Mutation in lamin A/C sensitizes the myocardium to exercise-induced mechanical stress but has no effect on skeletal muscles in mouse.


Abstract

LMNA gene encodes lamin A/C, ubiquitous proteins of the nuclear envelope. They play crucial role in maintaining nuclear shape and stiffness. When mutated, they essentially lead to dilated cardiomyopathy with conduction defects, associated or not with muscular diseases. Excessive mechanical stress sensitivity has been involved in the pathophysiology. We have previously reported the phenotype of Lmna(delK32) mice, reproducing a mutation found in LMNA-related congenital muscular dystrophy patients. Heterozygous Lmna(delK32/+) (Het) mice develop a progressive dilated cardiomyopathy leading to death between 35 and 70 weeks of age. To investigate the sensitivity of the skeletal muscles and myocardium to chronic exercise-induced stress, Het and wild-type (Wt) mice were subjected to strenuous running treadmill exercise for 5 weeks. Before exercise, the cardiac function of Het mice was similar to Wt-littermates. After the exercise-period, Het mice showed cardiac dysfunction and dilation without visible changes in cardiac morphology, molecular remodelling or nuclear structure compared to Wt exercised and Het sedentary mice. Contrary to myocardium, skeletal muscle ex vivo contractile function remained unaffected in Het exercised mice. In conclusion, the expression of the Lmna(delK32) mutation increased the susceptibility of the myocardium to cardiac stress and led to an earlier onset of the cardiac phenotype in Het mice.

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KEYWORDS: A-type lamin; Chronic exercise; Dilated cardiomyopathy; L-CMD; Mechanical stress

PMID: 27287550 DOI: 10.1016/j.nmd.2016.05.010

[PubMed - in process]