thought to indicate a diastolic abnormality in the early filling stage, but it is not clear what caused the shortening of the IIa–O time in 2002 in the present case (Fig 3D).

Recent phenotype–genotype analysis has revealed the association between the clinical features of HCM and mutations in several genes. The phenotype of the present patient changed markedly during the follow-up period, so it is difficult to speculate on the severity and prognosis of patients with HCM solely on the basis of the mutation. Patients with this type of mutation must be observed prospectively to determine whether it is aging alone or its conjunction with other factors that causes the phenotypic expression of cardiac MYBPC mutations.

References