Cardiomyopathies are defined as cardiac diseases in which heart muscle disease and/or measurable deterioration of cardiac muscle function occurs due to various causes, such as genetic and sporadic mutations of muscle proteins, as well as external factors such as hypertension, ischemia, and inflammation. In 1995, the WHO/International Society and Federation of Cardiology (ISFC) classified primary cardiomyopathy caused by intrinsic factors into five groups according to the dominant pathophysiology: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restricted cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and unclassified cardiomyopathy. Among these cardiomyopathies, DCM is the most prevalent and the most common reason for cardiac transplantation in adults and children. Many recent findings indicate that genetic and sporadic mutations of a number of muscle proteins, such as myofibrillar, structural, and Ca$^{2+}$ regulating proteins, can cause DCM. In such cases, certain mutations often induce DCM with cardiac arrhythmia that is recognized as a potential trigger of sudden cardiac death. Thus, effective prognostic determination and appropriate cardiac care depend on accurate molecular and genetic diagnoses.

**Key words** cardiomyopathy; contractile protein; structural protein

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### 1. INTRODUCTION

Cardiomyopathy was originally defined as “heart muscle disease of unknown cause” and was distinguished from other heart disease caused by a specific etiology, such as ischemic heart disease. However, new approaches based on molecular biological techniques have been developed over the past two decades, which have brought new findings related to the etiology and pathogenesis of various cardiomyopathies, to the extent that defining the differences between cardiomyopathy and a specific heart disease has become difficult. Currently, cardiomyopathies are defined as cardiac diseases of the myocardium that are associated with cardiac dysfunction. These are cardiac diseases in which heart muscle disease and/or measurable deterioration in cardiac muscle function occurs due to genetic and sporadic mutations in muscle proteins, as well as external factors such as hypertension, ischemia, and inflammation. In 1995, the WHO/International Society and Federation of Cardiology (ISFC) classified primary cardiomyopathy caused by intrinsic factors into five groups according to the dominant pathophysiology: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restricted cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and unclassified cardiomyopathy. Numerous research findings have elucidated the disease-causal genetic and sporadic mutations of cardiac proteins, such as myofibrillar, structural, and signal proteins, for each type of cardiomyopathy. The clinical aspects of the cardiac disease in these cardiomyopathies, such as the symptoms, disease severity, and onset timing, are quite heterogeneous despite the identical nature of the muscle protein mutation, but different locations of a mutation in a muscle protein such as β-myosin heavy chain, or myosin binding protein C, can cause different types of cardiomyopathy, such as DCM or HCM.

Among the cardiomyopathies, DCM is clinically characterized by cardiac chamber dilatation and reduced systolic function that commonly results in congestive heart failure (CHF). DCM is the commonest form of cardiomyopathy and is most often the reason for cardiac transplantation in adults and children. It is known that coronary artery disease, inflammatory heart disease, myocardial toxins, and genetic defects can cause DCM in adult patients. In contrast, the most common causes of DCM in children are myocarditis and neuromuscular diseases such as Duchenne or Becker muscular dystrophy, both of which are caused by mutations in the structural protein dystrophin, and Emery–Dreifuss muscular dystrophy, caused by mutations in the nuclear membrane proteins, lamin A, and lamin C (Lamin A/C). In child DCM patients, the cardiac disease characteristics are much more diverse than those in adults, and incidence largely depends on age, race, and gender. Approximately 30 to 35% of young patients are reported to have a genetic form of DCM. Many DCM-causal genetic and sporadic mutations of cardiac proteins have been identified, some of which are discussed below.

### 2. SARCOMERE PROTEINS AS A CAUSE OF DCM

Sarcomere proteins include heavy and light chain myosin and myosin binding proteins, cardiac actin, α-tropomysosin, troponin complexes, and others. Mutations in relevant genes can cause both HCM and DCM. It is estimated that myofibrillar protein mutations account for roughly 10% of familial DCM cases but a recent finding suggests that 25% of idiopathic DCM cases are due to sarcomeric gene mutations. Common sarcomere gene mutations identified
in DCM as a cause of familial and sporadic disease include \(\beta\)-myosin heavy chain (MYH7, 160760) missense mutations such as I201T, T412N, and A550V in the head region, or T1019N, R1193S, E1426K, and R1634S in the tail domains.\(^{17}\) Other disease-causal gene mutations include Troponin T (TNNT2, 191045) missense or deletion mutations such as R131W, R205L, D270N, and delta K210; Troponin C (TNNCI, 191040) missense mutations such as G159D\(^{17-19}\), Troponin I (TNNI3, 191044) missense mutations such as A2V, K36Q, and N185K\(^{20,21}\); \(\alpha\)-tropomyosin (TPM1, 191010) missense mutations such as E54K and E40K\(^{22-24}\), and cardiac actin (ACTC, 102540) missense mutations such as R312H and E361G.\(^{25}\)

Concerning mutations, the MYH7 gene is the most frequently mutated in the familial DCM population (approxi-
mately 10% of cases), although disease onset is delayed, with incomplete disease penetrance, compared with that for mutations of TNNT2 and TNNCI genes.\(^{17}\) It is known that mutant troponin T or troponin C can impair protein–protein interaction among the troponin complex, compared with wild-type controls, indicating that regulation of myocardial contractility has been altered.\(^{17,19}\) Since the generation of contractile forces by sarcomeric proteins, and force transmission to the extracellular matrix, are fundamental heart cell functions, inadequate performance of either function may result in ventricular cavity dilatation that leads to subsequent heart failure.\(^{17,26,28}\)

Although it is known that disease-causal gene alterations in sarcomeric proteins show definite overlaps between HCM and DCM, the underlying mechanisms responsible for these differences are not yet understood. In some cases, a possible explanation is that an HCM-causal gene mutation in TNNT2 enhances \(Ca^{2+}\) sensitivity of the myofibril, while a DCM-causal gene mutation reduces it.\(^{27,28}\) However, recent clinical reports have shown that genes affected by mutations, such as MYH7, may determine the magnitude of structural and functional alterations in both HCM and DCM, and that other factors, such as environmental factors that stimulate the expression of HCM phenotypes, can lead to DCM phenotypes where both right and left ventricles are affected, leading to heart failure.\(^{29,30}\) Thus, in some cases, DCM may occur secondarily to a pro-
gressed and end-stage HCM.\(^{29,30}\) Left ventricular noncom-
paction cardiomyopathy that is caused by a MYH7 missense mutation such as A1766T\(^{10}\) is another disease that should be recognized as characteristic in DCM patients.\(^{32,33}\) This dis-
ease is a myocardial disorder thought to occur as a result of arrested embryogenesis and is characterized by a spongy mor-
phological appearance of the myocardium.\(^{32,33}\) It is estimated that sarcomere gene mutations account for as much as 17% of left ventricular non-compaction (LVNC) cases, and may be present in DCM with hypertrabeculation.\(^{31,33}\)

3. STRUCTURAL PROTEINS AS A CAUSE OF DCM

In addition to gene mutations that affect sarcomeric pro-
teins, gene mutations of structural proteins such as the in-
termediate filament proteins and the dystrophin-associated glycoprotein complex are known as a cause of DCM. Inter-
mediate filaments are important components of the cytoskeletal system that stabilize organelles by linking the Z-disc to the sarcolemma. Desmin (des, 125660) is a component of type III intermediate filaments, and missense mutation I451M can cause DCM.\(^{34}\) In addition, many missense and deletion mutations have been shown to cause myofibrillar myopathy (MFM, also called desmin-related myopathy).\(^{35,36}\) The MFM caused by desmin gene mutations, such as a putative 7-amino acid deletion (R173 through E179; D7-des) and missense mutations (A337P, A360P/N393I, L345P, N342D, and R406W), are heterogeneous myopathies characterized by abnormal intrasar-
coplasmic desmin accumulation.\(^{35,36}\)

Cypher/Z-band alternatively spliced PDZ-motif-containing protein (ZASP) (LDB3, 605906) is another Z-disc component in skeletal and cardiac muscle in which mutations (D117N, K136M, S196L, T213I, I352M, and D626N) play a causative role in DCM and DCM with LVNC.\(^{37}\) It is known that the PDZ domain of the ZASP protein can interact with the carboxy-terminus of \(\alpha\)-actinin-2.\(^{37}\) Thus, the ZASP can act as a linker-strut in muscle, which is critical to sarcomere stability and the transmission of force to the extracellular matrix.\(^{26,37}\) Similar to how disease can be caused by desmin gene mutations, ZASP mutations can cause MFM (also called ZASP-
related myopathy) that is characterized by abnormal accumu-
lution of multiple proteins.\(^{38}\)

Cysteine- and glycine-rich protein 3 (also called muscle LIM protein) (CSRP3, 608824) is another Z-disc protein that plays a role in mechanical stretch sensing.\(^{39,40}\) However, missense mutation of this gene, such as W4R, contributes to less than 1% of familial DCM.\(^{39,42}\) Titin (TTN, 188840) is a large protein found in cardiac and skeletal muscles that spans half of the sarcomere, from the Z-line to the M-line.\(^{43}\) Titin plays a key role in muscle assembly, force transmission at the Z-line, and maintenance of resting tension in the I-band region.\(^{44}\) Titin’s amino-terminus is anchored to the Z-disc and the carboxy-terminus is bound to the myosin thick filament.\(^{45}\) Idiopathic familial DCM-causal missense mutations such as Val54Met, Ala743Val, W930R, and S4465N in the TTN gene, and a 2-bp insertion mutation (43628AT) in exon 326 of the TTN gene that causes a frame shift that truncates A-band titin, and nonsense mutations such as gln4053-to-ter (Q4053X), have been identified.\(^{44,46}\) These mutations can decrease the binding affinities of titin to Z-line proteins T-cap/telethonin and \(\alpha\)-actinin, which are important to the integration of tro-
phic and elastic functions of the heart.\(^{44}\)

Concerning sarcomere stability and force transmission to the extracellular matrix, the importance of protein inter-
actions among dystrophin (DM1, 300377), actin (ACTC1, 102540), and the dystrophin-associated glycoprotein complex composed of \(\alpha\)- and \(\beta\)-dystroglycans (DAG1, 128239), \(\gamma\)- and \(\delta\)-sarcoglycans (SGCG, 608896, and SGCD, 601411), caveo-
lin-3 (CAV3, 601253), and dystrobedrin (DTNA, 601239) is well recognized.\(^{47,48}\) Muscular dystrophy with associated DCM and heart failure is caused by many kinds of dystrophin mutation, such as deletion of the first muscle exon and the muscle-promo-
ter region of the DMD gene, a splice donor site mutation in the first exon, or mutations in intron regions of the DMD gene that inactivate the universally conserved 5-prime splice site consensus sequence of the first intron.\(^{49,50}\) Mutation of a dystrophin-associated protein, such as an S151A substitution in the SGCD gene, can also cause familial and sporadic dil-
ated cardiomyopathy.\(^{51}\)

Fukutin (FKTN, 607440) is essential for the protein com-
plex between dystrophin and dystroglycan, to preserve gly-
cosyltransferase activity, and fukutin-related protein (FKRP, 606596) can regulate the post-translational modification of
dystroglycan. Missense mutations such as Q358P and R179T mutations in the FKTN gene, as well as insertion of a 3,062-bp transposon situated in the 3-prime untranslated region of the FKTN gene, can cause a less diagnosed form of idiopathic dilated cardiomyopathy and congestive heart failure. Mutations in the FKRP gene cause a phenotypic spectrum arising from limb-girdle muscular dystrophy with DCM.

4. NUCLEAR ENVELOPE PROTEINS AS A CAUSE OF DCM

Nuclear laminas are intermediate filament proteins that polymerize to form the nuclear lamina on the inner aspect of the inner nuclear membrane. It is believed that laminas are essential for maintaining nuclear structure and for disassembly/reassembly during mitosis. Numerous kinds of LMNA mutations encoding lamin A/C cause a broad range of diseases, which may be termed laminopathies. While lamins are expressed in all mammalian somatic cells, mutations in their genes lead to relatively tissue-selective disease phenotypes such as DCM, Emery–Dreifuss muscular dystrophy, Hutchinson–Gilford progeria syndrome, lipodystrophy, and, in most cases, Charcot–Marie–Tooth disease type 2. LMNA mutations account for 5–8% of familial DCM cases. In patients with LMNA mutations, severe defects of the conduction system that are associated with sudden cardiac death (SCD) are often observed. The estimated penetrance of cardiac-related phenotypes in patients with LMNA mutations is 7% under age 20, 66% between ages 20 to 39, 86% between ages 40 to 59, and 100% after age 60.

5. CALCIUM REGULATING PROTEINS AS A CAUSE OF DCM

Calcium regulating proteins and disturbed ion channel function have been identified as causative of DCM. Phospholamban (PLN, 172405) is known as a regulator of calcium uptake into the sarcoplasmic reticulum (SR) via inhibition of SR Ca2+-ATPase (SERCA2) in cardiomyocytes. The PLN R9C mutation and arginine 14 deletion mutation (R14del) in PLN lead to disease through cardiomyocyte calcium dysregulation. It is thought that PLN R9C protein can trap protein kinase A, which blocks PKA-mediated phosphorylation of wild-type PLN, and PLN R14Del protein can inhibit SR ATPase, despite phosphorylation by protein kinase A. Thus, chronic calcium dysregulation can result in Nemours mutations of the cardiac sodium channel gene (SCN5A, 600163), identified as causative of Long QT syndrome type 3 and Brugada syndrome. In addition to these diseases, mutations of SCN5A such as T220I, R814W, D1275N, and D1595H, and SCN5A truncation (2550-2551insTG) mutations have been found to be causative of DCM. Thus, SCN5A defects are associated with susceptibility to DCM with associated conduction system disease.

6. SUMMARY

DCM is a disease of the myocardium, and is the most common reason for cardiac transplantation in adults and children. As mentioned above, many recent findings indicate that the genetic and sporadic mutations of many muscle proteins, such as sarcomeric, structural, nuclear envelope, and calcium regulating proteins, can cause DCM (Table 1). Since DCM often induces cardiac arrhythmia that is recognized as a potential trigger of sudden cardiac death, accurate molecular genetic diagnosis is critical for achieving effective prognostic determination and appropriate cardiac care.

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REFERENCES


Table 1. Summary of Causal Genes of Dilated Cardiomyopathy (DCM)

<table>
<thead>
<tr>
<th>Protein names (gene names) are shown.</th>
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<tbody>
<tr>
<td>Sarcomere proteins</td>
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<tr>
<td>β-Myosin heavy chain (MYH7)</td>
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<tr>
<td>Troponin T (TNNT2)</td>
</tr>
<tr>
<td>Troponin C (TNNC1)</td>
</tr>
<tr>
<td>α-Tropomyosin (TPM1)</td>
</tr>
<tr>
<td>Cardiac actin (ACTC)</td>
</tr>
<tr>
<td>Structural proteins</td>
</tr>
<tr>
<td>Desmin (des)</td>
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<tr>
<td>Cypher/Z-band alternatively spliced PDZ-motif containing protein (ZASP) (LDB3)</td>
</tr>
<tr>
<td>Cystein- and glycin-rich protein 3 (also called muscle LIM protein) (CSRP3)</td>
</tr>
<tr>
<td>Nuclear envelope proteins</td>
</tr>
<tr>
<td>Lamin A/C (LMNA)</td>
</tr>
<tr>
<td>Calcium signaling proteins</td>
</tr>
<tr>
<td>Phospholamban (PLN)</td>
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<tr>
<td>Cardiac sodium channel (SCN5A)</td>
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