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Abstract

Eludication of pathomechanism of and development of therapy for autophagic vacuolar myopathies

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Autophagic vacuolar myopathy (AVM) is an entity defined by the presence of autophagic vacuoles on muscle pathology. There are two emerging categories in AVM in addition to the best characterized Pompe disease.

One is Danon disease and its related disorders, which are characterized by autophagic vacuoles with unique sarcolemmal features (AVSF). AVSF express virtually all sarcolemmal proteins, in addition to acetylcholinesterase, on their vacuolar membranes. Danon disease is caused by primary deficiency of a lysosomal membrane protein, LAMP-2. Interestingly, in this disease, the number of AVSF increases as the patients age. Other AVSF myopathies include X-linked myopathy with excessive autophagy which is now known to be caused by *VMA21* mutations.

The other AVM is typified by the presence of rimmed vacuoles, which are actually clusters of autophagic vacuoles on electron microscopy. One of the well known diseases in this group is distal myopathy with rimmed vacuoles (DMRV), also called hereditary inclusion body myopathy (HIBM). DMRV is caused by mutations in *GNE* gene that encode a rate-limiting enzyme in the sialic acid biosynthetic pathway. Interestingly, in DMRV model mice, sialic acid supplementation almost completely precluded the disease phenotype, indicating that decreased sialic acid is the cause of myopathic phenotype and sialic acid supplementation can prevent the disease process.

Interestingly, both genetically diagnosable AVSF myopathies are primarily due to lysosomal dysfunctions. In contrast, rimmed vacuoles are secondarily caused by extra-lysosomal defects, such as hyposialylation in DMRV/HIBM, and are formed at later stages of the disease.

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Key words: autophagy, distal myopathy, hereditary inclusion body myopathy, rimmed vacuole, sialic acid, GNE

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REVIEW

Molecular basis of hereditary cardiomyopathy: abnormalities in calcium sensitivity, stretch response, stress response and beyond

Akinori Kimura

Cardiomyopathy is caused by functional abnormality of cardiac muscle. The functional abnormality involved in its etiology includes both extrinsic and intrinsic factors, and cardiomyopathy caused by the intrinsic factors is called as idiopathic or primary cardiomyopathy. There are several clinical types of primary cardiomyopathy including hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM). Linkage studies and candidate gene approaches have explored the disease genes for hereditary primary cardiomyopathy. The most notable finding was that mutations in the same disease gene can be found in different clinical types of cardiomyopathy. Functional analyses of disease-related mutations have revealed that characteristic functional alterations are associated with the clinical types, such that increased and decreased Ca^{2+} sensitivity due to sarcomere mutations are associated with HCM and DCM, respectively. In addition, our recent studies have suggested that mutations in the Z-disc components found in HCM and DCM may result in increased and decreased stiffness of sarcomere; that is, stiff sarcomere and loose sarcomere, respectively, and hence altered stretch response. More recently, mutations in the components of I region were found in hereditary cardiomyopathy and the functional analyses of the mutations suggested that the altered stress response was associated with cardiomyopathy, further complicating the etiology and pathogenesis. However, elucidation of genetic etiology and functional alterations caused by the mutations shed lights on the new therapeutic approaches to hereditary cardiomyopathy, such that treatment of DCM with a Ca^{2+} sensitizer prevented the disease in a mouse model.
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Keywords: calcium sensitivity; cardiomyopathy; mutation; stress response; stretch response

INTRODUCTION

Cardiomyopathy is a heterogeneous disease caused by functional abnormality of cardiac muscle and classified into primary cardiomyopathy and secondary cardiomyopathy.[1] Secondary cardiomyopathy is defined as cardiomyopathy caused by extrinsic factors including ischemia, hypertension and metabolic disorders. On the other hand, diagnosis of primary cardiomyopathy is based on the exclusion of secondary cardiomyopathy and there are several different clinical types.[2,3] Hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) are two major clinical types of primary cardiomyopathy that had been defined as 'idiopathic'; that is, of unknown etiology. HCM, a major cause of sudden death in young and heart failure, is characterized by left ventricular hypertrophy, often asymmetric, accompanied by myofibrillar disarrays and reduced compliance (diastolic dysfunction) of cardiac ventricles. In contrast, DCM is characterized by dilated ventricular cavity with systolic dysfunction. Clinical symptom of DCM is heart failure and often associated with sudden death. There are other clinical types of cardiomyopathy. Restrictive cardiomyopathy (RCM) is accompanied by increased stiffness of the myocardium with diastolic dysfunction without significant hypertrophy.[4] In addition, arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by a dilated dysfunctional right ventricle (RV), ventricular arrhythmias and fibrofatty replacement of the RV. Another cardiomyopathy is left ventricular noncompaction (LVNC) characterized by less trabeculations in the left ventricle (LV), as well as LV hypertrophy and/or dilation.[1]

The etiology of primary cardiomyopathy had been unknown, but various genetic abnormalities associated with the cardiomyopathy have been unraveled in the past two decades. More than half of HCM patients have family history of the disease consistent with autosomal dominant genetic trait.[5] In the case of DCM, about 20–35% patients had family history of the disease, mainly consistent with the autosomal dominant inheritance, although some familial cases can be explained by autosomal recessive or X-linked recessive trait.[6,7] Familial occurrence is also noted in RCM, ARVC and LVNC.[1–4] As the presence of family history suggested the genetic etiology of the

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disease, linkage studies in multiplex families were taken to identify the disease loci in each family. Identification of the disease loci has enabled one to decipher the disease-linked mutations in the genes located within the loci. Subsequently, other candidate gene analyses, focused on the genes encoding for proteins related or interacting with products of the disease genes, have been successful in unraveling novel disease genes. As shown in Table 1 many different disease genes were identified. The most important point is the overlapping of disease genes for different clinical types.

SARCOMERE MUTATIONS IN HCM

Identification of a missense mutation in cardiac β-myosin heavy chain gene (*MYH7*) linked to HCM in a large multiplex family was the first demonstration of the disease gene for HCM.[8] Subsequently, many investigators have analyzed *MYH7* for mutations in HCM patients and many different missense mutations were identified as the cause. However, frequency of *MYH7* mutations in the patients was less than half and there were many families not linked to the *MYH7* locus. Linkage studies in such non-*MYH7*-linked HCM families have revealed mutations in α-tropomyosin gene (*TPM1*), cardiac troponin T gene (*TNNT2*) and cardiac myosin binding protein-C gene (*MYBP3*) as the causes of HCM. As these genes encode for components of sarcomere involved in muscle contraction, genes for other sarcomere components were analyzed and lead to the identification of HCM-associated mutations in ventricular myosin essential light chain gene (*MYL3*), ventricular myosin regulatory light chain gene (*MYL2*), cardiac troponin I gene (*TNNI3*), cardiac α-actin (*CACT*) and cardiac troponin C (*TNNC1*). Therefore, mutations in any components of sarcomere can result in HCM.[3,5]

Our study has showed that sarcomere mutations are found in about 40% of East Asian (Japanese and Korean) patients with familial HCM in the heterozygous state, consistent with the autosomal dominant inheritance (Table 2). About 20, 10 and 10% of patients carried mutations in *MYH7*, *TNNT2* and *MYBPC3*, respectively, whereas a few cases had mutations in other components of sarcomere such as *MYL2*, *MYL3* and *TNNI3*. So far investigated, we found no patient who had mutations in two or more disease genes, although there were some patients who were homozygous for the sarcomere mutation. The homozygous patients showed severer clinical manifestations than the heterozygous patients in the family, demonstrating the gene dose of mutation.[9] Disease-related mutations can also be found in sporadic HCM (Table 2). We found one *de novo* case,[10] but the other sporadic cases were probably due to the low penetrance of the mutation, because most of the mutations found in the sporadic HCM patients can also be found in other patients with familial HCM.

The most striking impact of unraveling disease genes and disease-causing mutations is not only that the etiology and pathogenesis of cardiomyopathy are understood but also that the genetic testing will be at least in part available for the cardiomyopathy. The genetic testing is useful for the provision of prognosis and more specifically predicting risk for unfavorable outcome such as sudden cardiac death or heart failure. From the beginning of unraveling disease-causing mutations, genotype–phenotype correlation analyses was one of the main focus and such analyses were mainly reported for HCM. Clinical manifestations of HCM due to the sarcomere mutations were in general different from each other, but there were some tendencies of genotype–phenotype correlations.[11,12] For example, Watkins *et al.*[13] hypothesized that the *MYH7* mutations leading to amino acid changes with charge alteration was associated with poor survival prognosis. However, it is not simply applicable to all the *MYH7* mutations. As shown in Figure 1, three different *MYH7* mutations, Arg249Gln, Gly716Arg and Asp778Gly, with poor survival prognosis[14,15] were all categorized into charge altered mutation. On the other hand, there were three other different *MYH7* mutations, Arg143Gln, Arg870His and Arg870Cys, with relatively benign survival prognosis[16,17] and two of them, Arg143Gln and Arg870Cys, were also associated with charge alteration. As Arg249Gln, Gly716Arg and Asp778Gly were mapped within the functionally important domain of myosin heavy chain,

Table 1 Disease genes for hereditary cardiomyopathy

Clinica phenotype	*Heredity*	*Gene symbol*	*Coding protein*
HCM/DCM/RCM/LVNC	AD	*MYH7*	Cardiac β-myosin heavy chain
HCM/DCM/RCM/LVNC	AD	*TNNT2*	Cardiac troponin T
HCM/DCM	AD	TPM1	α-tropomyosin
HCM/DCM	AD	*MYBPC3*	Cardiac myosin binding protein-C
HCM	AD	*MYL3*	Ventricular myosin essential light chain
HCM	AD	*MYL2*	Ventricular myosin regulatory light chain
HCM/DCM/RCM	AD	*TNNI3*	Cardiac troponin I
HCM/DCM/LVNC	AD	*ACTC*	Cardiac α-actin
HCM/DCM	AD	*TTN*	Titin, connectin
HCM/DCM	AD	*TNNC1*	Cardiac troponin C
HCM	AD	*MYH6*	Cardiac α-myosin heavy chain
HCM/DCM	AD	*CSRP3*	Muscle LIM protein, MLP
HCM	AD	*CAV3*	Caveolin-3
HCM/DCM	AD	*TCAP*	Titin-cap, Tcap, telethonin
HCM/DCM	AD	*VCL*	Metavinculin
HCM	AD	*JPH-2*	Junctophilin-2
HCM	AD	*OBSCN*	Obscurin
HCM	AD	*MYOZ2*	Myozenin, calsartin-1
HCM/DCM	AD	*ANKRD1*	CARP
DCM/RCM	AD	*DES*	Desmin
DCM/LVNC	AD	*LMNA*	Lamin A/C
DCM	AD	*SAGD*	δ-sarcoglycan
DCM	AD	*ACTN2*	α-actinin-2
DCM/LVNC	AD	*LDB3*	Cypher, ZASP, oracle
DCM/HCM	AD	*PLB*	Phospholamban
DCM	AD	*ABCC9*	K_{ATP} channel
DCM	AD	*SCN5A*	Cardiac Na channel
DCM/HCM	AD	*CRYAB*	αB crystallin
DCM	AD	*PSEN1*	Presenilin-1
DCM	AD	*PSEN2*	Presenilin-2
DCM	AD	*FHL2*	Four and half LIM protein-2, FHL2
DCM	AD	*LMNA4*	Laminin α4
DCM	AD	*ILK*	Integrin-linked kinase
DCM	AD	*MYPN*	Myopalladin
DCM	AD	*CHRM2*	Acetylcholine receptor
DCM	XR	*DMD*	Dystrophin
DCM	XR	*EMD*	Emerin
LVNC/DCM	XR	*TAZ*	Tafazzin, G4.5
DCM	XR	*FKTN*	Fuktin
ARVC/DCM	AR	*DSP*	Desmoplakin
ARVC/DCM	AR, AD	*JUP*	Plakoglobin
ARVC	AD	*PKP2*	Plakophilin-2
ARVC	AD	*TGFB3*	TGFβ3
ARVC	AD	*RYR2*	Ryanodine receptor 2
ARVC	AD	*DSG3*	Desmoglein 3
LVNC	AD	*DTNA*	α-dystrobrebin

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction; RCM, restrictive cardiomyopathy; XR, X-linked recessive.

Table 2 Frequencies of disease-associated mutations in Japanese and Korean patients with HCM

Gene symbol	*Familial case (%) (n=162)*	*Sporadic case (%) (n=100)*
MYH7	19.1	2.0
TNNT2	11.7	3.0
TPM1	0.6	0.0
MYBPC3	11.1	5.0
MYL3	0.6	1.0
MYL2	1.2	0.0
TNNI3	2.5	3.0
ACTC	0.0	0.0
TTN[a]	>2.5	>2.0
CSRP3	0.0	0.0
TNNC1	0.0	0.0
CAV3	0.6	0.0
MYH6	nt	nt
TCAP	1.2	0.0
CRYAB	0.0	0.0
VCL	0.0	0.0
JPH-2	nt	nt
MYPN	0.0	nt
OBSCN	0.6	0.0
ANKRD1	0.6	0.0
Sum	>54.8	>15.0

Abbreviations: DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; nt, not tested.
[a]Z-disc, N2-B, N2-A, Novex3 and is2 domains (about 20% of entire *TTN*) were analyzed.

Table 3 Phenotype of HCM patients carrying mutations in *MYH7*, *TNNT2* and *MYBPC3*

	MYH7 mutation	*TNNT2 mutation*	*MYBPC3 mutation*
Number of patients	41	30	41
Number of mutations	16	5	9
IVS (mm)	19.3±7.6	15.9±5.0	18.0±5.7
PW (mm)	11.1±2.6	10.3±5.0	11.0±3.0
LVDd (mm)	44.0±8.4	49.7±9.9	44.2±8.2
LAD (mm)	40.8±9.4	40.6±10.3	38.7±7.9
FS (%)	37.7±11.1	30.3±9.1	35.7±11.1
EF (%)	73.5±14.0	64.3±14.9	71.2±14.2
Age at diagnosis (years)	36.5±18.7	41.2±17.6	39.7±15.8
Duration of follow-up (years)	10.0±8.0	11.2±5.7	7.7±6.2
Prognosis of patients (%)			
Improved	0.0	3.3	0.0
No change	59.5	25.0	64.1
Worse	24.3	42.9	28.2
Death	16.2	28.6	7.7
Worse+death	40.5	71.4	35.9
Rate of death (% per year)	1.5	2.5	1.1

Abbreviations: EF, ejection fraction; FS, fractional shortening; IVS, thickness of intraventricular septum; LAD, left atrial dimension; LVDd, diastolic left ventricular dimension; PW, thickness of posterior ventricular free wall.

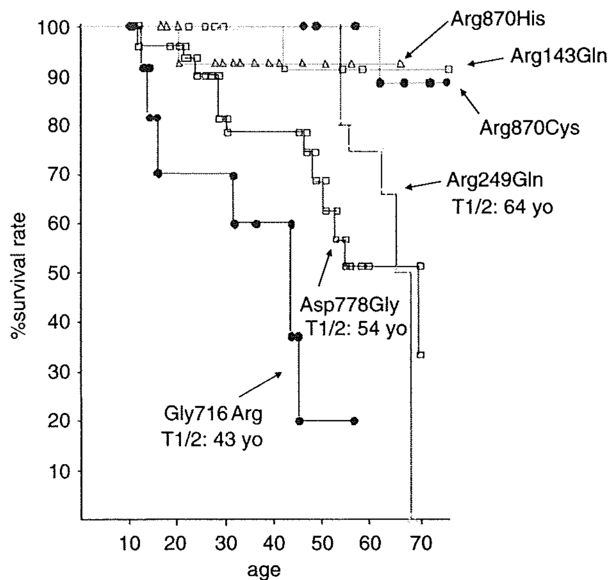

Figure 1 Survival prognosis of HCM patients with different MYH7 mutations. Cumulative survival of HCM patients with MHY7 mutations are demonstrated. Arg249Gln, Gly716Arg and Asp778Gly were associated with relatively poor prognosis, whereas Arg143Gln, Arg870His and Arg870Cys showed relatively benign prognosis.

ATP-binding domain, converter domain and myosin light chain-interacting domain,[18] respectively, while the benign mutations Arg143Gln and Arg870Cys were not mapped within these important domains. As the mutations reported by Watkins *et al.*[13] were all mapped within the ATP-binding domain, actin-interacting domain, converter domain or myosin light chain-interacting domains,[18] it was speculated that the mutations with charge alteration and mapped within the functionally important domains were correlated with poor survival prognosis.

In addition, there were several interesting characteristics of mutation-prone HCM patients in East Asians (Japanese and Korean), such that cardiac hypertrophy was more prominent in *MYH7* and *MYBPC3* cases than *TNNT2* cases (Table 3). It may be worth noting that the age at diagnosis was relatively late and cardiac function at the diagnosis was relatively lowered in *TNNT2* cases than the others.[10] This was in good agreement with that *TNNT2* mutations are generally associated with poor prognosis and sudden cardiac death in European populations.[19,20] Although *MYBPC3* cases were initially reported to follow relatively benign clinical course in an European population,[21] our data showed that 36% of *MYBPC3* cases in East Asians followed worse prognosis during the follow-up period (Table 3). In general, cardiac hypertrophy developed at the diagnosis gradually reduced during the follow-up period, and cardiac function becomes decreased later in the life even in the *MYBPC3* cases.[22]

Initial analysis of functional changes caused by the *MYH7* mutations demonstrated decreased power generation by the mutant myosin heavy chains[23] and the identification of HCM-related mutations in sarcomere components, troponin T and α-tropomyosin, had lead to a hypothesis that HCM is the disease of sarcomere and the cardiac hypertrophy was a compensation of decreased power generation.[24] However, we found HCM-associated *TNNI3* mutations at the contraction inhibitory domain,[10] which implied that the decreased power was not a common functional change caused by the sarcomere mutations. Indeed, subsequent functional analyses of mutations in genes for other sarcomere components than *MTH7* have revealed that contractile performance was not decreased by the mutations and most HCM-associated sarcomere mutations resulted in increased Ca^{2+} sensitivity of muscle contraction.[25–30] As an *MYH7* mutation that

caused HCM in transgenic mice also increased Ca^{2+} sensitivity at the muscle fiber level,[31] a common functional alteration caused by HCM-related sarcomere mutations may be the increased Ca^{2+} sensitivity. Muscle contraction is regulated by the concentration of intracellular Ca^{2+} that is released from sarcoplasmic reticulum (SR) via ryanodine receptor (RyR2) and re-up taken to SR via SR Ca^{2+}-ATPase (SERCA). When the concentration of Ca^{2+} is increased or decreased, muscle is contracted or relaxed, respectively. Increased Ca^{2+} sensitivity is a leftward shift of Ca^{2+}-tension curve; more tension is generated by mutant sarcomere than normal sarcomere at the same Ca^{2+} concentration (hypercontraction) or muscle with mutant sarcomere is under less relax states (diastolic dysfunction) than normal sarcomere. This is consistent with the finding that characteristic features of HCM are hypercontraction and diastolic dysfunction.

Z-DISC MUTATIONS IN HCM

As mutations in the sarcomere components were found in only less than half of familial HCM patients, there should be other disease gene(s) for HCM, and candidate gene approaches were taken to identify the disease-related mutations in other genes expressed in cardiac muscle (Figure 2). Identification of an HCM-associated mutation in titin gene (*TTN*) was the first example of disease gene other than the sarcomere components,[32] and the functional alteration due to the *TTN* mutation was an increased binding to α-actinin (Figure 3). In addition, we demonstrated that the HCM-associated Tcap gene (*TCAP*) mutations increased the binding of Tcap to titin, MLP and carsarcin-1,[33] leading to a hypothesis that Z-disc mutations in HCM may result in increased binding of Z-disc components and hence 'stiff sarcomere' (Figure 3). 'Stiff sarcomere' would increase passive tension on stretch of sarcomere. As the increased passive tension was associated with increased Ca^{2+} sensitivity,[34–36] we have speculated that HCM-associated abnormality in both Z-disc components and sarcomere components cause the increased Ca^{2+} sensitivity. It should be noted that a possible controversy exists; that is, HCM-associated MLP gene (*CSRP3*) mutations were reported to decrease the binding to α-actinin and N-RAP.[37,38] However, as discussed in the later section, DCM-associated mutations were found in *CSRP3* and α-actinin gene (*ACTN2*), and these mutations decreased binding to each other.[39] Therefore, the decreased binding between MLP and α-actinin was associated with both HCM and DCM. This discrepancy should be resolved by further studies.

OTHER MUTATIONS IN HCM

There are several other disease genes for HCM, including mutations in caveolin-3 gene (*CAV3*),[40] meta-vinculin gene (*VCL*),[41] αB-crystallin gene (*CRYAB*),[42] junctophilin-2 gene (*JPH-2*),[43] obscurin gene (*OBSCN*)[44] and most recently reported CARP gene (*ANKRD1*)[45] (Figure 2). Functional analyses were reported for *CRYAB*, *CAV3*, *OBSCN* and *ANKRD1* mutations; aggregation of αB-crystalline in cytoplasm,[42] decreased cell surface expression of caveolin-3,[40] decreased binding to titin,[44] and increased binding to titin and myopalladin,[45] respectively. It is not clear how the aggregated αB-crystalline resulted in cardiac hypertrophy, but impaired stress response may exaggerate hypertrophic response.[46] It should be noted here that an HCM-associated *TTN* mutation in N2B region increased binding to FHL2 protein[47] and decreased binding to αB-crystalline.[48] As for the function of caveolin-3 in cardiac function, it was reported that cell surface expression of caveolin-3 was associated with cardiac hypertrophy.[49] It was also reported that overexpression of caveolin-3 inhibit the hypertrophic response,[50] suggesting that reduced caveolin-3-mediated signaling would result in cardiac hypertrophy. Function of obscurin is not fully understood, but obscurin may be involved in calmodulin/CaMK-mediated signaling because obscurin was reported to bind and tether calmodulin to titin,[51] of which process was impaired by the HCM-associated *OBSCN* mutation. The functional significance of increased binding of CARP to titin and myopalladin caused by the *ANKRD1* mutations is not clarified, but mutant CARP showed nuclear or peri-nuclear localization, whereas normal CARP was exclusively localized in the cytoplasm.[52] As CARP is a hypertrophy-related transcriptional co-factor[52] and is known to be localized

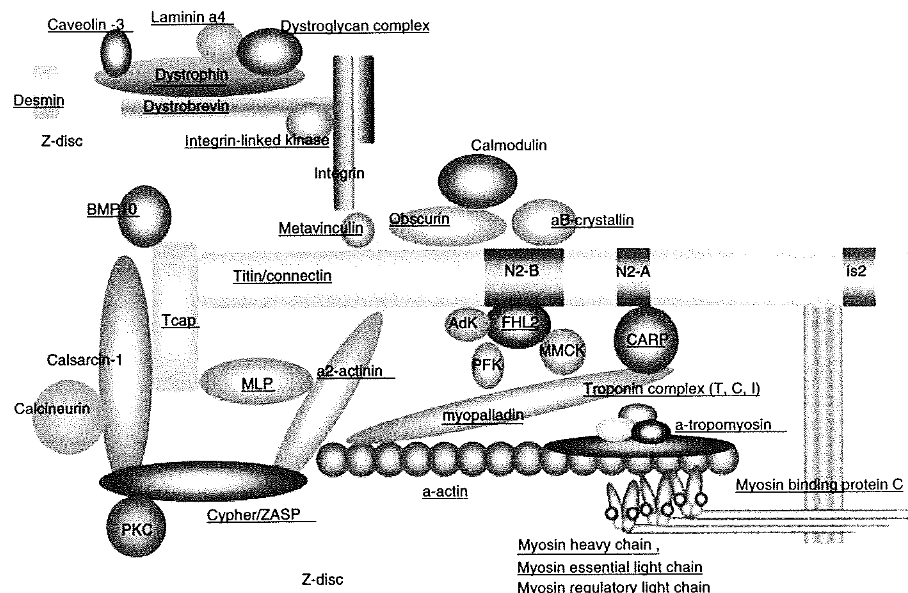

Figure 2 Schematic representation of sarcomere components. Half sarcomere is schematically shown. Components in which cardiomyopathy-associated mutations are found are underlined.

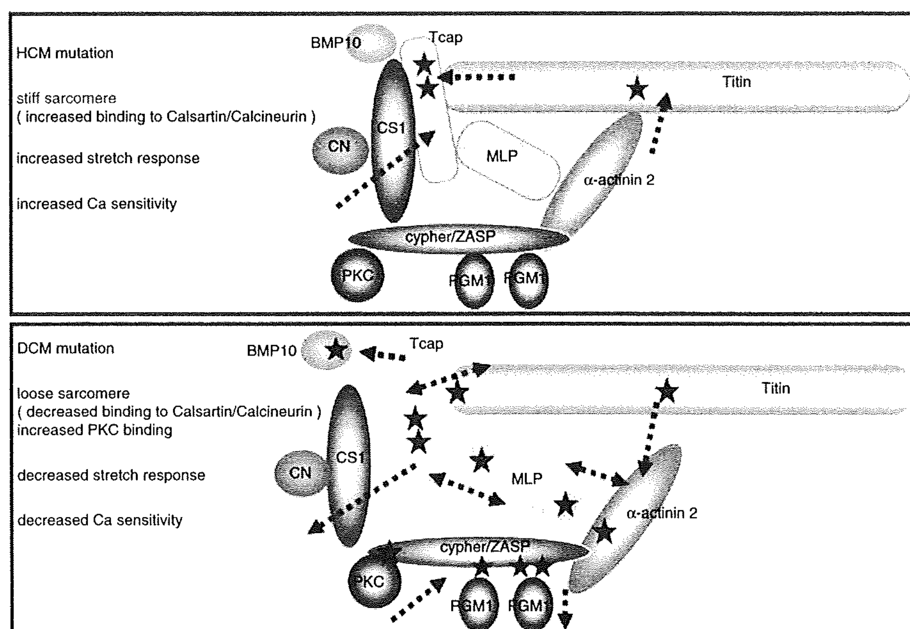

Figure 3 Schematic representation of functional alterations caused by Z-disc mutations. Functional alterations found with HCM-associated mutations (red stars) are shown in the upper panel, whereas the lower panel indicated the functional changes caused by DCM-associated mutations (blue stars). Broken arrows show the altered interactions caused by the mutations. CN, calcineurin; CS1, calsarcin-1. A full color version of this figure is available at *the Journal of Human Genetics* journal online.

in the cytoplasm and shifted to nucleus when cardiomyocytes were stretched,[53] presence of mutant CARP to nucleus suggested that the mutation rendered the cardiomyocytes hypersensitive to the stretch response leading to hypertrophy.

MEMBRANOUS AND CYTOSKELETAL MUTATIONS IN DCM

The first discovery of disease gene for DCM is a mutation in dystrophin gene (*DMD*) found in male siblings of X-linked DCM.[54] X-linked DCM is a rare form of familial DCM almost exclusively affecting males.[55] *DMD* mutations are known to cause Duchenne type and Becker type muscular dystrophy. In general, muscular dystrophy mainly affects skeletal muscles, and cardiac involvement is observed usually later in the clinical course.[56,57] However, X-linked DCM cases usually manifest with cardiac symptoms and subtle skeletal muscle involvement,[55] and phenotypic variance of *DMD* mutation may be caused by which domain of dystrophin was affected.[56] As shown in Table 4, our study showed that *DMD* mutations could be found in 5% of sporadic cases. None of these patients showed skeletal muscle symptoms, demonstrating that X-linked DCM should be considered not only for male sibling of familial DCM but also for male cases of sporadic DCM.

Dystrophin is a membranous protein having an important function in mechanical links from extracellular matrix to intracellular cytoskeleton in association with other proteins forming dystroglycan complex (DGC).[58] As muscle contraction forces myocytes with deformity and shortening/stretching, myofilaments should be tightly anchored to membrane and extracellular matrix via DGC to properly transmit the force with avoiding damages of cell membrane. Components of DGC in skeletal and cardiac muscles include dystrophin, dystroglycans (α and β), laminin αs, sarcoglycans (α, β, γ and δ), dystrobrebins (α and β), syntrophin and caveolin-3. In addition to DGC, integrins (α and β) are concentrated at the costemeres that overly Z-lines in striated muscles, and the integrin complex also has a function in mechanical links of power transmission.[58] Therefore, abnormalities in DGC and integrin complex may result in muscular dystrophy and cardiomyopathy. Indeed, mutations in δ-sarcoglycan gene (*SAGD*),[59]

Table 4 Frequencies of disease-associated mutations in Japanese and Korean adult patients with DCM

Gene symbol	*Familial case (%) (n=48)*	*Sporadic case (%) (n=100)*
ACTC	0.0	0.0
DES	2.1	0.0
DMD	0.0	5.0
LMNA	0.0	nt
SAGD	0.0	nt
MYH7	0.0	0.0
TNNT2	0.0	0.0
TPM1	0.0	0.0
TTN[a]	>6.3	>2.0
CSRP3	0.0	0.0
VCL	0.0	0.0
CRYAB	2.1	0.0
MYBPC3	0.0	0.0
TCAP	2.1	0.0
ACTN2	0.0	0.0
LDB3	2.1	0.0
FKTN	0.0	0.0
FHL2	2.1	0.0
PDLIM3	nt	nt
MYPN	0.0	0.0
LMNA4	0.0	0.0
ILK	0.0	0.0
ANKRD1	0.0	0.0
Sum	>16.7	>7.0

Abbreviations: DCM, dilated cardiomyopathy; nt, not tested.
[a]Z-disc, N2-B, N2-A, Novex3 and is2 domains (about 20% of entire *TTN*) were analyzed.

laminin α4 gene (*LMNA4*),[60] and integrin-linked kinase gene (*ILK*)[60] were found to cause DCM of autosomal dominant inheritance (Table 1). It was proposed that DCM was the disease of cytoskeleton or its interacting proteins.[61] However, recent studies showed that etiology of DCM is not confined to the abnormality of the cytoskeleton-related proteins.

SARCOMERE MUTATIONS IN DCM

Identification of cardiac α-actin gene (*CACT*) mutations was the first discovery of genetic cause of autosomal dominant DCM.[62] In addition, *CACT* mutation was also found in HCM,[63] demonstrating that sarcomere mutations cause both HCM and DCM; that is, overlapping disease genes for different cardiomyopathy. Molecular basis of different phenotypes caused by *CACT* mutations was suggested that DCM-associated mutations were found at the α-actinin-interacting domain,[62] whereas HCM-associated mutations were at the interacting domain to myosin heavy chain.[63] On the other hand, recent data suggested that there is a difference in folding property between the DCM-associated mutant actin and HCM-associated mutant actin.[64] Another example of overlapping disease gene was the identification of *TNNT2* mutation in DCM.[65] Functional study of *TNNT2* mutations clearly demonstrated the difference between DCM-associated mutation and HCM-associated mutation; that is, DCM-associated *TNNT2* mutation decreased Ca^{2+} sensitivity of muscle contraction, which is in clear contrast to the increased sensitivity caused by the HCM-associated mutation.[66] Therefore, sarcomere mutations can be found in both HCM and DCM, but difference in the functional alterations may determine the different phenotypes.[67]

Z-DISC MUTATIONS IN DCM

Mutations of membranous, cytoskeletal or sarcomere components were not found in our panel of familial DCM, whereas mutations in Z-disc components were relatively frequent (Table 4). We have reported several DCM-associated Z-disc protein gene mutations in *TTN*,[68] *CSRP3*,[69] *TCAP*[33,69] and Cypher/ZASP gene (*LDB3*),[70] albeit that *CSRP3* mutation was not found in Japanese or Korean patients.[69] As described in the HCM section, the DCM-associated *TCAP* mutations showed opposite functional alterations to the HCM-associated mutations.[33] Similarly, a DCM-associated *TTN* mutation found in the actinin-binding domain showed decreased binding to actinin.[68] In addition, another DCM-associated *TTN* mutation found in the Tcap-binding domain decreased the binding to Tcap.[68] As the Z-disc element mutations result in decreased binding among the elements, we hypothesize that DCM is the disease of 'loose sarcomere'[12,33] (Figure 3). The loose sarcomere is evident in an animal model of DCM, *CSRP3* (MLP) knock-out mouse, in which Z-disc was wide and stretch response was impaired.[69] As the stretch response is a hypertrophic response of cardiomyocytes against passive tension and Z-disc elements is suggested to be a stretch sensor of cardiomyocytes, abnormality in Z-disc elements may alter the regulation of stretch response.

Cypher/ZASP is a Z-disc element connecting calsarcin and actinin.[70] It is interesting to note that calsarcin binds calcineurin,[71] a Ser/Thr phosphatase involved in the process of hypertrophic program of cardiomyocytes.[72,73] Functional significance of calcineurin anchorage to Z-disc is not fully understood, but it was involved in stress-induced calcineurin-NFAT activation, because heterozygous *MLP* knock-out mice showed reduction in NFAT activation along with dislocation of calcineurin from Z-disk.[74] On the other hand, Cypher/ZASP binds protein kinase C (PKC)[70] and a DCM-associated *LDB3* mutation in the PKC-binding domain was found to increase the binding,[75] it was suggested that phosphorylation/dephosphorylation of Z-disc elements might be involved in the stretch response. Identification of target protein(s) for phosphorylation (by PKC)/dephosphorylation (by calcineurin) will unravel the molecular mechanism(s) of stretch response and/or signaling molecule(s) of cardiac hypertrophy.

Several other *LDB 3* mutations not in the PKC-interacting domain were reported in DCM or LVNC.[76] As the functional changes caused by these mutations had not been demonstrated, we have searched for binding protein to Cypher/ZASP by using yeast two-hybrid method, and found that phosphoglucomutase-1 (PGM1) as a novel-binding protein.[77] PGM1 is an enzyme involved in the conversion between glucose-6-phospate and glucose-1-phosphate, which is involved in the glucose/glycogen metabolism. Functional significance of the binding between PGM1 and the Z-disc element Cypher/ZASP was not known, but the DCM-associated mutations reported by Vatta *et al.*[76] showed decreased binding to PGM1.[77] In addition, PGM1 was demonstrated to be localized at the Z-disc under the stressed culture conditions, low serum and low glucose, suggesting the role of PGM1 in the energy metabolism at the Z-disc.[77] These observations suggested that the decreased stress response might be involved in the pathogenesis of DCM.

There are other DCM-associated mutations found in genes for other Z-line associated proteins, desmin (*DES*)[78] and metavinculin (*VCL*).[79] The *VCL* mutation was showed to impair the binding to actin,[79] whereas the *DES* mutations resulted in subtle change in the cytoplasmic *DES* network.[80] In addition, mutations in myopalladin gene (*MYPN*) have recently been reported in DCM. Although the molecular mechanisms of *MYPN* mutations leading to DCM remained unclear, the DCM-associated mutations impaired the myofiblinogenesis.[81]

OTHER MUTATIONS IN DCM

Etiology of familial DCM is quite heterogeneous, and there are several other disease genes for DCM categorized into several groups. The first group includes mutations in genes for nuclear membrane proteins, lamin A/C (*LMNA*)[82,83] and emerin (*EMD*),[84] which cause autosomal dominant and X-linked Emery-Dreifuss muscular dystrophy (EDMD), respectively. EDMD manifests with muscular dystrophy and DCM associated with conduction block.[85] Molecular mechanisms underlying the development of DCM caused by the nuclear membrane abnormality remain not fully understood,[86] but a study of an *LMNA* mutation knock-in mouse[87] showed that the mutation activated the MAPK pathway, suggesting an impaired signal transduction was involved in the pathogenesis of DCM.[88]

The second group consists of mutations affecting ion channel function; regulatory subunit of ATP-sensitive potassium channel (*ABCC9*)[89] and cardiac sodium channel (*SCN5A*).[90] Clinical phenotypes of *ABCC9* and *SCN5A* mutations were DCM accompanied by ventricular tachyrcardia[89] and conduction defects,[90] respectively. It should be noted here that the channelopathy is etiologically overlapping with the cardiomyopathy, such as *SCN5A* mutations in DCM and long QT syndrome, *CAV3* mutations in HCM and long QT syndrome, and *RYR2* mutations in ARVC and catecholaminergic polymorphic ventricular tachycardia.[91]

The third group is composed of mutations in genes for titin-N2B-interacting proteins, four and half LIM protein (*FHL2*)[92] and αB-crystallin (*CRYAB*).[48] As a titin-N2B region mutation found in DCM reduced binding to FHL2[47] and an *FHL2* mutation reduced binding to titin-N2B,[92] impaired interaction between titin and FHL2 appeared as a result in DCM. Molecular mechanisms underlying this phenomenon may be that FHL2 function as a tethering molecule of adenyl kinase,

phosphofructokinase and muscle creatine kinase; that is, proper recruitment of metabolic enzymes was impaired, although abnormality in other functions of FHL2[93] could not be neglected. The DCM-associated *CRYAB* mutation decreased binding to titin-N2B region and a DCM-associated titin-N2B region mutation decreased binding to αB-crystallin,[48] suggesting that impaired interaction between titin-N2B and αB-crystallin resulted in DCM. However, an HCM-associated titin-N2B mutation also reduced the binding to αB-crystallin,[47] and it is not clear why the impaired binding of titin-N2B and αB-crystallin could express as both HCM and DCM. There may be additional factors involved in the phenotypic expression of titin-N2B mutations, such that binding to FHL2 was different between the HCM- and DCM-associated mutations and that the DCM-associated titin-N2B mutation was a truncation mutation, whereas the HCM-associated mutation was a missense mutation.[47] In addition, we found DCM-associated mutations in *ANKRD1*.[94]

The fourth group is related to intracellular Ca^{2+} handling. As muscle contraction is depending on the Ca^{2+} concentration, SERCA function in re-uptaking the intracellular Ca^{2+} to SR leads to relaxation of muscle. Phospolamban is an inhibitory molecule of SERCA, which is physiologically active when phosphorylated by protein kinase A (PKA).[95] Functional analysis of phospholamban gene (*PLN*) mutations found in DCM showed that the mutation was constitutive active; that is, inhibiting SERCA.[96,97] In contrast, a truncation mutation of *PLN*, that is loss of *PLN* function, is recently reported in familial HCM.[98] Although *PLN* deficiency in mice resulted in enhanced contractility,[99] no cardiac hypertrophy was observed in the mice. In addition, loss of *PLN* rescued DCM phenotype[100] in MLP knock-out mice, and a dominant-negative form of *PLN* prevented heart failure in cardiomyopathic hamster BIO14.6,[101] which is known to be caused by *SAGD* deficiency.[102] These observations suggest that functional impairment of phospholamban may prevent systolic dysfunction but not directly involved in the cardiac hypertrophy. Moreover, promoter mutations of *PLN*, which increased transcription, were recently reported in HCM.[103,104] As transgenic mice over-expressing *PLN* did not show cardiac hypertrophy, rather they showed systolic dysfunction,[105] pathological significance of P*LN* promoter mutations in HCM remains to be clarified.

The other mutations found in DCM include G4.5 gene (tafazzin, *TAZ*, Barth's syndrome),[106] fukutin gene (*FKTN*),[107] desmoplakin gene (*DSP*),[108] plakoglobin gene (*JUP*)[109] mutations. These mutations, however, were not found in 'pure' DCM and found in 'syndromic' DCM that is accompanied by disorders and/or dysfunction in skeletal muscle, skin or hair. An example is that *FKTN* mutation was not found in pure DCM, but was found in skeletal myopathy accompanied by DCM and an early sign of *FKTN* mutation-associated DCM was hyper-CKemia.[110]

MUTATIONS IN OTHER CARDIOMYOPATHIES

Disease-causing gene mutations can also be identified in other cardiomyopathies. As shown in Table 1, mutations in sarcomere proteins were found in RCM. It is interesting to note that *MYH7*, *TNNT2* and *TNNI3* mutations were associated with RCM, HCM and DCM. Molecular basis of the differences between RCM-associated mutations and HCM-associated mutations was that the RCM-associated mutations showed much greater Ca^{2+} sensitization than the HCM-associated mutations, as demonstrated for *TNNT2*[111] and *TNNI3*[112] mutations. In accordance with these findings, it was reported that restrictive phenotype (RCM-like HCM) was uncommon in HCM and may represent a poor prognosis form with severe diastolic dysfunction.[113] On the other hand, the difference between RCM-associated mutations and DCM-associated mutations is not clear, but a gene-dose effect could be involved in the difference because RCM-associated *TNNI3* mutation was found in heterozygous state,[114] whereas the DCM-associated *TNNI3* mutation was found in homozygous state.[115]

LVNC is a recently described cardiomyopathy where ventricular trabeculations was poorly developed, and mutations in *MYH7*,[116] *CACT*,[117] *DES*,[78] *LMNA*,[118] *TAZ*,[119] *DTNA*,[120] and *LDB3*[76] were reported in LVNC (Table 1). Molecular mechanisms of the mutations in causing LVNC are not elucidated. In a mouse model, deficiency of BMP10 resulted in LVNC phenotype.[121] BMP10 is a member of TGFβ family, which is expressed mainly in the heart, and has an important function in morphogenesis of the heart.[122] Therefore, LVNC might be a developmental error in the hearts carrying the mutations in components of sarcomere and/or sarcolemma. Interestingly, a rare polymorphism of BMP10 gene was found in hypertensive DCM, which decreased binding to Tcap and increased extracellular secretion of BMP10 facilitating the remodeling of hypertensive hearts.[123]

Another primary cardiomyopathy AVRC has also been investigated for disease-causing mutations[124] (Table 1). As the ARVC-associated mutations can be found in genes for plakoglobin (*JUP*),[125] desmoplakin (*DSP*),[126] plakophilin-2 (*PKP2*)[127] and desmoglein (*DSG3*),[128] they were considered to disrupt cell–cell contacts via desmosomes. *RYR2* mutations were also reported in ARVC,[129] linking cardiomyopathy to channelopathy. Promoter variant of TGFβ3 was also reported in ARVC,[130] but its pathological significance remains to be resolved.

CONCLUSION

In this review, gene mutations found in the hereditary cardiomyopathy are summarized. Each family or patient has usually only one disease-causing mutation, but the primary cardiomyopathy is both clinically and etiologically heterogeneous even in a specific clinical type (HCM, DCM, RCM, ARVC and LVNC). As different causes result in the same phenotype, there may be several pathways in the pathogenesis of primary cardiomyopathy, such as abnormalities in the Ca^{2+} sensitivity, stretch response, stress response and others. Intervention of these common pathways will be a therapeutic or preventive strategy for hereditary cardiomyopathy caused by different mutations. In this respect, it is noteworthy that administration of a Ca^{2+} sensitizing chemical compound SCH00013[131] prolonged the disease onset, improved the survival prognosis and ameliorated the cardiac remodeling in a DCM model animal, *LMNA* knock-in mice.[132]

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