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Case report

Grand paternal inheritance of X-linked myotubular myopathy due to mosaicism, and identification of necklace fibers in an asymptomatic male

Carola Hedberg-Oldfors [a,*], Kittichate Visuttijai [a], Alexandra Topa [b], Mar Tulinius [c], Anders Oldfors [a]

[a] Department of Pathology and Genetics, University of Gothenburg, Gothenburg, Sweden
[b] Department of Clinical Pathology and Genetics, Sahlgrenska University Hospital, Gothenburg, Sweden
[c] Department of Pediatrics, The Queen Silvia Children's Hospital, University of Gothenburg, Gothenburg, Sweden

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Abstract

X-linked recessive myotubular myopathy (XLMTM) is a disorder associated with mutations in the myotubularin gene (*MTM1*) that usually affects boys, with transmission of the mutated allele from the mother. Here we describe a family with unexpected grand paternal transmission of a novel mutation in *MTM1* (c.646_648dupGTT; p.Val216dup) identified in a severely affected infant boy with a centronuclear myopathy. We confirmed the carrier status of the mother, but surprisingly we found that her father was a carrier of the mutated *MTM1* gene together with wild-type *MTM1*. A muscle biopsy from the grandfather revealed occasional typical necklace fibers with internalized nucleus, which is typically found in *MTM1*-associated myopathies. Further analysis of the grandfather revealed equal amounts of DNA with the wild-type sequence and DNA with the c.646_648dupGTT variant in five different tissues examined. In the presence of a normal karyotype (46,XY) in the grandfather and no evidence of intragenic duplication of *MTM1*, the result was interpreted as postzygotic mosaicism and the mutation had probably occurred at the first mitosis of the zygote. This study demonstrates the importance of considering the possibility of paternal transmission in families with severe X-linked disorders. The muscle biopsy with the finding of typical necklace fibers was important to further establish the pathogenicity of the novel *MTM1* mutation.

Keywords: Myotubular myopathy; Centronuclear myopathy; Myotubularin 1; MTM1; X-linked; Paternal transmission; Necklace fiber

1. Introduction

X-linked recessive myotubular myopathy (XLMTM; MIM #310400) is a disorder associated with mutations in the myotubularin gene (*MTM1*) on chromosome Xq28. *MTM1* encodes for a dual-specificity phosphatase that acts on both phosphotyrosine and phosphoserine [1–3]. The disorder ranges from mild to severe, and is characterized by muscle weakness. The severe form of XLMTM presents prenatally, with reduced fetal movement and polyhydraminos. The clinical presentations in newborns include weakness, hypotonia, and respiratory distress. XLMTM usually affects boys, with transmission of the mutated allele from the mother [4]. Female carriers are usually asymptomatic, but they may show muscle weakness [3,5].

Here we describe a family with unexpected grand paternal transmission of a novel mutation in *MTM1*, which was identified in a severely affected infant boy with a centronuclear myopathy. It is therefore important to be aware of the possibility of paternal transmission in families with severe X-linked disorders.

2. Report on the family

2.1. Patient, individual III:1

This newborn boy was the first child (III:1) of unrelated parents (Fig. 1A). The father had been operated because of ventricular septal defect (VSD), and the father's elder brother had died at the age of 2 weeks because of coarctation of the aorta. After a normal pregnancy following in vitro fertilization, the boy was delivered by cesarean section due to fetal distress, as diagnosed by cardiotocographic (CTG) monitoring during labor at 39 + 3 weeks. Birth weight was 3100 g, length was 52 cm, and head circumference was 36.5 cm. The APGAR score was 7-7-7. He had generalized muscle hypotonia, and

* Corresponding author. Department of Pathology and Genetics, Institute of Biomedicine, University of Gothenburg, Gula Straket 8, 413 45, Gothenburg, Sweden. Fax: +46 31 7412458.
E-mail address: carola.oldfors@gu.se (C. Hedberg-Oldfors).

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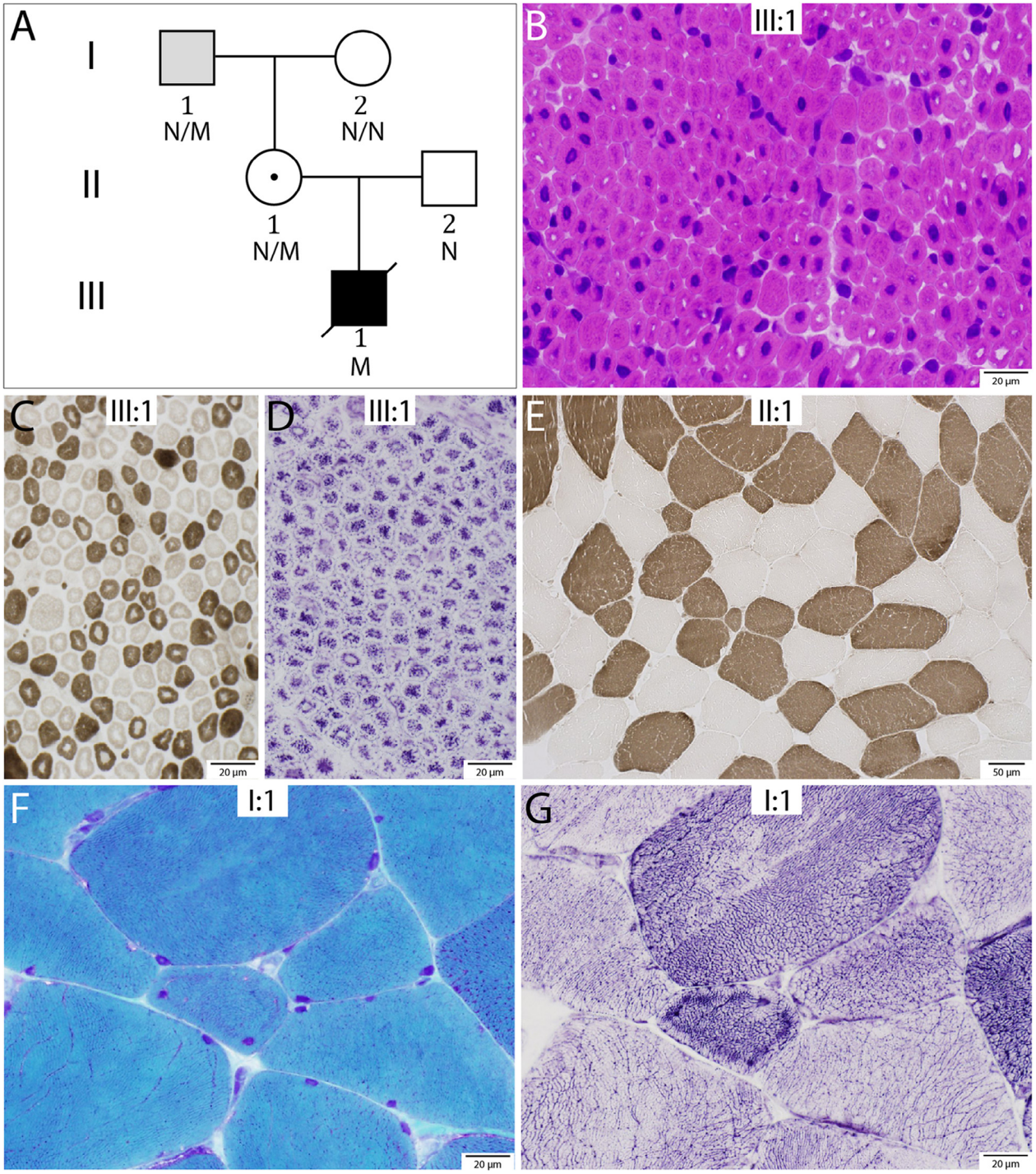

Fig. 1. Pedigree of the family and muscle morphology. (A) Pedigree of the family (N, normal *MTM1* sequence; M, *MTM1* with the c.646_648dupGTT mutation). (B–D) The muscle biopsy from patient III:1 showed small fibers with centrally located nuclei (panel B, H&E staining; panel C, ATPase pH 9.3) and a peripheral halo (panel D, NADH-TR staining). (E) The muscle biopsy from the mother (II:1) showed variability in fiber size and generally small muscle fibers of type 1 (ATPase pH 4.3). (F–G) The muscle biopsy of the grandfather (I:1) showed increased variability of fiber size mainly with type-2 fiber atrophy and predominance of type-2 fibers. Occasional typical necklace fibers with internalized nucleus were detected (panel F, Gomori trichrome staining; panel G, NADH-TR).

was admitted to the neonatal intensive care unit due to ventilatory failure. Ultracardiography did not show any major abnormalities, with no signs of cardiomyopathy or malformations. He was noticed to have a slightly high-arched palate, a triangular face, and a high forehead. He had reduced spontaneous movements, including facial muscles, but no signs of ophthalmoplegia. His hips were abducted and there were contractures of the knees with an extension defect of 20°. He had feeding difficulties, with failure to thrive that necessitated tube feeding. Prader–Willy syndrome, myotonic dystrophy type 1, and spinal muscular