Two novel COL6A3 mutations disrupt extracellular matrix formation and lead to myopathy from Ullrich congenital muscular dystrophy and Bethlem myopathy spectrum.

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Abstract

Here we present a case report of collagen VI related myopathy in a patient, 8y.o. boy, with intermediate phenotype between severe Ullrich congenital muscular dystrophy and milder Bethlem myopathy. Whole exome sequencing revealed two novel single nucleotide variants in COL6A3 gene: paternal p.Glu2402Ter, resulting in premature translation termination codon and degradation of mRNA from this allele probably due to nonsense-mediated decay, and maternal p.Arg1660Cys leading to amino-acid substitution in N2-terminal domain. COL6A3 expression analysis of proband's fibroblasts reveals functional homozygosity of the latter variant. Paternal fibroblasts showed only WT allele expression, which could lead to a reduction in mature transcript level, while maternal fibroblasts expressed both alleles. Functional assay of immunofluorescent staining of COL6A3 protein in fibroblasts culture reveals profound changes in COL6A3 localization and reduction of protein level in studied cultures when comparing with the controls. This study not only broadens the allelic spectrum of pathogenic COL6A3 variants in myopathy but also gives an additional support to Ullrich congenital muscular dystrophy and Bethlem myopathy clinical continuum.

KEYWORDS: Clinical spectrum; ColVI-myopathy; Extracellular matrix; Functional hemizygous

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