aberrant O-glycosylation of the membrane/extracellular matrix (ECM) protein α-dystroglycan. However, further knowledge on the FKRP structure and biological function is lacking, and its intracellular localization is controversial. Based on immunogold electron microscopy of human skeletal muscle sections we demonstrate that FKRP co-localises with the medial-to-trans-Golgi marker MG160, between the myofibrils in human rectus femoris muscle fibres. Pairwise yeast 2-hybrid experiments supported by co-immune precipitation, demonstrate that FKRP exists as homodimers when expressed in cell culture. The FKRP homodimer is kept together by a disulphide bridge provided by the most N-terminal cysteine, Cys6. FKRP contains two N-glycans of high mannose and/or hybrid oligosaccharides; however, FKRP N-glycosylation is not required for FKRP homodimer. We propose a model for FKRP which is consistent with that of a Golgi resident type II transmembrane protein.

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P2.18
Heterozygous mutations in putative glycosyltransferase modulating the severity of the phenotype of muscular dystrophies
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Dystroglycanopathies are genetic muscular dystrophies caused by defects in the glycosylation of α-dystroglycan, an important component of the dystrophin–glycoprotein complex. Among them, LGMD2I and CMD1C are both caused by mutations in the FKRP gene, while CMD1D is caused by mutations in the large gene. The large mouse is an animal model for dystroglycanopathies and shows a severe phenotype, while the mdx mouse is a model for Duchenne muscular dystrophy (DMD) but with a mild phenotype. For diagnosis purpose, we screened for mutation the coding region of the FKRP gene. 105 patients (91 families) with a broad spectrum of clinical severity, but clinically and histologically classified as CMD. We identified only 6 patients with mutations in both alleles of FKRP, compatible with the diagnosis of LGMD2I/CMD1C. Surprisingly, however, 9 other patients (10%) were heterozygous for one pathogenic mutation in this gene. To test whether 50% of alteration in the function of a glycosyltransferase could acts modulating the phenotype in other forms of MD, we created and studied functionally the mdx mouse, heterozygote for the large mutation. We observed that among the 15 tested animals, at the ages of 21, 30, 60, 90, 120, 150 and 180 days, a more severe weakness than the parental mdx strain was observed, which was statistically significant up to the age of 60 days. Most forms of MD show a wide inter and intra familial clinical variation, but the physiopathological mechanism is not understood. Our results showed that a reduction in the glycosylation activity can worsen the clinical course of the mdx mouse, and possibly of other forms of human MDs, acting as a modifying gene of the phenotype. These results are also compatible with recent studies involving the super expression of glycosyltransferase leading to clinical improvements in different mouse models for MD. FAPESP-CEPID, CNPq-INCT, FINEP, ABDIM.

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P2.19
Norwegian patients with Limb Girdle Muscular Dystrophy 2I structural changes and immunohistochemistry related to clinical findings and genotype–phenotype
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Mutations in the FKRP (Fukutin Related Protein) gene produce a range of phenotypes including Limb Girdle Muscular Dystrophy Type 2I (LGMD2I). In order to investigate prevalence, mutation spectrum and genotype – phenotype correlation, we studied a cohort of Norwegian patients with LGMD2I ascertained in a 4-year period. A total of 88 Norwegian LGMD patients with FKRP mutation were identified giving a minimum prevalence of 1/54,000 and corresponding carrier frequency of 1/116 in the Norwegian population. Seven different FKRP mutations, including 3 novel changes, were detected in these 88 patients who came from 69 families. Seventy-six patients were homozygous for the common c.326C>T mutation. Patients homozygous for the c.826C>T mutation showed a later disease onset than patients compound heterozygous for this mutation – 14.0 vs. 6.1 years. While we detected substantial variability in disease severity among homozygous patients, these patients appeared to retain ambulation longer than compound heterozygous patients. The muscle biopsies all showed varying degree of structural and immunohistochemical changes. The changes were graded in a quantitative scoring system and correlated to clinical findings and mutations of FKRP. Significantly higher structural score, particularly inflammatory changes in biopsies corresponding to the group of compound heterozygous mutations. Good correlation between endomyal fibrosis and severity of disease. No significant correlation between α-dystroglycan expression and severity of disease in the homozygous group.

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P2.20
Fukuyama congenital muscle dystrophy: A rare mutation
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The dystroglycanopathies comprise a clinically and genetically heterogeneous group of muscular dystrophies characterized by deficient glycosylation of alpha-dystroglycan. Mutations in the fukutin (FKTN) gene have primarily been identified among patients with classic Fukuyama congenital muscular dystrophy (FCMD), a severe form of dystroglycanopathy. Young girl 30 months old with moderate limb-girdle muscle weakness and history of congenital hip dislocation, from a non consanguineous family, without history of muscle disease. She never achieved independent walk, and clinical examination revealed a predominance of scapular weakness, a myopathic face and a severe mental retardation. Cardiac and ophthalmological evaluations were normal. Investigation performed showed creatine kinase 6777 IU/L; muscle histopathology and immunofluorescence suggestive of α-dystroglycan glycosylation abnormality. MRI showed cerebellar cists, leukodystrophy and cortical dysplasia (polymicrogyria). POMGnT1 was negative. Fukutine gene was performed and revealed a rare mutation, not previously reported, which was confirmed in muscle and in parents ADN. In this report the diagnosis suspicion was based on MRI achievements, which showed in one child all the main image phenotypes described in FCMD.

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