EDITORIAL

Titin Truncation Variant in Dilated Cardiomyopathy
Still on the Way Toward Clinical Application

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(Int Heart J 2021; 62: 221-223)

Titin (TTN) is the largest protein in humans, with a molecular weight of approximately 3,800 kDa, spanning half the length of the sarcomere from the Z disk to the M line in skeletal and cardiac muscle (Figure A). In the heart, TTN filament is involved in the contraction and relaxation of cardiomyocytes as a molecular spring, the formation of the proper arrangement of sarcomeres, and the control of mechanical force transduction.1 The structure and function of TTN have suggested a linkage between the TTN gene mutation and the occurrence of cardiomyopathy, due to the extreme size of TTN gene consisting of 364 exons, which the recent advancements of gene sequencing technology using next-generation sequencers have at last enabled us to accurately evaluate.

The epoch-making study by Herman in 20122 reported that truncation variants of TTN (TTNtv) were found in 27% of patients with dilated cardiomyopathy (DCM), but 3% even in the general population without cardiac disease. Since this report, TTNtv has been known as the most major genetic variant causing DCM. However, the fact that TTNtv is also detected in seemingly non-affected individuals has made it difficult to define the causal relationship between this genetic variant and the disease.

As for TTN, basically, there are several types of alternatively-spliced transcripts: the N2BA isoform, which is a long and fetal isoform, the N2B isoform, in which much of the exons in the I-band region have been spliced-out, and the Novex3 isoform containing only the N-terminal-sided regions (Figure B). Whether an individual TTNtv causes DCM or not could depend on the frequency with which the corresponding exon is involved in finally-spliced transcripts (percent spliced-in; PSI) in the heart.3,4 The genetic regions with a higher PSI are thought to be important information-giving results, but it would be more convincing if the authors could show functional abnormalities using human cells. One promising approach is modeling with patient-derived iPS cells: in 2015, Gramlich, et al5 first generated iPS cells from patients bearing TTNtv, which were differentiated into cardiomyocytes. The analytical results using iPS cell-derived cardiomyocytes showed abnormal sarcomere organization and reduced ACTC1 expression. Another analysis by Hinson, et
al.9) similarly revealed abnormalities in sarcomere structure and gene expression using TTNtv iPS cell-derived cardiomyocytes. Although there are some issues to be solved such as the preparation of appropriate controls created by genome editing and the immature nature of the cells, the development of methods for functional verification using human iPS cell-derived cardiomyocytes will help us to understand the results of the genetic testing accurately.

So far, there are several reports that DCM patients with TTNtv are likely to be responsive to medical treatment, showing left ventricular reverse remodeling.10,11) Nevertheless, the present case5) did not respond to drug therapy, which may be due to the coexistence of other genetic and environmental predispositions to modify the TTNtv-induced clinical manifestations. Experimental study with genome editing to elucidate the functional consequences will enable us to distinguish the modifying effect of the genetic abnormality from that of the environmental risk factors and predict the responsiveness to therapeutic intervention.

As shown in this report,5) by linking genetic mutations with clinical manifestations and molecular consequences, genomic medicine will contribute to the realization of precision medicine, predicting clinical prognosis and optimizing therapeutic intervention.

**Disclosure**

Conflicts of interest: None.

**References**

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