EDITORIAL

Cardiomyopathy with *LMNA* Mutation
From Genotype to Phenotype

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Dilated cardiomyopathy (DCM) is characterized by enlargement of the heart chambers and a reduction of systolic function, resulting in heart failure and fatal arrhythmia. The clinical course of DCM is heterogeneous; disease onset, severity, prognosis, and more importantly, response to therapies including cardiac resynchronization therapy (CRT) and oral β-blockers vary dramatically among patients. Non-responders to these therapies need left ventricular assist device (LVAD) implantation or heart transplantation. Therefore, establishing a more precise risk stratification and understanding the disease mechanism are urgent matters. Genetic mutation accounts for approximately 40% of the causes of DCM.[1] More than 50 genes have been identified as responsible genes for DCM.[2] Genetic testing using a multigene panel now plays a pivotal role in elucidating the genetic basis and genotype-phenotype associations in DCM.[3]

Secondary to *TTN*,[4] *LMNA* is one of the most common DCM-causing genes.[5] *LMNA* encodes intermediate filament proteins lamin A and C, which polymerize to form a scaffold called the nuclear lamina (NL) at the nuclear periphery. The NL, a major component of the inner layer of the nuclear envelope, not only provides the structural integrity to the nucleus, but also acts as a mechanotransducer by linking to actin and the extracellular matrix.[6] Furthermore, NL associates with chromatin to maintain its higher-order organization and contributes to the regulation of gene expression.[6] Patients with an *LMNA* mutation show dysfunction in specific tissues including the heart. These syndromes are collectively called laminopathies, which are characterized by premature aging and a vulnerability against mechanical stress.[7]

LMNA-related cardiomyopathy explains 5-10% of familial DCM and 2-5% of sporadic DCM.[8,9] More than 160 different mutations in the *LMNA* gene have been identified as a cause of cardiomyopathy.[10] The clinical course of DCM is considered to be worse among patients harboring *LMNA* mutations than among those without *LMNA* mutations.[11] Several groups reported that sudden cardiac death, atrioventricular block, or fatal ventricular tachycardia can be frequently observed in *LMNA*-related cardiomyopathy even though the left ventricular systolic function is preserved.[12,13] Therefore, ESC guideline recommend that DCM patients with an *LMNA* mutation should (class IIa) undergo ICD therapy irrespective of their left ventricular ejection fraction (LVEF).[14] Our group also analyzed 120 Japanese patients with DCM and found that DCM patients with an *LMNA* mutation had worse prognosis and barely achieved left ventricular reverse remodeling even after optimal medical therapy.[3]

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Among *LMNA*-related DCM, investigations of specific genotype-phenotype associations are quite limited. Pasotti, *et al.* reported that *LMNA* splice-site mutations were an independent risk factor for sudden death.[15] Nishiuchi, *et al* found that patients with *LMNA* truncating mutations were associated with a severe conduction disturbance and lower LVEF than those with *LMNA* missense mutations.[16] Kawakami, *et al.* performed target resequencing of the familial DCM cohort using a customized gene panel, and identified a novel frame shift mutation of *LMNA* (c.774delG) as a culprit for DCM with conduction disturbance.[17] They also found that male patients with the mutation showed more severe disease phenotypes than female patients. Arimura, *et al.* demonstrated that the androgen receptors accumulated in the cardiomyocyte nuclei and androgen receptor agonists deteriorated cardiac function in homozygous H222P-*Lmna* mutant mice.[18] Clearly, the relationship between androgen receptors and nuclear lamina for gene regulation should be investigated. In order to achieve more precise prediction of the clinical course of *LMNA*-related cardiomyopathy, considerably more cases should be accumulated from multiple cohorts (Figure).

To appropriately interpret the sequencing results, a deeper understanding of the disease mechanisms is indispensable. Knock-in animal models would help to examine the physiological and pathogenic roles of each domain or amino acid of lamin A protein.[19] Furthermore, induced pluripotent stem cell (iPSC) lines from DCM patients harboring an *LMNA* mutation might be a powerful tool for analyzing how each genomic mutation leads to cellular

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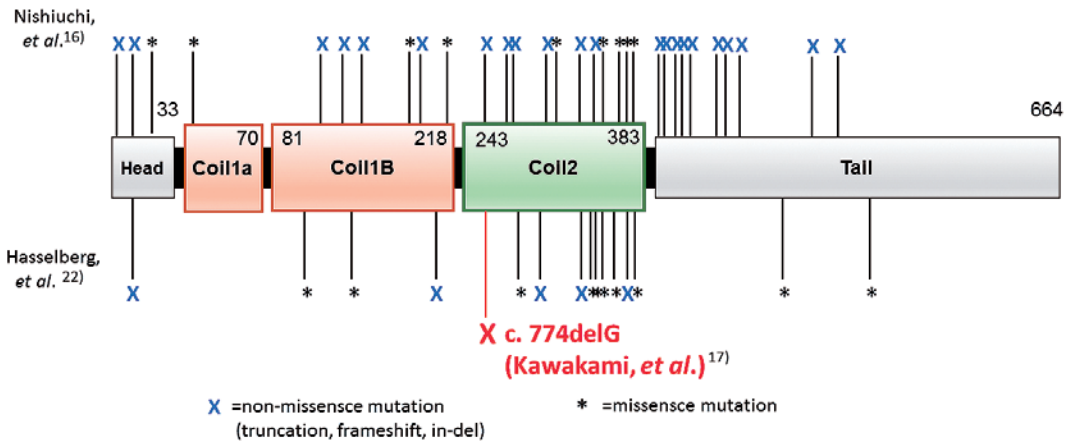

Figure. Structure of lamin A/C protein and the sites of *LMNA* mutations culprit for dilated cardiomyopathy from 2 major recent cohorts. Lamin A protein consisted of the globular head (Head), α-helical rod domain (Col1a, 1b and 2), and C-terminal globular domain (Tail). The mutations identified in patients with DCM from 2 major recent cohorts are indicated according to their position and the type of mutation. Upper row; mutations reported by Nishiuchi, *et al* .[16] Lower row; mutations reported by Hasselberg, *et al* .[22] The mutation identified by Kawakami, *et al*[17] is highlighted in red. * indicates missense mutation; and X, non-missense mutation (truncation, frame shift, in-del).

dysfunction.[20,21] Elucidating the underlying molecular mechanisms would accelerate the development of precision medicine for *LMNA*-related cardiomyopathy.

Disclosures

Conflicts of interest: None.

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