A New Mouse Model of Limb-Girdle Muscular Dystrophy Type 2I Homozygous for the Common L276I Mutation Mimicking the Mild Phenotype in Humans.

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Abstract

Limbgirdle muscular dystrophy type 2I (LGMD2I) is caused by mutations in the Fukutin-related protein (FKRP) gene, leading to inadequate glycosylation of α-dystroglycan, an important protein linking the extracellular matrix to the cytoskeleton. We created a mouse model of the common FKRP L276I mutation and a hemizygous FKRP L276I knockout model. We studied histopathology and protein expression in the models at different ages and found that homozygous FKRP L276I mice developed a mild progressive myopathy with increased muscle regeneration and fibrosis starting from 1 year of age. This was likely caused by progressive loss of α-dystroglycan-specific glycosylation, which was decreased by 78% at 20 months. The homozygous FKRP knockout was embryonic lethal, but the hemizygous L276I model resembled the homozygous FKRP L276I model at comparable ages. These models emphasize the importance of FKRP in maintaining proper glycosylation of α-dystroglycan. The mild progression in the homozygous FKRP L276I model resembles that in patients with LGMD2I who are homozygous for the L276I mutation. This animal model could, therefore, be relevant for understanding the pathophysiology of and developing a treatment strategy for the human disorder.

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