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. More than 50 genes have been identified as responsible genes for DCM. Genetic testing using a multigene panel, and genotype-phenotype associations in DCM. Patients with an LMNA gene have been identified as a cause of cardiomyopathy. The clinical course of DCM is considered to be worse among patients harboring LMNA mutations than among those without LMNA mutations. 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. Therefore, ESC guideline recommend that DCM patients with an LMNA mutation should undergo ICD therapy irrespective of their left ventricular ejection fraction (LVEF). 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.

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. Nishihuchi, 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. 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. 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. 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. 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...
Conflicts of interest: None.

References


Disclosures

Conflicts of interest: None.