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Expanding the MTM1 mutational spectrum: novel variants including the first multi-exonic duplication and development of a locus-specific database

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Abstract

Myotubular myopathy (MIM#310400), the X-linked form of Centronuclear myopathy (CNM) is mainly characterized by neonatal hypotonia and inability to maintain unassisted respiration. The MTM1 gene, responsible for this disease, encodes myotubularin - a lipidic phosphatase involved in vesicle trafficking regulation and maturation. Recently, it was shown that myotubularin interacts with desmin, being a major regulator of intermediate filaments. We report the development of a locus-specific database for MTM1 using the Leiden Open Variation database software (http://www.lovd.nl/MTM1), with data collated for 474 mutations identified in 472 patients (by June 2012). Among the entries are a total of 25 new mutations, including a large deletion encompassing introns 2-15. During database implementation it was noticed that no large duplications had been reported. We tested a group of eight uncharacterized CNM patients for this specific type of mutation, by multiple ligation-dependent probe amplification (MLPA) analysis. A large duplication spanning exons 1-5 was identified in a boy with a mild phenotype, with results pointing toward possible somatic mosaicism. Further characterization revealed that this duplication causes an in-frame deletion at the mRNA level (r.343_444del). Results obtained with a next generation sequencing approach suggested that the duplication extends into the neighboring MAMLD1 gene and subsequent cDNA analysis detected the presence of a MTM1/MAMLD1 fusion transcript. A complex rearrangement involving the duplication of exon 10 has since been reported, with detection also enabled by MLPA analysis. It is thus conceivable that large duplications in MTM1 may account for a number of CNM cases that have remained genetically unresolved.