SHORT COMMUNICATION

TWO COMMON MUTATIONS IN THE ALPL GENE IN JAPANESE PATIENTS WITH HYPOPHOSPHATASIA

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Hypophosphatsia is a skeletal disorder due to mutations of the ALPL gene which encodes tissuenonspecific alkaline phosphatase (TNSALP). Hypophosphatasia is highly variable in its clinical expression, and we have proposed diagnostic criteria for hypophosphatasia at http://www.bone.med.osaka-u.ac.jp/english/b5/. Based on the age of manifestation and its severity, hypophosphatasia is divided into 6 subtypes. The most severe form of hypophosphatasia is a perinatal form, which is also called a lethal form. The patients with this form suffer from respiratory failure. Recently, non-lethal benign form of perinatal hypophosphatasia has been recognized, which is associated with no apparent defects of mineralization. We firstly described this form in 1996, and reported its association with a missense mutation p.F327L (formerly described as F310L). The mutant F327L has significant residual enzymatic activity, which may account for the mild symptoms in the patients with this mutation. In our experience of examining mutations in the ALPL gene in 45 Japanese patients with hypophosphatasia, p.F327L was the second frequent mutation and detected in 12 alleles (13%) sequenced. Patients who had p.F327L in one of the alleles were diagnosed to be hypophosphatasia in their perinatal period based on the deformity of long bones. However, they survived and grew up without life-threatening complications. The most frequent mutation, c.1559delT (formerly delT1735) was found in 38 alleles (42%). This frameshift-type mutant has additional 80 amino acids at near C-terminal position of wild type TNSALP with no enzymatic activity. Both p.F327L and c.1559delT were the mutations specific to Japanese patients, suggesting founder effects. All patients homozygous for c.1559delT exhibited the clinical manifestations of perinatal severe form of hypophosphatasia. However, recent advances of neonatal medicine contribute to the survival of patients with severe form of hypophosphatasia, including those homozygous for c.1559delT. Thus, enzyme replacement therapy may be applicable for these patients as well.