
Phenotypic Spectrum of α-Dystroglycanopathies Associated With the c.919T>a Variant in the FKRP Gene in Humans and Mice

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Abstract

Mutations in the fukutin-related protein gene, FKRP, are the most frequent single cause of α-dystroglycanopathy. Rare FKRP mutations are clinically not well characterized. Here, we review the phenotype associated with the rare c.919T>A mutation in FKRP in humans and mice. We describe clinical and paraclinical findings in 6 patients, 2 homozygous, and 4-compound heterozygous for c.919T>A, and compare findings with a mouse model we generated, which is homozygous for the same mutation. In patients, the mutation at the homozygous state is associated with a severe congenital muscular dystrophy phenotype invariably characterized by severe multisystem disease and early death. Compound heterozygous patients have a severe limb-girdle muscular dystrophy phenotype, loss of ambulation before age 20 and respiratory insufficiency. In contrast, mice homozygous for the same mutation show no symptoms or signs of muscle disease. Evidence therefore defines the FKRP c.919T>A as a very severe mutation in humans. The huge discrepancy between phenotypes in humans and mice suggests that differences in protein folding/processing exist between human and mouse Fkrp. This emphasizes the need for more detailed structural analyses of FKRP and shows the challenges of developing appropriate animal models of dystroglycanopathies that mimic the disease course in humans.

Keywords: Congenital muscular dystrophy; Limb girdle muscular dystrophy; c.919T>A variant in the FKRP gene.

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