Abstract

BACKGROUND: Collagen VI-related disorders are a group of muscular diseases characterized by muscle wasting and weakness, joint contractures, distal laxity, serious respiratory dysfunction and cutaneous alterations, due to mutations in the COL6A1, COL6A2 and COL6A3 genes, encoding for collagen VI, a critical component of the extracellular matrix. The severe Ullrich congenital muscular dystrophy (UCMD) can be due to autosomal recessive mutations in one of the three genes with a related 25% recurrence risk. In the majority of UCMD cases nevertheless, the underlying mutation is thought to arise de novo and the recurrence risk is considered as low.

METHODS AND RESULTS: Here we report a family with recurrence of UCMD in two half-sibs. In both, the molecular analysis revealed heterozygosity for the c.896G > A missense mutation in COL6A1 exon 10 (Gly299Glu) and for the COL6A1 c.1823-8G > A variation within COL6A1 intron 29. The intronic variation was inherited from the father and RNA analysis in skin fibroblasts allowed to exclude its role in affecting COL6A1 transcript processing. The Gly299Glu mutation occurred apparently de novo in the two sibs.

CONCLUSION: The described mutational segregation strongly suggests the occurrence of paternal germline mosaicism. This is the first report of UCMD recurrence due to a germline mosaic COL6 gene mutation. Mosaicism deserves to be considered as possible inheritance pattern in genetic counseling and recurrence risk estimation in collagen VI-related diseases.

KEYWORDS: Collagen VI; Germline mosaicism; UCMD

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