Med Sci (Paris). 2020 Dec;36 Hors série n° 2:28-33. doi: 10.1051/medsci/2020239.
Epub 2021 Jan 11.

[Limb-Girdle Muscular Dystrophy type R9 linked to the FKRP gene: state of the art and therapeutic perspectives]

[Article in French]

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PMID: 33427633 DOI: 10.1051/medsci/2020239

Abstract in English, French

Mutations in the FKRP gene encoding the fukutin-related protein (FKRP) cause a wide spectrum of myopathies, ranging from severe forms of congenital muscular dystrophies associated with structural abnormalities of the central nervous system, to exertional myalgia or asymptomatic hyperCKemia, and to a form of limb girdle muscular dystrophy, LGMD-R9, (ex-LGMD-2I). LGMD-R9 is characterized by a proximal girdle deficit predominantly in the lower limbs to start with, with respiratory and cardiac damage that may affect the vital prognosis. Serum CK levels are markedly elevated and, on muscle biopsy, is detected a dystrophic formula associated with a reduction in the glycosylation of α-dystroglycan by immunostains and immunoblotting. Muscle MRI typically shows damage to proximal muscles (iliopsoas, adductors, gluteus maximus, quadriceps) with relative preservation of the muscles of the anterior compartment of the thighs (gracilis and sartorius). Genetic analysis, by specific sequencing of the FKRP gene or of a panel grouping together all the genes involved in the glycosylation of α-dystroglycan, or a larger panel of genes, generally confirms the diagnosis, the most frequent mutation being the missense p.(Leu276Ile). Currently, treatment of LGMD-R9 is symptomatic, requiring a multidisciplinary approach. A prospective study of the natural history of the disease is currently underway in Europe (GNT-015-FKRP). New therapeutic approaches are envisaged, such as gene therapy mediated by vectors derived from the adeno-associated virus (AAV). This is effective in animal models, allowing correction of defects in the glycosylation of alpha-dystroglycan and an increase in its binding capacity to the extracellular matrix. At the same time, preclinical studies have shown, in an animal model, the efficacy of ribitol, an alcohol pentose found in natural compounds, which has led to a phase I trial whose clinical development is underway.