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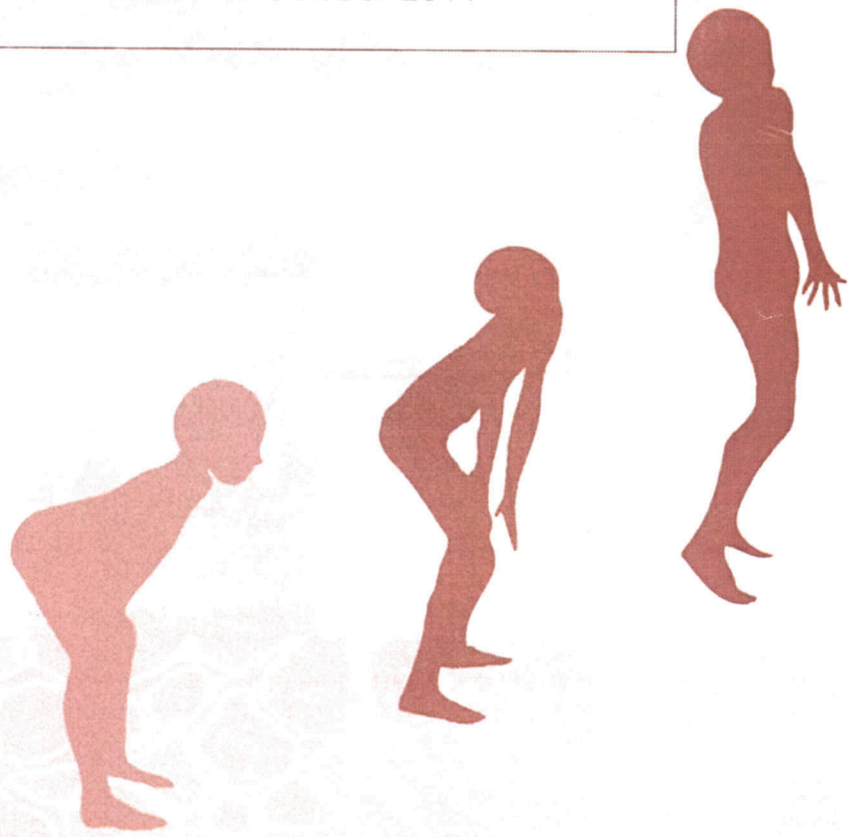

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Amhiphysins have been implicated in membrane remodeling in brain and skeletal muscle. Mutations in amphiphysin-2 were recently identified in autosomal recessive centronuclear myopathies. In order to understand the dynamics of amphiphysin-2 during its regeneration, we chronologically evaluate the expression of amphiphysin-2 and caveolin-3 in rat tibial muscles during a cycle of regeneration induced by cardiotoxin injection using immunohistochemistry and Western blot. Tibial muscles of male Wistar rats (7–8 weeks old) were injected with cardiotoxin. The cardiotoxin-injected muscles were removed on 1, 3, 5, 7, 14, and 28 days after the injection. Western blotting was performed as Laemmli's methods. In immunohistochemical studies, amphiphysin-2 and caveolin-3 were weakly stained at T-tubules of some regenerating muscles. In the western blot analysis, amphiphysin-2 was first detected as a visible band on day 5, whereas caveolin-3 was first recognized as a visible band on day 3. During 3–5 days after cardiotoxin injection, satellite cells fuse and differentiate to mature muscle fibers. These results provide evidence that both amphiphysin-2 and caveolin-3 contribute muscle differentiation and membrane deformation.

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P3.34

Correlation of morphological features of skeletal muscle biopsy with the gestational age of newborns with X-linked Myotubular myopathy, and comparison with the muscle pathology of myotubularin1-deficient mice

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The X-linked Myotubular myopathy (XLMTM) due to mutations in the MTM1-gene (myotubularin 1) has been clinically well characterised and usually gives rise to a severe phenotype in males presenting at birth with severe congenital myopathy. Although the muscle morphological characteristics are currently well documented (significant number of small muscle fibres with centralised nuclei), the formation and maintenance of this particular structure is not well characterised in human. We aimed to correlate the pathologic features of skeletal muscle biopsy of newborns with MTM1-mutations according to the corrected gestational age, and to compare these morphological findings with the pathological characteristics of muscle in myotubularin1-deficient mice. Clinical and muscle biopsies data from 20 XLMTM-newborns were studied. At birth, the age of newborns ranged from 29 to 42 gestational weeks and the age at the time of the muscle biopsy ranged from 0 to 95 days old. Nineteen patients died before the age of 5 months. Indeed, the sequential analysis of morphological features was performed according with the corrected gestational age. Thus, the proportion of myofibers with central nuclei, the myofiber diameters, the ultrastructural abnormalities, the immunocytochemical expression of muscle development markers will be correlated with the corrected age of XLMTM-newborns, as well as with the *MTM1* mutation type (missense, nonsense, splice site, deletion, small insertion or duplication) to try an assessment of the involvement of these different features in the pathological expression of the disease.

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P3.35

Expanding the mutation spectrum of the MTM1 gene: The first multi-exonic duplication and establishment of a locus-specific database

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Centronuclear myopathies (CNM) are a group of diseases with variable onset and severity sharing as a distinctive histological feature, a high frequency of muscle fibers with centralized nuclei. Myotubular myopathy (MIM#310400) the X-linked form of CNM is characterized by neonatal hypotonia and inability to maintain unassisted respiration. The *MTM1* gene, responsible for this disease, encodes myotubularin, a protein involved in myofiber differentiation and muscle cell architecture. In this work, eight patients were subjected to *MTM1* MLPA analysis, selected according to the following criteria: (i) muscle biopsy compatible with CNM and (ii) exclusion of *MTM1* point mutations by sequencing. We identified the first gross duplication spanning exons 1–5 (c.-76-?_342+?dup) in a 7 year old boy with progressive tetraparesis, ophtalmoparesis, facial diparesis and independent ambulation, the clinical course being milder than the classical myotubular myopathies. Analysis at the mRNA level revealed both normal transcripts and a mutated isoform lacking exon 6 (r.343_444del), suggesting somatic mosaicism. As suspected, this duplication was not detected in the patient's mother. Considering the phenotypic expression in the patient, this mutational event most likely occurred *de novo* during early embryogenesis. We also describe the implementation of a locus-specific database (LSDB) for this gene using the Leiden Open Variation database (LOVD) software. The MTM1-LOVD (http://www.lovd.nl/MTM1) contains 372 mutation entries identified in 370 patients (last accessed March 2011). A total of 223 unique *MTM1* mutations are listed in this LSDB, including: 207 point mutations, 15 single or multi-exonic deletions and the large duplication described in the present work. Despite the significant advances in this field during the last decade about one third of the CNM cases remain genetically unresolved. Here we show that gross *MTM1* gene duplications may account for a fraction of these cases.

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P3.36

Phenotypic spectrum in myopathies with tubular aggregates

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The sarcoplasmic reticulum of muscle fibers is known to form tubular aggregates (TAs) in various diseases, in some constituting the most striking