Contribution of Genetic Factors to the Pathogenesis of Dilated Cardiomyopathy

– The Cause of Dilated Cardiomyopathy: Genetic or Acquired? (Genetic-Side) –

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Dilated cardiomyopathy (DCM) is characterized by dilated ventricles and systolic dysfunction. Its etiology is not fully unraveled, but both extrinsic and intrinsic factors are considered to be involved. The intrinsic factors include genetic variations in the genes (ie, disease-causing mutations and disease-associated polymorphisms), which play key roles in controlling the susceptibility to the disease by affecting the performance, regulation, and/or maintenance of cardiac function. DCM can be classified into 2 types: hereditary and non-hereditary. The genetic variations, or disease-causing mutations, contributing to the pathogenesis of hereditary DCM can be found in various genes, especially those for sarcolemma elements, contractile elements, Z-disc elements, sarcoplasmic elements, and nuclear lamina elements of cardiomyocytes. On the other hand, disease-associated polymorphisms, which control the susceptibility to non-hereditary DCM, may be found in genes expressing not only in cardiomyocytes but also other non-cardiac cells involved in the immune system. Because functional alterations caused by these genetic variations can be classified into several categories, it is necessary to understand the pathogenesis and hence to develop diagnostic and therapeutic strategies for both hereditary and non-hereditary DCM from the viewpoint of genetic factors. (*Circ J* 2011; **75**: 1756–1765)

Key Words: Cardiomyopathy; Dilated cardiomyopathy; Genetics; Stiffness; Stress

Cardiomyopathy is a heterogeneous disease caused by functional abnormality of cardiac muscle and classified as primary or secondary cardiomyopathy.¹ Secondary cardiomyopathy is caused by extrinsic factors, including infection, ischemia, hypertension and metabolic disorders, whereas the diagnosis of primary cardiomyopathy is based on exclusion of secondary cardiomyopathy and there are several different clinical types.^{2,3} Dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) are 2 major ones. DCM is characterized by a dilated ventricular cavity with systolic dysfunction and the clinical symptom of DCM is heart failure, which is often associated with arrhythmia and sudden death. On the other hand, HCM, a major cause of sudden death in the young and heart failure, is characterized by left ventricular hypertrophy, often asymmetric, accompanied by myofibrillar disarrays and reduced compliance (diastolic dysfunction) of the cardiac ventricles.

The etiology of familial DCM had been unknown until 1993 when a mutation in the dystrophin gene (*DMD*) was found in male sibling cases with X-linked DCM.⁴ Family history of the same disease is indicative that genetic factors con-

tribute to the etiology and pathogenesis of the disease. The genetic factor can be classified into 2 categories: a disease-causing gene mutation as the etiology of monogenic disease or a disease-associated gene polymorphism that is involved in the pathogenesis of multifactorial disease.

Contribution of Genetic Factors in DCM

The concept of genetic factors involved in the disease is shown schematically in **Figure 1**. It is conceivable that full biological function in healthy subjects is impaired to the threshold for the development of disease by both genetic factors and environmental factors. In the monogenic disease, most of the dysfunction is caused by a disease-causing gene mutation, although additional genetic factors or modifier genes might also contribute to the pathogenesis, and other environmental factors including gender, age, and life-style factors may be involved in disease development. The ratio of disease development among carriers of the disease-causing mutation is defined as penetrance, which is determined by factors other than the disease-causing mutation. In clear

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contrast, the genetic factor is composed of multiple disease-associated gene polymorphisms in the multifactorial disease. In general, the contribution of genetic factors to the disease is approximately 60–100% in the monogenic disease, whereas it is approximately 20–30% in the multifactorial disease. Therefore, the disease-causing mutation can determine the development of disease by 60–100%, although it depends on each mutation. On the other hand, each disease-associated polymorphism can determine the disease at a few percent, because there should be multiple polymorphisms involved in the multifactorial disease. Family history of the same disease is indicative of genetic factors in the disease, and family history or aggregation of the disease can be seen in both the monogenic and multifactorial disease. The main difference is that the family history of monogenic disease can be explained by the Mendelian rule of inheritance, whereas the aggregation of multifactorial disease does not follow this rule. However, it is sometimes difficult to distinguish monogenic disease from multifactorial disease when the size of the family is small or the penetrance of the disease is low.

Mutations in Hereditary Cardiomyopathy

It has been reported that as much as 35% of DCM patients have a family history, mainly consistent with autosomal dominant inheritance, although some familial cases can be explained by autosomal recessive or X-linked recessive trait.⁵ This report is based on the extensive analysis of family members of the DCM patients, and hence is considered to be the maximal estimation of familial cases in DCM. In general, a family history can be found in approximately 10–20% of DCM patients. In clear contrast, more than half of HCM patients have a family history consistent with an autosomal

dominant genetic trait. Therefore, a certain proportion of primary cardiomyopathy is monogenic disease caused by a single disease-causing mutation. However, family history may not be found in patients with hereditary cardiomyopathy, and then sporadic cases might also be with hereditary cardiomyopathy, which cannot easily be distinguished from patients with cardiomyopathy of multifactorial etiology.

Molecular genetic approaches have recently been taken to unravel the disease genes. As shown in [Table 1](#) many different disease genes (ie, disease-causing mutation in the analyzed gene) have been identified for different clinical types of primary cardiomyopathy.⁶ Most of the disease genes encode for sarcomere proteins ([Figure 2](#)). It should be noted here that each patient or each multiplex family usually carries only one mutation in the disease gene, although there are exceptional cases harboring mutations in 2 or more disease genes. Another noteworthy issue is the overlapping of disease genes for different clinical types (ie, mutations in the same disease gene can be found in different cardiomyopathies).

Frequency of Disease-Causing Mutations in DCM

Disease-causing mutations in Japanese patients stratified into familial or sporadic cases based on family history have been investigated ([Table 2](#)). Although not all the known disease genes were analyzed, approximately 21% of familial DCM patients possessed one. Of note was that there was no major disease gene for Japanese DCM patients, because the mutations were very heterogeneous and each mutation was found in only one proband patient. Although titin gene (*TTN*) mutations were relatively frequent, this might be due to *TTN* being quite large, encompassing at least 383 exons.⁷ On the other hand, approximately 7% of sporadic DCM patients

Table 1. Disease Genes for Primary Cardiomyopathy

Clinical types	Inheritance	Gene symbol	Coding protein
HCM/DCM/RCM	AD	<i>MYH7</i>	Cardiac β myosin heavy chain
HCM/DCM	AD	<i>TNNI2</i>	Cardiac troponin T
HCM/DCM	AD	<i>TPM1</i>	α tropomyosin
HCM/DCM	AD	<i>MYBPC3</i>	Cardiac myosin binding protein C
HCM	AD	<i>MYL3</i>	Ventricular myosin essential light chain
HCM	AD	<i>MYL2</i>	Ventricular myosin regulatory light chain
HCM/DCM/RCM	AD, AR	<i>TNNI3</i>	Cardiac troponin I
HCM/DCM	AD	<i>ACTC</i>	α cardiac actin
HCM/DCM	AD	<i>TTN</i>	Titin/connectin
HCM/DCM	AD	<i>TNNC2</i>	Cardiac troponin C
HCM	AD	<i>MYH6</i>	Cardiac α myosin heavy chain
HCM/DCM	AD	<i>CSRP3</i>	Muscle LIM protein
HCM	AD	<i>CAV3</i>	Caveolin-3
HCM/DCM	AD	<i>TCAP</i>	Telethonin (Tcap)
HCM/DCM	AD	<i>VCL</i>	Metavinculin
HCM	AD	<i>JPH-2</i>	Junctophilin
HCM	AD	<i>OBSCN</i>	Obscurin
HCM	AD	<i>MYOZ2</i>	Calsartin 1/myozenin 2
HCM/DCM	AD	<i>ANKRD1</i>	CARP
DCM/RCM	AD	<i>DES</i>	Desmin
DCM	AD	<i>LMNA</i>	Lamin A/C
DCM	AD	<i>SAGD</i>	δ sarcoglycan
DCM	AD	<i>ACTN2</i>	α actinin 2
DCM/LVNC	AD	<i>LDB3</i>	ZASP/Cypher
DCM	AD	<i>PLB</i>	Phospholamban
DCM	AD	<i>ABCC9</i>	K _{ATP} channel
DCM	AD	<i>SCN5A</i>	Cardiac Na channel
DCM/HCM	AD	<i>CRYAB</i>	α B crystallin
DCM	AD	<i>FHL2</i>	FHL2
DCM	AD	<i>LMNA4</i>	Laminin α 4
DCM	AD	<i>MYPN</i>	Myopalladin
DCM	AD	<i>RBM20</i>	RNA binding motif protein 20
DCM/HCM	AD	<i>MEXN</i>	Nexillin
DCM	AD	<i>BAG3</i>	bcl2-associated athanogene 3 protein
DCM	XR	<i>DMD</i>	Dystrophin
DCM	XR	<i>EMD</i>	Emelin
DCM/LVNC	XR	<i>TAZ</i>	Tafazzin/G4.5
DCM	XR	<i>FKTN</i>	Fukutin
DCM/ARVC	AR	<i>DSP</i>	Desmoplakin
DCM/ARVC	AR, AD	<i>JUP</i>	Plakoglobin
ARVC	AD	<i>PKP2</i>	Placophilin 2
ARVC	AD	<i>TGFB3</i>	TGF β 3
ARVC	AD	<i>RYR2</i>	Ryanodine receptor 2
ARVC	AD	<i>DSG3</i>	Desmoglein 3
ARVC	AD	<i>TMEM43</i>	LUMA
LVNC	AD	<i>DTNA</i>	α dystrobrevin

HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; AD, autosomal dominant; AR, autosomal recessive; XR, X-linked recessive; TGF, transforming growth factor.

also carried a gene mutation, most frequently in *DMD*. These observations strongly suggest that there are other disease genes for hereditary DCM and that a certain proportion of sporadic DCM cases is of hereditary DCM. The reason why gene mutations were found in several sporadic cases might be due to the small size of the patient's family, de novo mutation, and/or low penetrance of the disease-causing mutation.

Functional Aspects of Sarcolemmal Mutations in DCM

The first identification of a disease-causing mutation for DCM was the *DMD* mutation in X-linked DCM. Mutations in *DMD* are well known to cause Duchenne-type and Becker-type muscular dystrophy, both of which are often complicated by cardiac dysfunction in the later phase of the clinical course. In X-linked DCM caused by *DMD* mutations, skeletal muscle phenotypes are usually subtle and the difference

Figure 2. Schematic representation of sarcomere components. A half sarcomere is schematically shown. Elements for which gene mutation causes dilated cardiomyopathy are underlined.

Table 2. Mutation Rate in Japanese Patients With Dilated Cardiomyopathy

Gene symbol	Coding protein	% familial cases (n=72)	% sporadic cases (n=100)
ACTC	α cardiac actin	0.0	0.0
DES	Desmin	1.4	0.0
DMD	Dystrophin	0.0	5.0
LMNA	Lamin A/C	0.0	NT
SAGD	δ sarcoglycan	0.0	NT
MYH7	Cardiac β myosin heavy chain	5.6	0.0
TNNT2	Cardiac troponin T	0.0	0.0
TNNI3	Cardiac troponin I	0.0	0.0
TPM1	α tropomyosin	0.0	0.0
TTN	Titin/connectin*	>4.2	>2.0
CSRP3	Muscle LIM protein	0.0	0.0
VCL	Metavinculin	0.0	0.0
CRYAB	α B crystallin	1.4	0.0
MYBPC3	Cardiac myosin binding protein C	0.0	0.0
TCAP	Telethonin (Tcap)	1.4	0.0
ACTN2	α actinin 2	0.0	0.0
LDB3	ZASP/Cypher	1.4	0.0
FKTN	Fukutin	1.4	0.0
FHL2	FHL2	1.4	0.0
LMNA4	Laminin α 4	0.0	0.0
MYPN	Myopalladin	0.0	0.0
ANKRD1	CARP	0.0	0.0
NBLT	Nebulette	0.0	0.0
BAG3	bcl2-associated athanogene 3	2.8	0.0
	Sum	>20.8	>7.0

*Approximately 25% of titin/connectin, Z-region, N2-B region, N2-A region, kinase and adjacent regions, Novex3 region and is2 region, was analyzed.
NT, not tested.

in severity and distribution of affected muscles may in part be determined by which domain of *DMD* is affected. Dystrophin is a sarcolemmal protein that plays a key role in the anchoring of muscle cells. As shown in **Figure 1**, other proteins such as dystrobrevin, integrin, integrin kinase and metavinculin form a sarcolemma complex linking dystrophin and the Z-disc. In addition, the laminin and dystroglycan complex links muscle cells to the extracellular matrix. Furthermore, fukutin is involved in the glycosylation of α -dystroglycan. Mutations in genes for these sarcolemmal proteins are known to cause DCM (**Table 1**), which may lead to disruption of anchoring and hence dysfunction in transmission of the force generated by muscle contraction.

Muscle contraction, which is caused by the interaction between an actin filament and myosin heavy chain, is regulated by the concentration of intracellular Ca^{2+} that is released from the sarcoplasmic reticulum (SR) via the ryanodine receptor and re-uptake to the SR via SR Ca^{2+} -ATPase (SERCA), which is regulated by phospholamban (*PLB*). When the concentration of Ca^{2+} is increased or decreased, muscle contracts or relaxes, respectively. It has been reported that DCM is caused by a *PLB* mutation,⁸ by which uptake of Ca^{2+} to the SR is impaired such that release of Ca^{2+} from the SR per beat is decreased.

There are 2 sensing systems for fine tuning of Ca^{2+} -dependent muscle contraction: regulation by the troponin complex, and regulation by myosin light chain. The fine-tuning system controls the magnitude of muscle contraction at the same concentration of Ca^{2+} , which is also defined as calcium sensitivity. The calcium sensitivity in skeletal muscle is mainly controlled by the troponin complex via conformational changes of troponin T and troponin I depending on the capture or release of Ca^{2+} by troponin C, disruption of which can cause DCM in animal models.^{9,10} On the other hand, calcium sensitivity in smooth muscle is mainly regulated by myosin light chain through its phosphorylation. As for cardiac muscle, both the troponin complex system and myosin light chain system regulate the calcium sensitivity. Any impairment in the regulation of calcium sensitivity can be associated with dysfunction of muscle contractility and hence would cause cardiomyopathy.

Functional Aspects of Contractile Element Mutations in DCM

Mutations in contractile element genes were initially identified as the cause of HCM,¹¹ but recently were found in DCM cases (**Table 1**). Because some HCM patients develop systolic dysfunction similar to DCM, which is called dilated-phase HCM, DCM patients carrying contractile element mutations might indeed suffer from HCM. However, it was demonstrated that there are apparent functional differences related to the disease-causing mutations found in DCM and HCM. A typical example is reported for mutations in cardiac troponin T gene (*TNNT2*).

Troponin T binds troponin C and troponin I to form the troponin complex, which regulates the calcium sensitivity of muscle contraction via conformational change in the interaction between cardiac actin and myosin heavy chain. An in vitro assay of muscle contraction through replacement of normal troponin T with the DCM-causing *TNNT2* mutation, del_Lys210, showed that the mutant troponin T caused a rightward shift of the calcium-tension curve, which indicated a decreased calcium sensitivity of the muscle contraction.¹² It was reported that the del_Lys210 mutation altered the calcium sensitivity in the hearts of *TNNT2* mutant knock-in mice, which exhibited the cardiac phenotype of DCM.¹³ On

the other hand, HCM-linked *TNNT2* mutations were shown to increase the calcium sensitivity in vitro¹⁴ and in the in vivo model of transgenic mice that developed HCM.¹⁵ These observations indicate that the altered calcium sensitivity of muscle contraction because of *TNNT2* mutations is the direct cause of primary cardiomyopathy and the opposite functional alterations are associated with DCM and HCM.

The decreased calcium sensitivity was also reported for DCM-causing mutations in α -tropomyosin (*TPM1*)¹⁶ and cardiac troponin C (*TNNC1*),¹⁷ whereas the increased calcium sensitivity was noted for various HCM-causing mutations in the contractile element genes, including *TPM1*,¹⁶ cardiac troponin I gene (*TNNI3*),¹⁸ ventricular myosin regulatory light chain gene (*MYL3*)¹⁹ and *MYBPC3*.²⁰ Therefore, the altered calcium sensitivity may at least in part explain the functional alterations caused by the contractile element gene mutations.

Functional Aspects of Z-Disc Element Mutations in DCM

A unit of striated muscle is called a sarcomere, which aligns in tandem to maximize the generation of power. Because the generated power of muscle contraction is transmitted to adjacent sarcomeres through the Z-disc (**Figure 2**), mutations in Z-disc elements may cause hereditary cardiomyopathy (**Table 1**). Identification of a HCM-causing mutation in the Z-disc region of titin (*TTN*) was the first example of the Z-disc element mutation, which increased the binding of titin and α -actinin.²¹ On the other hand, 2 different disease-causing *TTN* mutations in the Z-disc region were identified in DCM: one at the actinin-binding domain and the other at the Tcap-binding domain.²² Functional analyses demonstrated that the former mutation decreased the binding to α -actinin, which was the opposite functional alteration to that caused by the HCM-causing mutation, whereas the latter mutation decreased the binding to Tcap, suggesting that decreased binding of titin and Z-disc elements was a common functional alteration caused by the DCM-causing *TTN* mutations (**Figure 3**).

In addition, 2 DCM-causing mutations in the Tcap gene (*TCAP*), which decreased the binding of Tcap to titin, MLP and calsarcin-1 (myozenin-2), have been found.²³ Moreover, a DCM-associated mutation, Trp4Arg, in the MLP gene (*CSR3*), was reported to decrease the binding of MLP to Tcap.²⁴ Because this mutation was found not only in the DCM patients but also in the general population, it may be a polymorphism not a DCM-causing mutation.²⁵ However, a knock-in mouse line carrying this mutation showed cardiac hypertrophy and heart failure phenotype under the catecholamine-induced cardiac stress.²⁶ Because *CSR3* knock-out mice develop the DCM phenotype,²⁷ along with a wide Z-disc and loss of stretch response,²⁴ the Z-disc may play a role as a stretch sensor and its dysfunction leads to the DCM phenotype.²⁴ Furthermore, another DCM-causing *CSR3* mutation and α -actinin gene (*ACTN*) mutations were reported to decrease the binding of MLP and α -actinin.²⁵ These observations suggest that the decreased binding among the Z-disc elements could develop into DCM because of the decreased stretch response. In this regard, it can be hypothesized that DCM is a disease of "loose sarcomeres" (**Figure 3**). In clear contrast, HCM-causing mutations in *TCAP* increase the binding of Tcap to titin and calsarcin-1,²³ leading to a hypothesis that HCM may be a disease of "stiff sarcomeres" (**Figure 3**). Loose and stiff sarcomeres would decrease and increase passive tension upon stretch of the sarcomere, respectively. Because the change in passive tension is associated with a change in the calcium sensitivity,^{28–30} it is speculated that

Figure 3. Functional alterations caused by the Z-disc mutations. Functional alterations caused by the DCM-causing mutations (blue stars, **Upper panel**) and functional changes caused by the HCM-causing mutations (red stars, **Lower panel**). Broken arrows show the altered interactions caused by the mutations. CN, calcineurin; CS1, calsarcin-1; DCM, dilated cardiomyopathy.

abnormality in both the Z-disc elements and contractile elements cause the abnormal calcium sensitivity.

There are several other Z-disc elements, desmin (*DES*) and metavinculin (*VCL*), of which mutations have been found in DCM. The *VCL* mutation impaired the binding to actin,³¹ whereas the *DES* mutations resulted in the disruption of cytoplasmic desmin network.³² In addition, mutations in the myopalladin gene (*MYPN*)³³ and nebulin gene (*NBL1*),³⁴ which impair myofibrinogenesis,^{36,37} have recently been reported in DCM. These findings suggest that the Z-disc also plays a role in myofibrinogenesis.

ZASP/Cypher is another Z-disc element connecting calsarcin and actinin³⁵ (**Figure 2**). Calsarcin binds calcineurin,³⁶ a Ser/Thr phosphatase involved in the hypertrophic progress of cardiomyocytes.³⁷ The functional significance of calcineurin anchorage to the Z-disc is not fully understood, but it may be involved in the stress-induced calcineurin–NFAT activation, because heterozygous *CSRP3* knock-out mice show a reduction in NFAT activation along with a dislocation of calcineurin from the Z-disc.³⁸ In addition, ZASP/Cypher is known to bind protein kinase C (PKC),³⁵ and as a DCM-causing mutation in the PKC binding domain of ZASP/Cypher increased the binding,³⁹ it has been suggested that phosphorylation/dephosphorylation of Z-disc elements might be involved in the stretch response.

In addition, several other ZASP/Cypher gene (*LDB3*) mutations not in the PKC interacting domain are reported in DCM and LVNC.⁴⁰ Phosphoglucosyltransferase-1 (PGM1) was recently identified as a novel binding protein to ZASP/Cypher⁴¹

(**Figure 2**). PGM1 is a metabolic enzyme involved in glucose–glycogen metabolism. The functional significance of the binding between PGM1 and ZASP/Cypher remains unclear, but the DCM-causing mutations decrease the binding between ZASP/Cypher and PGM1.⁴¹ Because PGM1 localizes at the Z-disc under the stressed culture conditions, a role for PGM1 in energy metabolism at the Z-disc may be required for the response against metabolic stress.⁴¹ These observations suggest that an impaired stress response due to abnormality in the Z-disc elements might be involved in the pathogenesis of DCM.

Functional Aspects of Sarcoplasmic Element Mutations in DCM

Nebulette is anchored to the Z-disc at the C-terminal portion, and the other side is positioned in the sarcoplasm where it binds actin (**Figure 2**). A polymorphism in the actin-binding motif of nebulette associated with DCM has been reported.⁴² On the other hand, myopalladin is anchored to the Z-disc at the N-terminal portion, while the other side is positioned in the sarcoplasm to bind a transcriptional cofactor, CARP.⁴³ CARP is known to shuttle between the sarcoplasm and nucleus to regulate gene expression associated with the stretch response, cardiac remodeling, and myofibrinogenesis.⁴⁴ Several DCM-causing CARP mutations that impair myofibrinogenesis were recently reported.⁴⁵

There are several other sarcoplasmic proteins of which gene mutations have been found in DCM. Four and half LIM protein 2 gene (*FHL2*) and α B-crystallin gene (*CRYAB*) are

examples. They bind titin at the N2-B region, where a DCM-causing mutation has been found, and functional studies revealed that the DCM-causing mutation decreased the binding of titin to both proteins.^{46,47} In addition, a DCM-causing *FHL2* mutation, which decreased the binding of FHL2 to titin, has been found.⁴⁸ Because FHL2 is tethering muscle-specific metabolic enzymes (ie, adenylate kinase, phosphofructokinase, and muscle type creatinine kinase⁴⁹), the DCM-causing *FHL2* mutation would impair the recruitment of these metabolic enzymes to titin. Moreover, a DCM-causing *CRYAB* mutation decreased the binding to titin.⁵⁰ Although the functional significance of binding between titin and α B-crystallin remains unclear, it might be involved in the α B-crystallin-mediated protection of cardiac muscle from ischemic stress.⁵⁰ These observations suggest that DCM-causing mutations in these sarcoplasmic protein genes would render cardiac muscle susceptible to the metabolic stress. It should be noted here that α B-crystallin is phosphorylated and translocated to the Z-disc under ischemic conditions, suggesting a role of the Z-disc in the stress response.⁵¹

Functional Aspects of Nuclear Lamina Mutations in DCM

Part of hereditary DCM is caused by mutations in the genes for components of the nuclear lamina, emerin (*EMD*) and lamina A/C (*LMNA*). It is well known that patients with skeletal muscle disease, such as muscular dystrophy or myofibrillar myopathy, often suffer from cardiac dysfunction. Because both skeletal muscle and cardiac muscle are striated muscle, there are several genes specifically expressed in both muscle types and mutations in such genes can be found in both skeletal muscle disease and cardiomyopathy. *EMD* mutations were reported in X-linked⁵² Emery-Dreifuss muscular dystrophy, and *LMNA* mutations were found in autosomal-dominant⁵³ and autosomal-recessive⁵⁴ Emery-Dreifuss muscular dystrophy. It is known that Emery-Dreifuss muscular dystrophy is often accompanied by conduction defects and heart failure in the later clinical phase,^{52–54} so there is a possible link between Emery-Dreifuss muscular dystrophy and DCM. Indeed, upon screening for mutations in X-linked⁵⁵ and autosomal-dominant⁵⁶ DCM accompanied by conduction defects without severe skeletal muscle phenotype, *EMD* and *LMNA* mutations were discovered, respectively. As discussed for *DMD* mutations, the difference in clinical phenotype (ie, skeletal muscle disease or cardiomyopathy) may be determined by which domain of the elements encoded by the disease gene was affected. However, there is no definite difference in the distribution of *LMNA* mutations found in the muscular diseases and cardiomyopathy.^{57,58} Molecular mechanisms for developing DCM by mutations in nuclear lamina genes remain unknown, but might be involved in the altered regulation of gene expression in the heart as reported for knock-in mice with a *LMNA* mutation.⁵⁹

On the other hand, altered calcium sensitivity may not be responsible for the development of DCM caused by the *LMNA* mutation, because no significant change in calcium sensitivity was found in the hearts of knock-in mice.⁶⁰ However, treatment by a calcium sensitizer, SCH00013, which had no activity for inhibiting phosphodiesterase, can delay the development of the DCM phenotype and prevent DCM-associated changes, including pathological fibrosis as well as cardiac remodeling-related gene expression in the heart,⁶⁰ suggesting that the decreased calcium sensitivity might be secondarily involved in the pathogenesis of DCM in the *LMNA* mutation knock-in mice.

Polymorphisms Associated With DCM

The contribution of a genetic factor to the pathogenesis of DCM largely depends on whether it is a disease-causing mutation or a disease-associated polymorphism. In most cases, disease-associated polymorphisms would increase the risk for disease by a factor of approximately 1.2, and at most of 3.0, suggesting that there is limited significance of their applications in the diagnosis and/or prediction of the disease. However, information on the disease-associated polymorphism, even if its contribution is small, should be useful in unraveling and understanding the molecular mechanisms of pathogenesis.

Polymorphisms in the genes expressed in cardiomyocytes can be associated with DCM. As described in the previous section, sequence variations in the Z-disc elements, Trp4Arg of *CSRP3* and Asn654Lys of *NBLT*, can be found in the general populations of Europeans and Japanese, respectively. Therefore, they are DCM-associated polymorphisms and not DCM-causing mutations. However, both are rare polymorphisms because of their low carrier frequency, 0.2% in Whites²⁴ and 1.2% in Japanese,⁴² and hence their detection in DCM patients might have, albeit limited, a diagnostic significance. Indeed, Trp4Arg of *CSRP3* proved to have a definite functional significance under certain conditions in the mouse model.²⁶ Another example of a rare polymorphism associated with DCM is Thr326Ile of BMP10, which was found in 2 out of 46 Japanese patients with DCM accompanied by hypertension.⁶¹ BMP10 is a member of the TGF family and specifically expressed in the cardiomyocyte.⁶² This variant is a rare polymorphism, 0.13% in healthy Japanese, but is a significant risk factor for DCM in the presence of hypertension.⁶¹ In addition, BMP10 binds to Tcap and the variant decreases the binding (Figure 3), which in turn results in the increased secretion of BMP10.⁶¹ That BMP10 facilitates hypertrophy and maturation of rat cardiomyocytes in primary culture has also been demonstrated.⁶¹ These observations suggest a pivotal role of the Z-disc in cardiac remodeling.

Apart from the Z-disc proteins, sarcolemma proteins are also important for the contractile performance of cardiac muscle and include the adrenergic receptors. There are several polymorphisms in the genes for β 1-, β 2-, and α 2c-adrenergic receptors. Among them, Ser49Gly and Arg389Gly of β 1-adrenergic receptors, Arg16Gly, Gln27Glu, and Thr164Ile of β 2-adrenergic receptors, and Ins/Del322–325 of α 2c-adrenergic receptors are reported to have functional differences,⁶³ and these polymorphisms are noteworthy with regard to responsiveness to β -blocker therapy in chronic heart failure (CHF) including DCM.^{64,65} Although a few initial studies, in which relatively small numbers of cases and controls were examined, reported possible associations of DCM or CHF with adrenergic-receptor gene polymorphisms, subsequent studies could not replicate the association.^{64–66} Therefore, the contribution of the adrenergic-receptor genes to the susceptibility to DCM or CHF might not be large enough to be readily proven. However, several independent clinical studies have reported that carriers of β 1-adrenergic receptor alleles, Gly49 or Arg389, showed a better response to β -blocker therapy.⁶³ Although these β 1-adrenergic receptor alleles are in strong linkage disequilibrium,⁶⁰ both are considered to participate in the beneficial effect.

On the other hand, polymorphisms in genes expressed in cells other than cardiomyocytes can also be associated with susceptibility to the DCM or CHF phenotype. Because immune responsiveness against foreign antigens such as viral

proteins and against auto-antigens is controlled by genome diversity in the HLA genes, susceptibility to viral myocarditis, which often precedes DCM, and autoimmunity to sarcolemmal or sarcoplasmic proteins accompanied by DCM may be associated with specific HLA alleles. Although the molecular mechanisms and/or antigenic peptides remain unknown, it has been reported that specific HLA alleles or haplotypes such as the DRB1*1401-DQB1*0503 haplotype are significantly associated with DCM in Japanese.⁶⁷ As for the susceptibility to DCM accompanied by hepatitis C virus (HCV), HLA-linked susceptibility within the class III–I boundary region where the *NFKBIL1*, *ATP6V1G2*, *BAT1*, *MICB*, and *MICA* genes reside has been mapped.⁶⁸ It is unclear which of these genes is responsible for the susceptibility to HCV–DCM, but the data indicate that the association is not found with specific HLA alleles and that a non-HLA gene was involved in the pathogenesis. It is interesting to note that MIC molecules, MICA and MICB, are the ligands for an activating receptor of NK cells, NKG2D.⁶⁹ On the other hand, a significant association with HLA-DPB1*0401 and -DPB1*0901 was found for HCM accompanied by HCV,⁷⁰ indicating that the HLA-linked genetic background for susceptibility differs between HCV–DCM and HCV–HCM even though both are accompanied by the same virus. Autoimmunity against sarcolemmal or sarcoplasmic elements, such as β -adrenergic receptor or myosin heavy chain, respectively, may worsen the disease severity of DCM.^{71,72} It is suggested that the weak association of DCM with HLA-DR4 in Caucasian populations might reflect an association between the production of specific autoantibody and HLA-DR4.⁷³ However, such associations have not been proven yet, possibly due to the small number of DCM patients with autoantibodies to specific antigen (ie, autoimmunity was directed various different auto-antigens in each DCM patient) and a large cohort study will be required.

Concluding Remarks

In this review, I have focused on the contribution of genetic factors in the pathogenesis of DCM, but environmental factors, including viral infection and secondary autoimmune mechanisms, which ultimately lead to loss of cardiomyocytes, may also play a considerable role in the pathogenesis of DCM. The etiology of DCM is quite heterogeneous even in hereditary DCM (ie, disease-causing mutations and moreover disease genes themselves are different in individual patients). However, because the pathological pathways of hereditary DCM can be classified into several categories (Figure 4), such information is helpful in assessing the prognosis of patients and possibly in the evaluation of therapeutics.

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Authors' Comments on the Acquired-Side Author

In this issue of the Journal, Dr Yoshikawa nicely summarizes the acquired conditions involved in the pathogenesis of the DCM phenotype.⁷⁴ Viral infection and autoimmunity are emphasized. I fully agree with the concept that both viral infection and the immune response against it contribute to the pathogenesis of DCM in a certain proportion of patients, especially for non-familial or sporadic cases, although there might be a few familial cases because of shared genetic factors for the susceptibility and the increased chance of infection by the same virus. Indeed, we experienced a DCM patient who carried a DMD mutation and showed infiltration of immune-related cells in the heart tissue, suggesting that some disease-causing mutations may increase the susceptibility to infection by some viruses. As for autoimmunity, it might be an immune response against damaged cardiomyocytes. It is speculated that the damage was induced by acquired factors, but certain disease-causing mutations, such as DMD mutations, can render cardiomyocytes susceptible to death stimuli. The most important issue is how to differentiate hereditary DCM and acquired DCM and whether different therapies are required. I propose that the presence of a family history is a marker for hereditary DCM, whereas the presence of HLA class II molecules in the cardiac tissue is a potential marker for acquired DCM, although these markers may not clearly distinguish the 2 types. In addition, β -blocker therapy may be applicable irrespective of the etiology of DCM, although additional therapies such as calcium sensitizer and immune-absorption therapy may be required for each patient.