Progressive Dystrophic Pathology in Diaphragm and Impairment of Cardiac Function in FKRP P448L Mutant Mice.

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Abstract

Mutations in the gene for fukutin-related protein represent a subset of muscular dystrophies known as dystroglycanopathies characterized by loss of functionally-glycosylated-alpha-dystroglycan and a wide range of dystrophic phenotypes. Mice generated by our lab containing the P448L mutation in the fukutin-related protein gene demonstrate the dystrophic phenotype similar to that of LGMD2I. Here we examined the morphology of the heart and diaphragm, focusing on pathology of diaphragm and cardiac function of the mutant mice for up to 12 months. Both diaphragm and heart lack clear expression of functionally-glycosylated-alpha-dystroglycan throughout the observed period. The diaphragm undergoes progressive deterioration in histology with increasing amount of centranucleation and inflammation. Large areas of mononuclear cell infiltration and fibrosis of up to 60% of tissue area were detected as early as 6 months of age. Despite a less severe morphology with only patches of mononuclear cell infiltration and fibrosis of ~5% by 12 months of age in the heart, cardiac function is clearly affected. High frequency ultrasound reveals a smaller heart size up to 10 months of age. There are significant increases in myocardial thickness and decrease in cardiac output through 12 months. Dysfunction in the heart represents a key marker for evaluating experimental therapies aimed at cardiac muscle.

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