A-Band Titin Truncation in Zebrafish Causes Dilated Cardiomyopathy and Hemodynamic Stress Intolerance.

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Abstract

Background Truncating variants in the TTN gene (TTNtv) are common in patients with dilated cardiomyopathy (DCM) but also occur in the general population. Whether TTNtv are sufficient to cause DCM or require a second hit for DCM manifestation is an important clinical issue. Methods We generated a zebrafish model of an A-band TTNtv identified in 2 human DCM families in which early-onset disease appeared to be precipitated by ventricular volume overload. Cardiac phenotypes were serially assessed from 0 to 12 months using video microscopy, high-frequency echocardiography, and histopathologic analysis. The effects of sustained hemodynamic stress resulting from an anemia-induced hyperdynamic state were also evaluated. Results Homozygous ttna mutants had severe cardiac dysmorphogenesis and premature death, whereas heterozygous mutants (ttna+/−) survived into adulthood and spontaneously developed DCM. Six-month-old ttna+/− fish had reduced baseline ventricular systolic function and failed to mount a hypercontractile response when challenged by hemodynamic stress. Pulsed wave and tissue Doppler analysis also revealed unsuspected ventricular diastolic dysfunction in ttna+/− fish with prolonged isovolumic relaxation and increased diastolic passive stiffness in the absence of myocardial fibrosis. These defects reduced diastolic reserve under stress conditions and resulted in disproportionately greater atrial dilation than observed in wild-type fish. Conclusions Heterozygosity for A-band titin truncation is sufficient to cause DCM in adult zebrafish. Abnormalities of systolic and diastolic reserve in titin-truncated fish reduce stress tolerance and may contribute to a substrate for atrial arrhythmogenesis. These data suggest that hemodynamic stress may be an important modifiable risk factor in human TTNtv-related DCM.

KEYWORDS: cardiomyopathies; echocardiography; genetics; hemodynamic; titin; zebrafish