A rare case of prolidase deficiency with situs inversus totalis, identified by a novel mutation in the *PEPD* gene

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Key words: deletion mutation; leg ulcer; novel mutation; *PEPD*; prolidase deficiency.

INTRODUCTION

Prolidase deficiency (PD) is a rare inherited autosomal recessive disorder of amino acid metabolism with an incidence of 1 to 2 for every one million.[1,2] First described in 1968,[1] PD is caused by many different types of mutations in the peptidase D (*PEPD*) gene encoding prolidase, an enzyme that breaks down iminodipeptides containing proline and hydroxyproline.[3] To date, 29 different mutations have been detected in this gene.[4]

Here we present a 20-year-old man with PD diagnosed through *PEPD* gene analysis. To our knowledge, the novel mutation detected in this case has never been reported. Therefore, our case provides important genetic information pertaining to PD.

CASE REPORT

A 20-year-old man was admitted to our clinic with the complaint of recurrent wounds in both legs since childhood. He had no personal history of disease, with the exception of situs inversus totalis, and was not taking any medication. His family history contained no consanguineous marriage. His physical examination was unremarkable. Dermatologic examination found a round approximately 4- × 5-cm ulcer with a distinct edge, which included dry necrotic debris and many small depressed ulcers and several atrophic scars caused by previous ulcers on the left leg (Fig 1).

Other manifestations included xerotic skin, low anterior hairline, synophrys, high-arched palate, premature graying of the hair, and generalized hypertrichosis (Fig 2). He had no mental retardation and reported no recurrent infections or photosensitivity.

Abbreviations used:

PD: prolidase deficiency
PEPD: peptidase D

His complete blood count showed microcytic, hypochromic anemia (hemoglobin, 11.1 g/dL) thrombocytopenia (platelet count, 102.000/μL), and normal white cell count. Laboratory results also showed normal serum electrolytes; normal kidney and liver function; and serologic markers for hepatitis A, B, and C, human immunodeficiency virus, syphilis, and autoimmune markers. IgA, IgE, IgM, C3, and C4 values were normal, but a high level of IgG was detected (2416 mg/dL). Further examination found hypoalbuminemia, hypergammaglobulinemia, and marginally elevated level of α-1 globulin in serum protein electrophoresis. Additionally, routine bacterial, mycobacterial, and fungal cultures of all wound sites were negative. Abdominal complete ultrasound scan found splenomegaly with a diameter of 160 mm. The patient also had multiple reactive lymphadenopathies, which were confirmed by excisional biopsy.

A skin biopsy found nonspecific changes including slight hyperkeratosis, edema, and parakeratosis in the epidermis of the edge of the ulcer, minimal neutrophil leukocyte and lymphocyte infiltration, and extravasated erythrocytes in the

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Fig 1. A round approximately 4- × 5-cm ulcer with a distinct edge, which included dry necrotic debris and lots of small depressed ulcers.



Fig 2. Note the dismorphic findings; low anterior hairline, synophrys, high-arched palate, and premature graying of the hair.

papillary dermis (Fig 3). His history of recurrent and recalcitrant leg ulcers since childhood, accompanied by anemia, thrombocytopenia, hypergammaglobulinemia, splenomegaly, and several dysmorphic facial features prompted us to suspect the diagnosis of PD, even without the presence of family history. Thus, we performed *PEPD* gene sequence analysis, and the results showed a biallelic deletion in this gene.

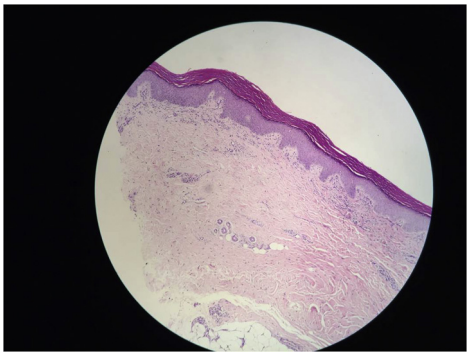


Fig 3. Skin biopsy shows nonspesific changes.

We detected an NM_000285.3 c.580delG (p.Val194Phefs*16) mutation (Fig 4). This single nucleotide deletion caused a frameshift mutation and encoded a premature stop codon, likely leading to PD. We classified this variant as a pathogenic mutation based on the American College of Medical Genetics criteria. To our knowledge, no relationship between the mutation detected here and PD has been reported previously.

With these clinical and laboratory findings, PD syndrome was diagnosed. His wounds healed with topical care and wound dressings after 41 days at our clinic. The patient remains under follow-up care in our dermatology department.

DISCUSSION

Prolidase is a dipeptidase, which is required for the final stage of collagen degradation. Prolidase hydrolyzes iminodipeptides containing proline and hydroxyproline. Collagen breakdown does not function properly in patients who lack the prolidase enzyme, resulting in the failure to recycle proline. This disorder causes impaired collagen synthesis and poor wound healing.[3-5]

PD can manifest with various clinical findings such as recurrent leg ulcerations, several dysmorphic facial features, intellectual disability, hematologic abnormalities, and several lymphoreticular and immune system findings.[3,4] Other skin indications of the disease can include telangiectasias, purpura, premature graying of the hair, photosensitivity, erythematous maculopapular rash, and hypertrichosis.[6-9] Various facial dysmorphic findings have also been reported.[4,6-8] Other manifestations related to PD include anemia, thrombocytopenia, elevated liver enzymes, hypergammaglobulinemia, hypocomplementemia, splenomegaly, and recurrent infections.[3-5]

Our patient complained mainly of recurrent leg ulcers, which healed poorly and appeared repeatedly. He also had low anterior hairline, synophrys, and a high-arched palate. However, he did not complain of recurrent infections; additionally, he

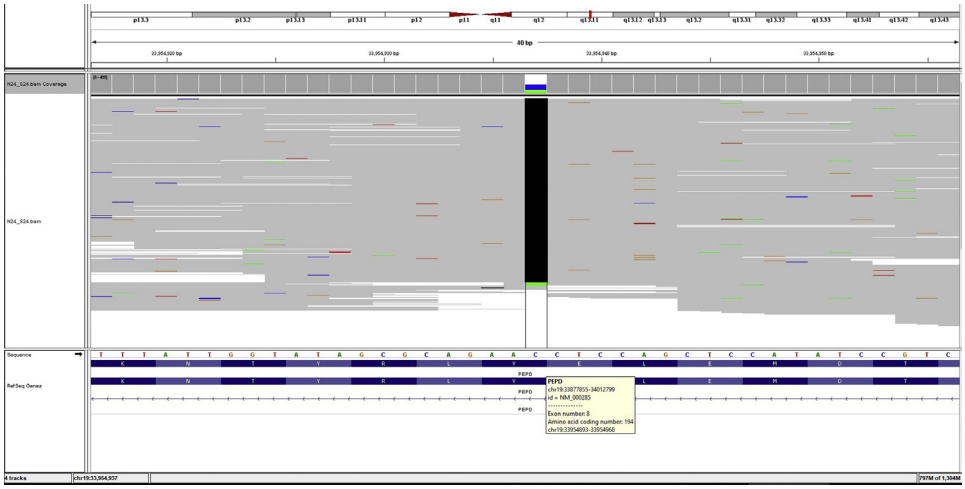


Fig 4. NM_000285.3 c.580delG (p.Val194Phefs*16). *PEPD* gene sequence analysis was performed by using MiSeq next generation sequencing platform (Illumina, San Diego, CA) according to the manufacturer's instructions. All coding exons and their flanking splice site junctions were amplified using polymerase chain reaction primers, designed with PRIMER – Primer Designer v.2.0 (Scientific & Educational Software programme) software. Sequences were aligned to the hg19 genome within MiSeq Reporter software (Illumina Inc). Visualization of the data was performed with IGV 2.3 (Broad Institute) software.

had normal intellectual ability. Notably, the patient had a remarkable characteristic—situs inversus totalis—which has never been reported in any PD cases to date.[4] This finding might be associated with the novel mutation found in our patient.

PD is confirmed by determining prolidase activity in erythrocytes, leukocytes, or fibroblasts in culture or by sequence analysis of the *PEPD* gene.[4-6] The diagnosis was based on our detection of a nucleotide homozygous deletion in the *PEPD* gene. *PEPD* is located at 19q13.11. Twenty-nine distinct mutant alleles associated with PD have been identified in this gene including 14 point mutations, 5 splice site mutations, 6 small deletions, 2 large deletions, 1 small duplication, and 1 insertion.[4] The mutation in our patient is caused by a single nucleotide deletion, which disrupts the function of prolidase enzyme by causing a frameshift mutation and encoding a premature stop codon in the gene.

We report on a patient with PD caused by a novel mutation discovered using DNA sequence analysis. Our patient had a novel single nucleotide deletion in the *PEPD* gene and had situs inversus totalis, unlike other PD cases in the literature. Currently, PD has no curative treatment. Understanding the genetic basis of PD may lead to the development of future PD therapies. This report contributes to the body of knowledge regarding the genetic and physical features of patients with PD.

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