SHORT COMMUNICATION

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

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Hypophosphatasia is a skeletal disorder due to mutations of the ALPL gene which encodes tissuenspecific alkaline phosphatase (TN-SALP). Hypophosphatasia is highly variable in its clinical expression, and we have pro-
posed diagnostic criteria for hypophosphatasa-

iat http://www.bone.med.osaka-u.ac.jp/en-

lish/b5/. Based on the age of manifesta-
tion and its severity, hypophosphatasia is di-

vided 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. Re-
cently, non-lethal benign form of perinatal hy-

pophosphatasia has been recognized, which

is associated with no apparent defects of mi-

neralization. We firstly described this form in

1996, and reported its association with a mis-
sense mutation p.F327L (formerly described

as F310L). The mutant F327L has significant

residual enzymatic activity, which may accoun-
t 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 diag-

nosed to be hypophosphatasia in their peri-

natal 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 ami-
nos 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 manifesta-
tions of perinatal severe form of hypophospha-
tasia. However, recent advances of neonatal

medicine contribute to the survival of patients

with severe form of hypophosphatasia, includ-
ing those homozygous for c.1559delT. Thus,

enzyme replacement therapy may be applica-
table for these patients as well.