SHORT COMMUNICATION

PERINATAL (LETHAL) TYPE OF HYPOPHOSPHATASIA RESULTING FROM PATERNAL ISODISOMY OF CHROMOSOME 1

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Hypophosphatasia (HPP) is an inherited disorder characterized by defective bone mineralization and caused by mutations in ALPL that encodes an isozyme of alkaline phosphatase, TNSALP. Clinically, the disease is heterogeneous and according to the age of onset, five different forms can be distinguished. The perinatal (lethal) type of HPP (pl-HPP). is an autosomal recessive disorder with the most severe symptoms in HPP and it has been diagnosed in utero by ultrasonography, which is performed while paying careful attention to the limbs and the skull. The pl-HPP is one of major types of skeletal dysplasia found in the prenatal period in Japan. One of the most frequent ALPL mutations in Japan is c.1559delT, which causes pl-HPP. Some patients with pl-HPP in Japan are homozygotes of the c.1559delT, and their parents usually had a heterozygous mutation at the same position (c.1559delT) with no evidence of consanguinity. We identified a patient with pl-HPP and an apparent homozygous mutation, c.1559delT, after full sequencing of his ALPL genes. Since the patient's father was heterozygous for this mutation, but sequencing of the maternal ALPL genes revealed only wild-type sequence, paternal uniparental disomy (UPD) was suspected. CGH analyses performed on parental gDNA did not show evidence of a maternal gene deletion. Amplification and fragment analysis of dinucleotide repeat markers spanning chromosome 1 and SNP array in the patient and both parents revealed paternal uniparental inheritance. We discuss the potential mechanisms causing UPD in this patient and review the literature on chromosome 1 UPD. The absence of non-HPP clinical features in this patient was consistent with previous literature supporting the absence of imprinted genes on chromosome 1. This first description of pl-HPP caused by UPD dramatically changes the parental recurrence risk, highlighting the value of obtaining parental genotypes the proband has a putative homozygous mutation by sequence analysis even if the homozygous mutation has been reported.