Uniparental disomy unveils a novel recessive mutation in POMT2.

Brun BN1, Willer T2, Darbro BW1, Gonorazky HD3, Naumenko S4, Dowling JJ3, Campbell KP5, Moore SA6, Mathews KD7.

Abstract
Mutations in POMT2 are most commonly associated with Walker-Warburg syndrome and Muscle-Eye-Brain disease, but can also cause limb girdle muscular dystrophy (LGMD2N). We report a case of LGMD due to a novel mutation in POMT2 unmasked by uniparental isodisomy. The patient experienced proximal muscle weakness from three years of age with minimal progression. She developed progressive contractures and underwent unilateral Achilles tenotomy. By age 11, she had borderline low left ventricular ejection fraction and mild restrictive lung disease. Muscle biopsy showed mild dystrophic changes with selective reduction in α-dystroglycan immunostaining. Sequencing of POMT2 showed a novel homozygous c.1502A>C variant that was predicted to be probably pathogenic. Fibroblast complementation studies showed lack of functional glycosylation rescued by wild-type POMT2 expression. Chromosomal microarray showed a single 15 Mb copy number neutral loss of heterozygosity on chromosome 14 encompassing POMT2. RNAseq verified homozygosity at this locus. Together, our findings indicate maternal uniparental isodisomy causing LGMD2N.

KEYWORDS: Dystroglycanopathy; LGMD; POMT2; Uniparental disomy; α-dystroglycan

PMID: 29759639 DOI: 10.1016/j.nmd.2018.04.003