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B4GALNT2 (GALGT2) Gene Therapy Reduces Skeletal Muscle Pathology in the FKRP P448L Mouse Model of Limb Girdle Muscular Dystrophy 2I.

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Abstract

Overexpression of B4GALNT2 (previously GALGT2) inhibits the development of muscle pathology in mouse models of Duchenne muscular dystrophy, congenital muscular dystrophy 1A, and limb girdle muscular dystrophy 2D. In these models, muscle GALGT2 overexpression induces the glycosylation of α dystroglycan with the cytotoxic T cell glycan and increases the overexpression of dystrophin and laminin α2 surrogates known to inhibit disease. Here, we show that GALGT2 gene therapy significantly reduces muscle pathology in FKRP P448Lneo(-) mice, a model for limb girdle muscular dystrophy 2I. rAAVrh74.MCK.GALGT2-treated FKRP P448Lneo(-) muscles showed reduced levels of centrally nucleated myofibers, reduced variance, increased size of myofiber diameters, reduced myofiber immunoglobulin G uptake, and reduced muscle wasting at 3 and 6 months after treatment. GALGT2 overexpression in FKRP P448Lneo(-) muscles did not cause substantial glycosylation of α dystroglycan with the cytotoxic T cell glycan or increased expression of dystrophin and laminin α2 surrogates in mature skeletal myofibers, but it increased the number of embryonic myosin-positive regenerating myofibers. These data demonstrate that GALGT2 overexpression can reduce the extent of muscle pathology in FKRP mutant muscles, but that it may do so via a mechanism that differs from its ability to induce surrogate gene expression.

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