Hypertrophic cardiomyopathy (HCM) is an intractable disease that causes heart failure mainly due to unexplained severe cardiac hypertrophy and diastolic dysfunction. HCM, which occurs in 0.2% of the general population, is the most common cause of sudden cardiac death in young people. HCM has been studied extensively using molecular genetic approaches. Genes encoding cardiac β-myosin heavy chain, cardiac myosin-binding protein C, and troponin complex, which were originally identified as causative genes, were subsequently reported to be frequently implicated in HCM. Indeed, HCM has been considered a disease of sarcomere gene mutations. However, fewer than half of patients with HCM have mutations in sarcomere genes. The others have been documented to have mutations in cardiac proteins in various other locations, including the Z disc, sarcoplasmic reticulum, plasma membrane, nucleus, and mitochondria. Next-generation sequencing makes it possible to detect mutations at high throughput, and it has become increasingly common to identify multiple cardiomyopathy-causing gene mutations in a single HCM patient. Elucidating how mutations in different genes contribute to the disease pathophysiology will be a challenge. In studies using animal models, sarcomere mutations generally tend to increase myocardial Ca$^{2+}$ sensitivity, and some mutations increase the activity of myosin ATPase. Clinical trials of drugs to treat HCM are ongoing, and further new therapies based on pathophysiological analyses of the causative genes are eagerly anticipated.

**Keywords:** hypertrophic cardiomyopathy, disease-causing genes, pathophysiology

**Introduction**

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained left ventricular (LV) hypertrophy and LV diastolic dysfunction. Pathologically, myocardial disarray is a characteristic finding, and interstitial fibrosis is usually present. Ventricular hypertrophy occurs at various sites in the ventricle and is often asymmetrical. In some cases, hypertrophy is concentric, and in others, only the apex is involved, a condition termed apical hypertrophy. LV hypertrophy of the outflow tract (LVOT) or hypertrophy forming an intra-LV cavity often produces a pressure gradient between the aorta and the LV or intra-LV cavity, leading to decreased exercise tolerance and worse prognosis. HCM is the major cause of sudden cardiac death (SCD) in the young. Therefore, early diagnosis, assessment of the risk of SCD, and appropriate prophylactic treatment are critical. HCM is the most common hereditary cardiovascular disease, affecting 0.2% of the general population, and the inheritance pattern is usually dominant. Over the past 30 years, molecular genetic analyses of HCM have revealed disease-causing genes, the pathogenesis, and the genotype–phenotype relationship. Furthermore, preclinical studies of HCM treatments and recent high-throughput analyses using next-generation sequencing have revealed that the pathophysiology of...
HCM is more complex than was previously thought. This review will mainly discuss the status of HCM pathophysiology based on currently known disease-causing genes and will also highlight recent preventive and therapeutic approaches.

**Identification of HCM and Its Genetic Causes**

In 1869, Liouville reported a patient with a systolic murmur and severe dyspnea who had an enlarged and thick LV with intraventricular obstruction at autopsy.1 In 1958, Teare reported nine patients characterized by asymmetrical left ventricular hypertrophy; eight of these patients had died suddenly.8 In 1964, Braunwald reported 64 patients with HCM; thereafter, HCM was more widely recognized.9 Familial and genetic traits are evident in 50%–70% of HCM cases, and the disease mostly has an autosomal dominant inheritance pattern. Consequently, many genetic studies of familial HCM have been initiated.9,10 In 1989, by linkage analysis of a large HCM family, Seidman’s group mapped the location on chromosome 14 of the first gene found to be responsible for HCM. Not long after, this disease-causing gene was identified to be MYH7, the gene that encodes cardiac β-myosin heavy chain, a component of the thick filament of sarcomeres.11,12 Subsequently, linkage analysis also revealed that MYBPC3 was associated with familial HCM.13,14 MYBPC3 encodes cardiac myosin binding protein C, which binds the cardiac β-myosin heavy chain, a component of thick filaments, and thin filaments of cardiac α-actin. Furthermore, disease-causing mutations in TNNT2, which encodes cardiac troponin T, were identified in familial HCM patients.15 Cardiac troponin T, a component of the troponin complex located in thin filaments, is involved in calcium regulation during muscle contraction. These three genes (MYH7, MYBPC3, and TNNT2) are still considered to be the major causative genes of HCM.

**Diversity of Disease-causing Genes in HCM and Their Related Functional Abnormalities**

To date, various causative genes of HCM have been reported; these are shown in Table 1.

**Sarcomere:** In addition to mutations in MYH7, TNNT2, and MYBPC3, disease-causing mutations in TPM1 (encoding α-tropomyosin), TNNI3 (encoding cardiac troponin I), MYL3 (encoding myosin essential light chain),
MYL2 (encoding myosin regulatory light chain), and ACTC1 (encoding cardiac α-actin) have been found in familial HCM patients. All these genes code for components of sarcomeres (thick and thin filaments) that are involved in muscle contraction.\textsuperscript{12–18} Figure 2 shows an electron micrograph of normal mouse LV myocardium; the sarcomere proteins mentioned above are located in the A band. Familial HCM patients with mutations in genes encoding sarcomere proteins typically have an autosomal dominant inheritance pattern, and the majority of mutations are missense mutations resulting from single base substitutions. Initially, functional studies on patients with mutant MYH7 (coding for the cardiac β-myosin heavy chain protein) suggested that it causes cardiac hypertrophy as a mechanism to compensate for reduced muscle contractility.\textsuperscript{19} It was subsequently reported that MYH7, TNNT2, TNNI3, and TPM1 mutations increase muscle contractility and actin-activated myosin ATPase activity.\textsuperscript{20–23} Calcium sensitivity was increased by each of these mutations. Therefore, increased calcium sensitivity, a common pathological change associated with sarcomere mutations in HCM, leads to diastolic dysfunction of myocardium and reflects the pathogenesis of HCM.

The MYBPC3 mutations found in patients with HCM are not only missense mutations, but also involve many

| Gene     | Protein                        | Location         |
|----------|--------------------------------|------------------|
| MYH7     | Cardiac β-myosin heavy chain    | A band           |
| TNNT2    | Cardiac troponin T             | A band           |
| TPM1     | α-Tropomyosin                  | A band           |
| MYBPC3   | Cardiac myosin binding protein C | A band          |
| MYL3     | Myosin essential light chain   | A band           |
| MYL2     | Myosin regulatory light chain  | A band           |
| TNNI3    | Cardiac troponin I             | A band           |
| ACTC1    | Cardiac α-actin                | A band           |
| TNNC1    | Cardiac troponin C             | A band           |
| MYH6     | Cardiac α-myosin heavy chain   | A band           |
| NEXN     | Nexilin                        | A band           |
| TTN      | Titin                          | M line–A band–Z disc |
| CSRP3    | MLP                            | Z disc           |
| TCAP     | Telethonin/Tcap                | Z disc           |
| LDB3     | ZASP/Cypher                    | Z disc           |
| MYOZ2    | Calsarcin 1                    | Z disc           |
| CALR3    | Calreticulin 3                 | Z disc           |
| FH1L1    | Four and a half LIM protein    | Z disc           |
| VCL      | Vinculin                       | Z disc/cell–cell junction |
| MYPN     | Myopalladin                    | Z disc           |
| Acan2    | Actinin α-2                    | Z disc           |
| JPH2     | Junctophilin 2                 | SR               |
| PLN      | Phospholamban                  | SR               |
| CAV3     | Caveolin 3                     | Caveolae/plasma membrane |
| DES      | Desmin                         | Intermediate filament |
| FLNC     | Filamin C                      | Z disc/membrane  |
| CryAB    | αB-Crystallin                  | Nucleus/I band   |
| TIEG1    | Transforming growth factor-β-inducible early | Nucleus/I band |
| MYLK2    | Myosin light chain kinase      | Nucleus          |
| EYA4     | Eyes absent 4                  | Nucleus          |
| ANKRD1   | CARP                           | Nucleus          |
| ALPK3    | Myocyte induction differentiation originator | Nucleus |
| MTO1     | Mitochondrial tRNA translation optimization 1 | Mitochondria |

MLP, muscle LIM protein; CARP, cardiac ankyrin repeat protein; KLF, Kruppel-like factor
mutations that cause frameshifts as a result of base deletions or insertions. This leads to haploinsufficiency, which results in defective proteins. Unexpectedly, mutant proteins have not been identified in the myocardium of HCM patients harboring MYBPC3 deletion mutations. This may be because the ubiquitin–proteasome system and the nonsense mutation-dependent mRNA degradation mechanism (nonsense-mediated mRNA decay) promote the degradation of mutant proteins and mRNAs. However, calcium sensitivity was also increased in patients with deletion mutations of MYBPC3.

Based on the history of the discovery of causative genes, HCM was considered to be a disease of the sarcomere. However, the mutations of genes encoding sarcomere proteins account for only about 50% of familial HCM cases. Further research has revealed pathogenic mutations in non-sarcomere-encoding genes.

**Z disc component**: In the Z disc, numerous proteins are arranged at high density and are involved in muscle tension. Electron micrographs indicate that proteins are densely packed (Fig. 2). Biochemical analyses have further revealed that many individual proteins are linked together. Titin, a giant protein encoded by TTN, is a muscle tension sensor that extends from the M line to the Z disc and increases the calcium sensitivity of muscle contraction under high tension. An important domain related to titin tension exists in the Z disc, and mutations in this domain increase the binding capacity of binding protein in HCM. Muscle LIM protein (MLP)-knockout mice develop dilated cardiomyopathy, and when tension is applied to their myocardium, their hypertrophic response is reduced compared with that of wild-type mice. In addition, MLP and titin-cap (Tcap) protein expression in heart muscle is reduced in patients with mutations of MLP. To form the MLP–Tcap complex, Tcap binds to the N-terminus of titin and MLP binds to Tcap. This component is thought to be a myocardial stretch sensor. Tcap mutations in HCM cause functional changes that increase the ability of Tcap molecules to bind to each other and may increase the hypertrophic response to constant tension. Furthermore, mutations in calsartin-1, an important signaling factor in hypertrophy that binds to Tcap and calcineurin,
have also been reported in HCM patients, suggesting that the entire Z disc may be a major tension sensor.31

**Calcium handling and hypertrophic signaling proteins:** Junctophilin 2, encoded by JPH2, is associated with intracellular calcium and is present in the sarcoplasmic reticulum (SR) (Fig. 2). Mutations in JPH2 alter the intracellular localization of mutant protein, induce a hypertrophic response in cultured cells, and is associated with HCM.32 HCM-associated mutations have been identified in the promoter region of PLN, which encodes phospholamban, an inhibitor of SR Ca$^{2+}$-ATPase. Functional analysis of these mutations has revealed changes in promoter activity, suggesting that PLN transcription is increased, calcium uptake into the SR is decreased, and intracellular calcium concentration is increased, leading to hypertrophy.33

Caveolin 3, encoded by CAV3, is present in caveolae on the plasma membrane (Fig. 2) and is associated with a hypertrophy signal. Two brothers with an HCM-associated mutation in CAV3 had relatively mild left ventricular hypertrophy, but exhibited high end-diastolic pressure and severe diastolic dysfunction.34 Cell biology studies have indicated that HCM-associated mutations alter the function of caveolin 3 proteins by decreasing their expression on caveolae.34

In addition, cardiac ankyrin repeat protein (CARP) is a transcription-related protein encoded by ANKRD1. CARP is thought to move between the sarcomere and the nucleus to mediate signal transduction during tension stimulation. Mutations in ANKRD1 are found in HCM patients, and the mutant CARP is present in or around the nucleus, a condition that is similar to normal CARP protein localization when cardiomyocytes are stretched. Such mutations result in a constant stretch condition that can lead to hypertrophy.35

**Myopathy-associated proteins:** Many of the proteins expressed in myocardium and in skeletal muscle are identical. Therefore, mutations in the genes encoding these proteins are likely to damage both cardiac and skeletal muscle; however, the phenotype is often one of cardiomyopathy or myopathy. If a patient develops cardiomyopathy, myopathy may also occur, depending on the course of the disease. Patients with myopathy and cardiomyopathy often present with dilated cardiomyopathy (DCM), but rarely with HCM. As mentioned above, CAV3 and TCAP are disease-causing genes of HCM, and they are also causative genes of limb-girdle type muscular dystrophy.36,37

Desmin, encoded by DES, is an important non-sarcomeric cytoskeleton protein. DES mutation results in a combined phenotype of myopathy and DCM, termed desmin-related myopathy.38 This condition reportedly follows a dominant form of inheritance. One patient with a homozygous DES T219P missense mutation in the desmin α-helical domain was diagnosed with HCM and initially had no skeletal muscle symptoms; however, the patient later developed progressive skeletal muscle symptoms.39 Both parents had heterozygous DES T219P mutations, but neither parent showed cardiomyopathy or myopathy. For this mutation, the parents were carriers, and the genetic trait was recessive.

**Mitochondria-associated proteins:** As shown in Fig. 2, mitochondria are abundant in the myocardium and provide an energy source. Mutations in genes encoding mitochondria-associated proteins reportedly relate to HCM. Analysis of mitochondrial gene mutations requires access to the mitochondrial genome of the target organ; this necessitates a myocardial biopsy sample. However, genes encoding mitochondria-associated proteins can be analyzed using general genomic DNA. A mutation of mitochondrial tRNA translation optimization 1, encoded by MTO1, a modifier of mitochondrial tRNA, was reported in an infant HCM patient with lactic acidosis.40 In the affected family, patients were homozygous or compound heterozygous with different mutations transmitted from their parents. MTO1 mutations resulted in the development of HCM during early childhood, and the mutations were associated with a marked decrease in mitochondrial respiratory chain activity.40

The pathogenesis of HCM is evidently diverse: mutations in genes encoding both sarcomeric proteins and various components of cardiac muscle are present in HCM patients. As discussed above, increased calcium sensitivity, particularly associated with sarcomere gene mutations, is thought to be a major cause of cardiac hypertrophy and diastolic dysfunction, although much remains unclear.

**Evaluation of Individual Genetic Mutations and Their Genotype–Phenotype Relationship in HCM**

Genetic analyses of HCM in various ethnic groups have been reported. In all ethnic groups, the most frequently found disease-causing genes are MYH7 and MYBPC3, followed by TNNT2, TNNI3, and TPMI. Accumulation of clinical and prognostic information is important for these mutation probands. The prognosis of individual HCM patients is variable. Morphologically similar septal hypertrophy may differ in prognosis depending on the causative gene mutation and expression of the mutant protein. It is important to accurately identify groups with poor prognosis at an early stage.

In a clinical study of HCM featuring MYH7, MYBPC3, and TNNT2 mutations in Japanese patients at multiple institutions, patients with TNNT2 mutations were found to have less cardiac hypertrophy on echocardiography but more cardiac enlargement and deterioration of cardiac function than did patients with MYH7 and MYBPC3 mutations. The annual mortality was 1.1% and 1.5% in HCM patients with MYBPC3 mutations and MYH7 mutations, respectively. In contrast, the annual mortality of patients with TNNT2 mutations was as high as 2.5%.25 In
the United Kingdom, the annual risk of sudden death in patients with HCM harboring \textit{TNNT2} mutations (0.93\%) was approximately double that of patients with HCM harboring \textit{MYBPC3} mutations (0.46\%).\textsuperscript{41,42} In Japan, the results were similar to those reported elsewhere.

Myocardial biopsy findings in patients with \textit{TNNT2} mutations are generally more complex in terms of myocardial disarray than those in patients with other mutations. In such patients, LV contractility decreases before cardiac hypertrophy becomes prominent.\textsuperscript{45} Clinically, it may be necessary to develop a noninvasive procedure to evaluate myocardial disarray.

For the identified pathologic mutations, additional factors to consider include penetrance and dose effects. The probability that a person with a pathologic mutation will develop a disease is called penetrance. In past studies on sarcomere genes, the penetrance rate was as high as 90\%. By age group, the rate was 55\% for those aged 10–29 years, 75\% for those aged 30–49 years, and 95\% for those aged ≥ 50 years. In general, the appearance of hypertrophy is earlier in men than in women, and it varies depending on the causative gene and mutation.\textsuperscript{44}

In general, individuals with \textit{MYBPC3} deletion mutations develop HCM at a relatively older age. However, missense mutations of \textit{MYBPC3} are often identified in early-onset HCM. Approximately 5\% of all HCM patients have multiple sarcomere mutations; these patients have more severe disease than those with a single mutation.\textsuperscript{45}

Patients with the same homozygous mutation are also more severely affected than those with the heterozygous mutation. Moreover, HCM patients with the same heterozygous mutation have a more severe phenotype if they have a higher level of mutant mRNA.\textsuperscript{46} This seems to be a quantitative factor, i.e., a dose effect, of the mutant protein.

Next-generation sequencing enables the simultaneous analysis of many genes. When all the genes reported to cause cardiomyopathy were analyzed, it was found that many HCM patients have both sarcomere and non-sarcomere gene mutations. As shown in Table 1 and Table 2, a recent causative gene-screening analysis of HCM revealed collective causative genes of HCM and of secondary cardiomyopathy, which may show an HCM phenotype, and other causative genes of cardiomyopathies such as DCM and arrhythmogenic right ventricular cardiomyopathy (ARVC) (not shown). This is because secondary cardiomyopathy may be associated with treatable diseases, such as Fabry disease or amyloidosis, and a causative gene for another cardiomyopathy (such as DCM) is often also an HCM-causing gene (Table 2). For example, genetic analysis of patients diagnosed with HCM revealed that they had mutations in \textit{MYBPC3} and \textit{GLA}, which is associated with secondary cardiomyopathy and is a causative gene for Fabry disease.\textsuperscript{47} These patients demonstrated typical findings of Fabry disease in mitochondria on myocardial biopsy. It is a major challenge to evaluate the influence of each genotype on the pathogenesis of HCM based on \textit{GLA} and \textit{MYBPC3} mutations. To construct a genotype–phenotype database, it is necessary to know which genes were finally examined. That is, it is also necessary to know whether the clinical information associated with an individual’s genotype is the result of the analysis of the sarcomere genes alone or of all the causative genes for cardiomyopathy.

### Sudden Cardiac Death Risk Group in HCM

As noted above, there are a variety of disease-causing genes for HCM, and the prognosis of HCM is also highly variable. The annual risk of SCD in adult HCM patients is reported to be between 0.5\% and 2\%. It is essential to accurately evaluate the risk of SCD and to ensure the prevention of SCD by measures such as the use of implantable cardioverter defibrillators (ICDs).\textsuperscript{48,49} The following factors are currently considered to be indicators of a high risk of SCD in HCM: (1) a history of ventricular fibrilla-
tion, sustained ventricular tachycardia, or the presence of non-sustained ventricular tachycardia; (2) a family history of SCD, especially in younger people; (3) syncope of unknown cause; (4) marked cardiac hypertrophy of >30 mm; (5) an abnormal reaction in which blood pressure falls during exercise; (6) LVOT obstruction; and (7) younger age.50–52 In addition, disease-causing gene mutations and LV apical aneurysm are considered potential indicators of SCD risk that require further evaluation. SCD, fatal arrhythmias, and apical aneurysms are thought to be associated with pathologic changes such as severe cardiac hypertrophy and myocardial disarray related to increased calcium sensitivity as well as with secondary myocardial ischemia associated with perivascular fibrosis; however, the detailed mechanisms remain unclear. A recent analysis of two populations that are considered to be high risk but have not usually undergone genetic characterization in the past is described below.

**Pediatric HCM:** The most common cause of cardiac transplantation in children is cardiomyopathy,53 although cardiomyopathy is less common in children than in adults. Unlike cardiomyopathy in adults, cardiomyopathy in children aged 10 years and younger is often severe and requires heart transplantation. In the past, metabolic diseases and storage diseases were thought to be common causes of poor prognosis in pediatric cardiomyopathy. However, genetic analyses have recently indicated that 80% of Japanese pediatric HCM patients with a family history of the disease had mutations in a causative gene for cardiomyopathy, and 75% had mutations in a sarcomere gene.54 In HCM patients with an uncertain family history, only 10%–20% of adults had mutations in a causative gene, whereas 77% of such pediatric HCM patients had mutations, and 73% had sarcomere mutations. Moreover, multiple gene mutations were found in 17% of these patients. In sporadic cases of pediatric HCM, many de novo mutations have been detected.54 These results suggest that the pathogenesis of pediatric HCM is different in adults and in children. In this study, the patients with ICD were all boys with sporadic HCM and, like other cardiomyopathies, were more likely to have androgen as a modifier in boys at risk of pediatric HCM.55

**HCM with mid-ventricular obstruction:** Approximately 10% of HCM patients have a mid-LV pressure gradient of >30 mmHg. This condition is called HCM with mid-ventricular obstruction (HCM-MVO) and has a worse prognosis than common HCM.5,56,57 An analysis of 67 cardiomyopathy-causing genes in HCM-MVO patients revealed disease-associated mutations in 44% of cases. Mutations in sarcomere protein-encoding genes were identified in 21% of patients, including MYH7 in 6% and MYBPC3 in approximately 12%.57 Moreover, 18% of patients had a genetic mutation associated with ARVC/DCM. In this regard, it has been reported that those with apical aneurysm constitute a high-risk group, and some HCM-MVO cases can evolve to apical aneurysm. As with morphology, HCM-MVO cases tend to differ pathophysiologically from common HCMs, and this requires further investigation.

### Development of Treatments for HCM

Various preclinical therapies have been developed using animal models of HCM in which the causative gene mutations have been identified; clinical trials are also in progress (Table 3). In an established HCM animal model, MYH6 R403Q mice carrying a homolog of a poor-prognosis MYH7 gene mutation revealed that from an early stage, Ca^{2+} stores in the SR were impaired leading to dys-functional Ca^{2+} homeostasis. These effects were ameliorated by L-type Ca^{2+} channel inhibitor diltiazem, which reduced hypertrophy.58 A pilot study in which humans were administered diltiazem also showed a positive effect on the improvement of end-diastolic diameter as a marker

### Table 3. Selected clinical trials and preclinical research related to HCM

| Clinical Trial | Treatment | ClinicalTrials.gov identifier | Trial phase |
|---------------|-----------|-------------------------------|-------------|
|               | Diltiazem | NCT00319982                   | Phase 2     |
|               | Losartan  | NCT01150461                   | Phase 2     |
|               | Valsartan | NCT01912534                   | Phase 2     |
|               | LCZ696 (sacubitril/valsartan) | NCT04164732 | Phase 2     |
|               | Perhexiline | NCT02862600/NCT02431221       | Phase 2/3   |
|               | MYK-461 (Mavacamten) | NCT02842242    | Phase 2     |

| Preclinical Research | Treatment | Reference No | Animal model |
|----------------------|-----------|--------------|--------------|
|                      | Adeno-associated virus-delivered RNA interference therapy | 66 | HCM model mice carrying MYH6 R403Q mutation |
|                      | MYBPC3 cDNA replacement by gene transfer | 67 | HCM model mice carrying MYBPC3 truncation mutation |
of myocardial remodeling. Because of the presence of fibrosis and hypertrophy in HCM, the trial administration of losartan, an angiotensin II receptor antagonist (ARB), did not produce favorable results. Nonetheless, the VANISH (Valsartan for Attenuating Disease Evolution in Early Sarcomeric HCM) trial is using valsartan, another ARB, and is currently underway for HCM with sarcomere mutations.60,61 Neprilysin is an endopeptidase for natriuretic peptide and angiotensin II, and neprilysin inhibitors increase levels of natriuretic peptide and angiotensin II. The neprilysin inhibitor/angiotensin II receptor antagonist LCZ 696 (sacubitril /valsartan) has been tested in clinical trials for HCM (Clinical Trial Identifier: NCT04164732).

Perhexiline maleate is orally administered to reduce the metabolism of free fatty acids via the inhibition of carnitine palmitoyltransferase, enhance myocardial carbohydrate, and thereby improve cardiac energetics cost via more efficient oxygen consumption.62 A pilot clinical study showed favorable results with regard to improved exercise capacity.63 An international, multicenter, phase-3 trial was started; however, a lack of drug efficacy in a preceding study was reported, and the trial was discontinued (Clinical Trial Identifier: NCT02431221).

Myosin ATPase activity is increased in several disease-causing gene mutations of HCM.20 MYK-461, mavacamten, which inhibits myosin ATPase activity, weakens the binding of myosin heads to actin fibers, keeps the myocardium relaxed, and reduces cardiac contractility.64 This orally administered drug was effective in preventing cardiac hypertrophy and fibrosis in HCM. Clinical trials have reported improved exercise tolerance and pressure gradients in patients with hypertrophic obstructive cardiomyopathy, and this promising agent is currently being tested in various clinical studies.65

Adeno-associated virus-delivered RNA interference (RNAi) therapy has been used in preclinical research in which only the mutant allele was suppressed by RNAi in the HCM mouse model with the MYH6 R403Q mutation.66 MYBPC3 cDNA replacement by gene transfer has been employed in the HCM model mouse with the MYBPC3 truncation mutation.67 Both approaches were reported to be promising therapies. Current gene-editing technology, in which off-target effects are a major problem, is difficult to apply in the clinical setting. Nevertheless, through technological innovation, gene-editing will be a fundamental therapy in the future.

In heart failure, diastolic dysfunction has been the focus of a number of large trials, particularly those involving angiotensin antagonists and aldosterone antagonists. However, none of these agents successfully improved patient prognosis.68,69 Drugs that are effective in HCM, which is primarily caused by diastolic dysfunction, may be extended for application in patients with diastolic heart failure. New causes of HCM identified through comprehensive genetic analyses will serve as new targets that will lead directly to new treatments.

Concluding remarks

The 21st century is considered to be the age of genomic medicine. For cardiomyopathy, chaperone therapy has been introduced for secondary cardiomyopathies, such as Fabry’s disease. Precision medicine, which examines the effect of each gene mutation, has begun to be introduced as a treatment that uses chaperone therapy.70 To realize the potential of genomic medicine, it is crucial for medical professionals to be cognizant of the current state of genome research. Even healthy individuals have genetic mutations in multiple recessive genes responsible for genetic diseases. When a large number of genes are analyzed, it is important to accurately determine whether the genetic variations are disease-specific or not. First, accurate clinical information within each family members of HCM is important. It is critical that a team consisting of various specialists, such as the physician in charge, geneticist, and counselor, exchange information with the patient, correctly understand the needs of the patient based on ethical considerations, and give support to eliminate unnecessary anxiety. As a doctor and researcher who has conducted such genetic analyses, I hope that the results of the analysis of the disease-causing mutations will appropriately lead to the prevention of individual diseases and the development of future therapies.

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Conflicts of Interest

The author declares no conflicts of interest.

References

1. Braunwald E: Cardiomyopathies. Circ Res 2017; 121: 711–721. PMID:28912178, DOI:10.1161/CIRCRESAHA.117.311812
2. McKenna WJ, Maron BJ, Thiene G: Classification, epidemiology, and global burden of cardiomyopathies. Circ Res 2017; 121: 722–730. PMID:28912179, DOI:10.1161/CIRCRESAHA.117.309711
Hayashi T: Genetic Research and Pathophysiology of HCM

30. Hayashi T, Arimura T, Itoh-Satoh M, Ueda K, Hohda S, Inagaki N, Takahashi M, Hori H, Yasunami M, Nishi H, Koga Y, Nakamura H, Matsuzaki M, Choi BY, Bae SW, You CW, Han KH, Park JE, Knöll R, Hoshijima M, Chien KR, Kimura A: Tcap gene mutations in hypertrophic cardiomyopathy and dilated cardiomyopathy. J Am Coll Cardiol 2004; 44: 2192–2201. PMID:15582318, DOI:10.1016/j.jacc.2004.08.058

31. Osio A, Tan L, Chen SN, Lombardi R, Naghue SF, Shete S, Roberts R, Willerson JT, Mariani AJ: Myozinien 2 is a novel gene for human hypertrophic cardiomyopathy. Circ Res 2007; 100: 766–768. PMID:17347475, DOI:10.1161/01.RES.0000263008.66799.aa

32. Landstrom AP, Weisleder N, Batalden KB, Martijn Bos J, Tester DJ, Ommen SR, Wehrens XH, Claycomb WC, Ko JK, Hwang M, Pan Z, Ma J, Ackerman MJ: Mutations in JPH2-encoded tetractinophilin-2 associated with hypertrophic cardiomyopathy in humans. J Mol Cell Cardiol 2007; 42: 1026–1035. PMID:17509612, DOI:10.1016/j.yjmcc.2007.04.006

33. Minamisawa S, Sato Y, Tatsuguchi Y, Fujino T, Imamura S, Uetake Y, Nakazawa M, Matsuoka R: Mutation of the phospholamban promoter associated with hypertrophic cardiomyopathy. Biochem Biophys Res Commun 2003; 304: 1–4. PMID:12705874, DOI:10.1016/S0006-291X(03)00526-6

34. Hayashi T, Arimura T, Ueda K, Shibata H, Hohda S, Takahashi M, Hori H, Koga Y, Oka N, Imaiizumi T, Yasunami M, Kimura A: Identification and functional analysis of a caveolin-3 mutation associated with familial hypertrophic cardiomyopathy. Biochem Biophys Res Commun 2004; 313: 178–184. PMID:14672715, DOI:10.1016/j.bbrc.2003.11.101

35. Arimura T, Bos JM, Sato A, Kubo T, Okamoto H, Nishi H, Harada H, Koga Y, Moulik M, Doi YL, Towbin JA, Ackerman MJ, Kimura A: Cardiac ankyrin repeat protein gene (ANKRD1) mutations in hypertrophic cardiomyopathy. J Am Coll Cardiol 2009; 54: 334–342. PMID:19608031, DOI:10.1016/j.jacc.2008.12.082

36. Minetti C, Sotgia F, Bruno C, Scartezzini P, Broda P, Bado M, Masetti E, Mazzocchi M, Egeo A, Donati MA, Volonté D, Gagliati F, Cordone G, Bricarelly FD, Lisanti MP, Zara F: Mutations in the caveolin-3 gene cause autosomal dominant limb-girdle muscular dystrophy. Nat Genet 1998; 18: 365–368. PMID:9537420, DOI:10.1038/ng0498-365

37. Moreira ES, Wilshteir TJ, Faulkner G, Nilforoushan A, Vainzof M, Suzuki OT, Valle G, Reeves R, Zatz M, Passos-Bueno MR, Jenne DJ, Ommen SR, Wehrens XH, Claycomb WC, Ko JK, Hwang M, Pan Z, Ma J, Ackerman MJ, Kimura A: Cardiac ankyrin repeat protein gene (ANKRD1) mutations in hypertrophic cardiomyopathy. J Am Coll Cardiol 2009; 54: 334–342. PMID:19608031, DOI:10.1016/j.jacc.2008.12.082

38. Goldfarb LG, Park KY, Cervenáková L, Gorokhova S, Lee HS, Naidu SS, Nishimura RA, Ommen SR, Rakowski H, Seidman JD, Ommen SR, Wehrens XH, Claycomb WC, Ko JK, Hwang M, Pan Z, Ma J, Ackerman MJ, Kimura A: Cardiac ankyrin repeat protein gene (ANKRD1) mutations in hypertrophic cardiomyopathy. J Am Coll Cardiol 2009; 54: 334–342. PMID:19608031, DOI:10.1016/j.jacc.2008.12.082

39. Page SP, Kouns S, Syrris P, Christiansen M, Frank-Hansen R, Andersen PS, Elliott PM, McKenna WJ: Cardiac myosin binding protein-C mutations in families with hypertrophic cardiomyopathy: disease expression in relation to age, gender, and long term outcome. Circ Cardiovasc Genet 2012; 5: 156–166. PMID:222267749, DOI:10.1161/CIRCGENETICS.111.960831

40. Arai N, Yamashita M, Yamashita T, Takeishi Y, Tanaka K, Ishii H, Hoshijima M, Chien KR, Kimura A: Tcap gene mutations in hypertrophic cardiomyopathy and dilated cardiomyopathy. J Am Coll Cardiol 2004; 44: 2192–2201. PMID:15582318, DOI:10.1016/j.jacc.2004.08.058

41. Pasquale F, Syrris P, Kaski JP, Mogensen J, McKenna WJ, Elliott P: Long-term outcomes in hypertrophic cardiomyopathy caused by mutations in the cardiac troponin T gene. Circ Cardiovasc Genet 2012; 5: 1017. PMID:22144547, DOI:10.1161/CIRCGENETICS.111.99973

42. Page SP, Kouns S, Syrris P, Christiansen M, Frank-Hansen R, Andersen PS, Elliott PM, McKenna WJ: Cardiac myosin binding protein-C mutations in families with hypertrophic cardiomyopathy: disease expression in relation to age, gender, and long term outcome. Circ Cardiovasc Genet 2012; 5: 156–166. PMID:222267749, DOI:10.1161/CIRCGENETICS.111.960831

43. Arimura T, Bos JM, Sato A, Kubo T, Okamoto H, Nishi H, Harada H, Koga Y, Moulik M, Doi YL, Towbin JA, Ackerman MJ, Kimura A: Cardiac ankyrin repeat protein gene (ANKRD1) mutations in hypertrophic cardiomyopathy. J Am Coll Cardiol 2009; 54: 334–342. PMID:19608031, DOI:10.1016/j.jacc.2008.12.082

44. Hor CF, Charron P, Richard P, Girolami F, Van Spaendt-Zwarts KY, Pinto Y: Genetic advances in sarcomeric cardiomyopathies: state of the art. Cardiovasc Res 2015; 105: 397–408. PMID:25634555, DOI:10.1093/acr/cerv025

45. Tripathi S, Schultz I, Becker E, Montag J, Borchert B, Francino A, Navarro-Lopez F, Perrot A, Özbilczik C, Osterziel KJ, McKenna WJ, Brenner B, Kraft T: Unequal allelic expression of wild-type and mutated β-myosin in familial hypertrophic cardiomyopathy. Basic Res Cardiol 2011; 106: 1041–1055. PMID:21769673, DOI:10.1007/s00373-011-0205-9

46. Dallabona C, Strom TM, Parini R, Burlina AB, Meitinger T, Prokisch H, Ferrero I, Zeviani M: Mutations of the mitochondrial-tRNA modifier MTO1 cause hypertrophic cardiomyopathy and lactic acidosis. Am J Hum Genet 2012; 90: 1079–1087. PMID:22608499, DOI:10.1016/j.ajhg.2012.04.011

47. Pasquale F, Syrris P, Kaski JP, Mogensen J, McKenna WJ, Elliott P: Long-term outcomes in hypertrophic cardiomyopathy caused by mutations in the cardiac troponin T gene. Circ Cardiovasc Genet 2012; 5: 1017. PMID:22144547, DOI:10.1161/CIRCGENETICS.111.99973

48. Arimura T, Bos JM, Sato A, Kubo T, Okamoto H, Nishi H, Harada H, Koga Y, Moulik M, Doi YL, Towbin JA, Ackerman MJ, Kimura A: Cardiac ankyrin repeat protein gene (ANKRD1) mutations in hypertrophic cardiomyopathy. J Am Coll Cardiol 2009; 54: 334–342. PMID:19608031, DOI:10.1016/j.jacc.2008.12.082

49. Arimura T, Bos JM, Sato A, Kubo T, Okamoto H, Nishi H, Harada H, Koga Y, Moulik M, Doi YL, Towbin JA, Ackerman MJ, Kimura A: Cardiac ankyrin repeat protein gene (ANKRD1) mutations in hypertrophic cardiomyopathy. J Am Coll Cardiol 2009; 54: 334–342. PMID:19608031, DOI:10.1016/j.jacc.2008.12.082

50. Arimura T, Bos JM, Sato A, Kubo T, Okamoto H, Nishi H, Harada H, Koga Y, Moulik M, Doi YL, Towbin JA, Ackerman MJ, Kimura A: Cardiac ankyrin repeat protein gene (ANKRD1) mutations in hypertrophic cardiomyopathy. J Am Coll Cardiol 2009; 54: 334–342. PMID:19608031, DOI:10.1016/j.jacc.2008.12.082
