Prolidase deficiency: Report of four cases diagnosed in Greece and description of a new mutation.

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Introduction
Prolidase is a peptidase that cleaves the imidodipeptides containing a proline or a hydroxyproline residue at the C-terminal end. Prolidase deficiency is a rare pan-ethnic, autosomal recessive disease with a broad phenotypic spectrum. It results from mutations in the PEPD gene and over 35 mutations have been described. We describe four cases diagnosed in Greece and a new mutation in PEPD.

Case Reports
Patient A: a five year old girl, with poor growth, evolving splenomegaly since the age of six months, chronic hypochromic microcytic anemia, recurrent respiratory infections, cytopenia and pancytopenia during acute infections, increased IgG, IgA, IgM and IgE.

Patient B: her sibling, a three year old boy, showed mild developmental delay, poor growth, severe dermatopathy, mild hepatosplenomegaly, history of intractable diarrhea (no longer present on diagnosis) and failure to thrive.
Patient C: a seven year old boy, showed developmental delay within the autism spectrum, elevated ferritin and B12 serum levels, low MCV and dysmorphic features. Patient D: a five year old girl, hospitalized for prolonged fever of 9 days, tonsillitis and evolving splenomegaly, since the age of 3 years, recurrent respiratory infections, reduced height velocity, mild learning difficulties, dysmorphic features, elevated ferritin and B12 serum levels and mild thrombocytopenia. Urinary amino acid analysis (Biochrom amino acid analyser) revealed massive imidopeptiduria in all patients. Deficient Prolidase activity (19.8% of control activity; Dr Forlino, University of Pavia) was found in patient C. DNA analysis in Patients C and D detected a previously not reported c.2T>G (p.Met1?) change in the initiator codon and the splicing pathogenic variants: c.1344 + 2T (Patient C) and c.549-1G>T (Patient D). In both cases their parents were shown to be heterozygous for the identified mutations.
Figure 1: Urine amino acid analysis in patient D (in blue) showing the characteristic peaks of imidodipeptides. In red the analysis of the standard amino acid mixture.

Conclusions
Our report illustrates the variable presentation of Prolidase deficiency observed even within siblings and describes a previously not reported mutation.

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