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Prolidase Deficiency

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Summary

Clinical characteristics

Prolidase deficiency is characterized by skin lesions (typically severe, chronic, recalcitrant, and painful skin ulcers of the lower extremities and telangiectasias of the face and hands), recurrent infections (particularly of the skin and respiratory tract), dysmorphic facial features, variable intellectual disability, and organomegaly (typically splenomegaly but occasionally associated with hepatomegaly) with elevated liver enzymes. Skeletal anomalies, chronic pulmonary disease, anemia, thrombocytopenia, hypergammaglobulinemia, and hypocomplementemia are observed in a minority of affected individuals. An association between prolidase deficiency and autoimmune conditions – particularly systemic lupus erythematosus (SLE) – has been described.

Diagnosis/testing

The clinical diagnosis of prolidase deficiency can be established in a proband with characteristic clinical findings and imidodipeptiduria or reduced prolidase enzyme activity. The molecular diagnosis can be established in a proband with suggestive findings and biallelic pathogenic variants in *PEPD* identified by molecular genetic testing.

Management

Treatment of manifestations: Skin ulcers may require treatment by a wound care specialist; topical proline (often 5%) or topical 5% proline-5% glycine ointment applied with dressing changes has been successful in some affected individuals. Standard treatment for developmental delay / intellectual disability, seizures, infections, reactive airways disease / pulmonary hypertension, SLE-like features, hemophagocytic lymphohistiocytosis, mast cell activation, osteopenia, dental anomalies, and refractive errors. Anemia and thrombocytopenia rarely require treatment, but packed red blood cell or platelet transfusions may be considered in those with severe anemia or thrombocytopenia, respectively.

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Surveillance: Measurement of growth parameters, monitoring for developmental progress and educational needs, assessment for new neurologic manifestations (changes in tone, seizures, movement disorders), monitoring for signs or symptoms of respiratory insufficiency, and assessment of mobility and self-help skills at each visit. Dental evaluation every six months after tooth eruption. Annual complete blood count, liver function tests, abdominal ultrasound to assess liver and spleen size, and skin examination for evidence of malignant transformation in persons with chronic recalcitrant skin ulcers. Ophthalmology evaluation annually or as clinically indicated.

Agents/circumstances to avoid: Individuals with prolidase deficiency who have splenomegaly should avoid contact sports given the increased risk for splenic rupture.

Genetic counseling

Prolidase deficiency is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible if the *PEPD* pathogenic variants in the family have been identified.

Diagnosis

No consensus clinical diagnostic criteria for prolidase deficiency have been published.

Suggestive Findings

Prolidase deficiency **should be suspected** in individuals with the following clinical, biochemical, other supportive laboratory, and family history findings.

Clinical findings

- Skin lesions, typically lower-extremity ulcers (Figure 1), although telangiectasias of the face and hands are also common
- Recurrent infections, particularly of the skin and respiratory tract
- Chronic lung disease with digital clubbing and a cystic fibrosis-like phenotype
- Dysmorphic facial features including widely spaced eyes, proptosis, depressed nasal bridge, prognathism, thin vermilion of the upper lip, and low anterior and posterior hairline (Figure 2)
- Developmental delay of variable degree
- Splenomegaly
- Immunologic abnormalities, including systemic lupus erythematosus-like phenotype and hypergammaglobulinemia

Biochemical findings

- Massive imidodipeptiduria * (10-30 mmol/day) on urine amino acid analysis, in conjunction with suggestive clinical findings or a positive family history, is highly suggestive of the disorder. The concentration of imidodipeptides is much lower in serum than in urine.
    - Imidodipeptiduria has been detected as early as in the newborn period, even in the absence of signs or symptoms of the disease.
    - The absence of detectable imidodipeptiduria in properly processed samples is sufficient evidence to rule out a diagnosis of prolidase deficiency.

  Click here (pdf) for information on laboratory methods used to detect imidodipeptiduria.

- Gly-Pro has been reported in the plasma by some investigators, but not others. Detection of Gly-Pro or other imidodipeptides in plasma require a sensitive method, and in the case of tandem mass spectrometry methods, specific ion monitoring [Taibi et al 2022].

* Note: A number of published reports mistakenly refer to imidodipeptiduria as "iminodipeptiduria." Iminodipeptides are dipeptides in which proline or hydroxyproline is the N-terminal amino acid (i.e., Pro/Hyp-X, for example, prolylglycine), whereas imidodipeptides are dipeptides in which proline or hydroxyproline is the C-terminal amino acid (i.e., X-Pro/Hyp, for example, glycylproline).

Other supportive laboratory findings

- Anemia, usually mild (hemoglobin >10 g/dL), but occasionally more severe
- Thrombocytopenia, usually mild (>100,000 platelets per µL), although it can be more severe
- Elevated liver enzymes, with elevation of aspartate aminotransferase in the hundreds
- Hypergammaglobulinemia, mainly elevation of IgG and IgA, although occasionally also elevation of IgM
  - IgG levels >2,000 mg/dL
  - IgA levels >500 mg/dL and as high as 850 mg/dL
  - IgM concentrations as high as 568 mg/dL

  Note: Reference ranges for immunoglobulins are age dependent, but upper limits of normal at any age are: IgG = ~1600 mg/dL, IgA = 350 mg/dL, and IgM = 280 mg/dL.
- Hypocomplementemia, with levels of C3 ranging from 30 to 74 mg/dL (normal: 75-175 mg/dL) and C4 as low as 9 mg/dL (normal: 20-40 mg/dL)

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The clinical diagnosis of prolidase deficiency **can be established** in a proband with characteristic clinical findings and imidodipeptiduria or reduced prolidase enzyme activity. The molecular diagnosis can be established in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *PEPD* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *PEPD* variants of uncertain significance (or of one known *PEPD* pathogenic variant and one *PEPD* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of prolidase deficiency has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

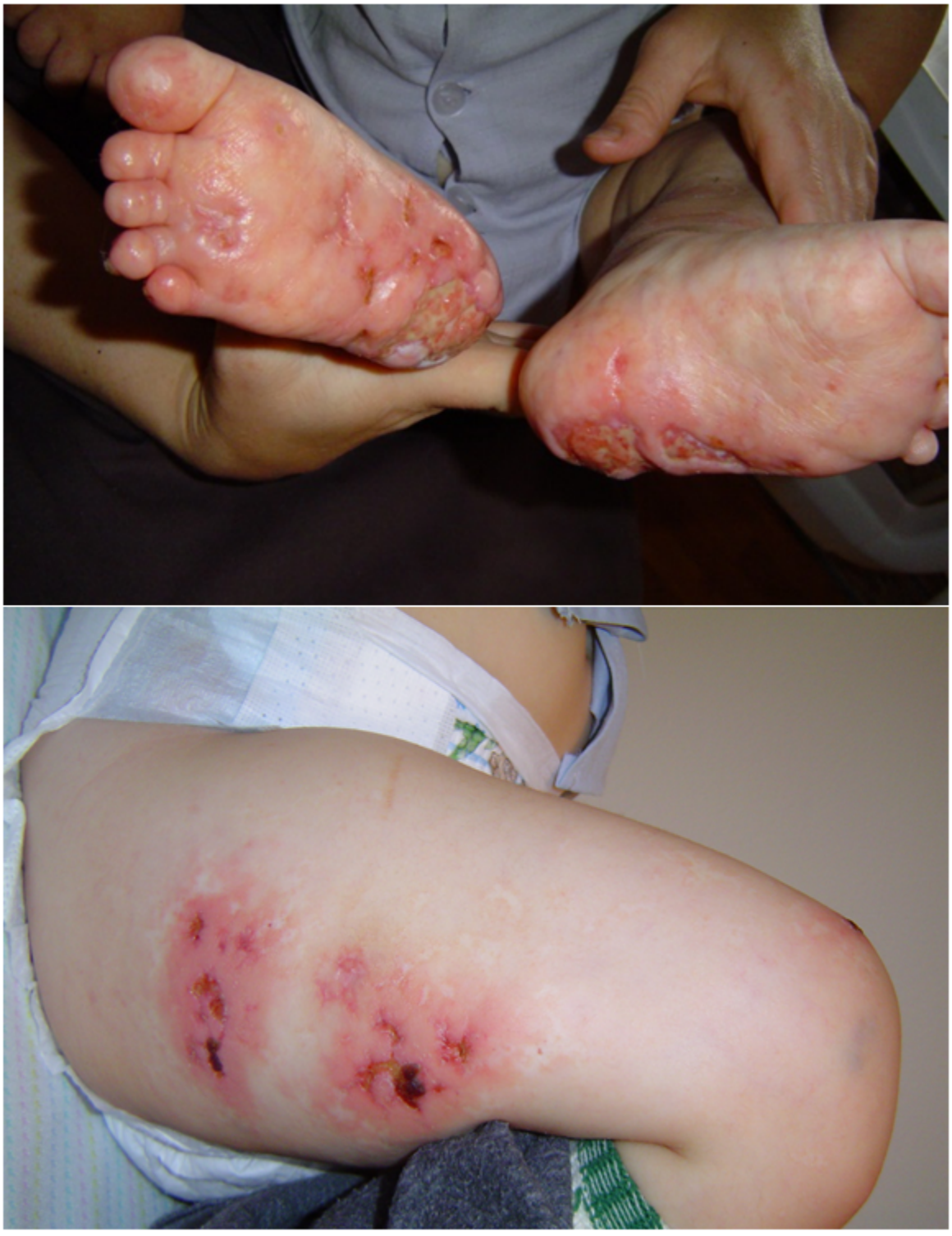

Figure 1. Typical skin ulcerations in individuals with prolidase deficiency

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of prolidase deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

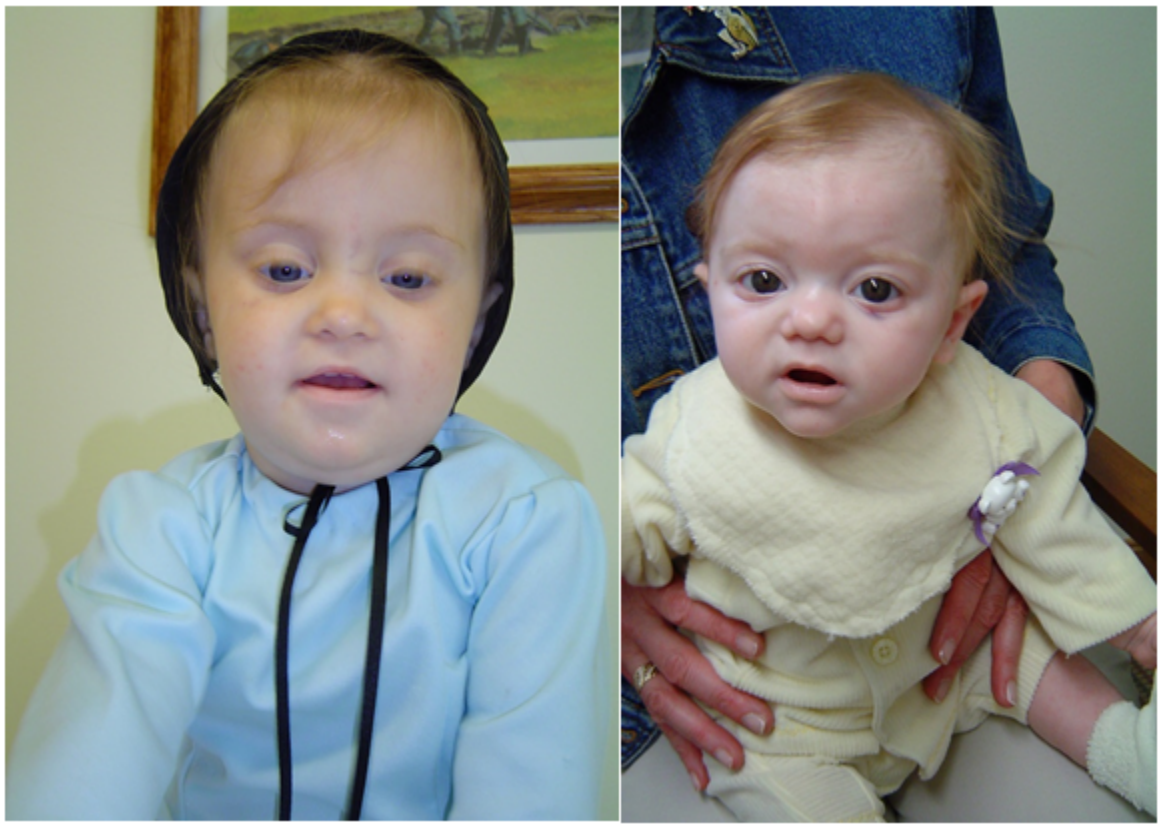

Figure 2. Typical facial features of prolidase deficiency: prominent forehead, proptosis, depressed nasal bridge, and thin vermilion of the upper lip

- **Single-gene testing.** Sequence analysis of *PEPD* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

  Note: Targeted analysis for pathogenic variants can be performed first for Amish individuals from Geauga County, Ohio, and Druze and Arab Muslim individuals from northern Israel (see Table 1 and Molecular Genetics).

- **An immunodeficiency/autoimmunity multigene panel** that includes *PEPD* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of prolidase deficiency has not been considered because an individual has atypical phenotypic features, comprehensive genomic testing may be considered.

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Prolidase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
PEPD	Sequence analysis [3]	184/188 (97.9%) [4, 5]
	Gene-targeted deletion/duplication analysis [6]	4/188 (2.1%) [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Rossignol et al [2021], Supplemental Table 4
5. Sequence analysis should also be able to detect the founder p.Arg265Ter pathogenic variant found in the Amish from Geauga County, Ohio [Wang et al 2006], and the founder p.Ser202Phe pathogenic variant found in the Druze and Arab Muslims from northern Israel [Falik-Zaccai et al 2010].
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Measurement of prolidase enzyme activity. In affected individuals, prolidase enzyme activity in erythrocytes, leukocytes, or cultured fibroblasts ranges from none to less than 10% [Lupi et al 2008]. However, this test is not widely available clinically.

Click here (pdf) for a short review of biochemical laboratory techniques used in the diagnosis of prolidase deficiency; see also Kurien et al [2006], Viglio et al [2006], and Taibi et al [2022].

Clinical Characteristics

Clinical Description

To date, more than 175 individuals from more than 90 families have been identified with prolidase deficiency, as recently reviewed by Spodenkiewicz et al [2020] and Rossignol et al [2021]. The following description of the phenotypic features associated with this condition is based on these reviews.

Note: A minority of individuals (n=5) have remained asymptomatic, despite biochemical or molecular confirmation of prolidase deficiency [Isemura et al 1979, Lemieux et al 1984, Ledoux et al 1996, Mandel et al 2000, Lupi et al 2006]. However, limited long-term information is available on these individuals; the oldest asymptomatic individual was 29 years old at the time of report.

Table 2. Prolidase Deficiency: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Dysmorphic facial features	66%	
Skin ulcers	62%	Most commonly affecting lower extremities, particularly feet
ID/DD	58%	IQ ranging from 30 to 90 [1] in those who have undergone IQ testing (n=18)
Recurrent infections	48%	Commonly sinopulmonary infections or gastroenteritis
Organomegaly	45%	Mostly splenomegaly, rarely (14%) accompanied by hepatomegaly
Skeletal findings	34%	Incl hand/feet (14%) & other limb (6%) abnormalities, osteopenia (7%), joint hypermobility (7%), or arthritis (5%)
Anemia	30%	
Thrombocytopenia	18%	
Chronic pulmonary disease	12%	Excl asthma (7%)
Autoimmune disease	12%	Incl SLE or SLE-like features, rhupus, [2] autoimmune GI disease or arthritis
Hypergammaglobulinemia	15%	Incl hyper IgG & hyper IgE

DD = developmental delay; GI = gastrointestinal; ID = intellectual disability; IgG = immunoglobulin G; IgE = immunoglobulin E; SLE = systemic lupus erythematosus

1. The formal medical definition of intellectual disability is an IQ score lower than 70. Individuals with an IQ score equal to or above 70 may still have delays in the acquisition of milestones but would not be considered to have intellectual disability.

2. Rhupus is a condition in which individuals have features of both rheumatoid arthritis and SLE, often in a sequential manner.

Dysmorphic Facial Features

Although not a universal finding, facial features typically described include prominent forehead, widely spaced eyes, proptosis, depressed nasal bridge, prognathism, thin vermilion of the upper lip, and low anterior and posterior hairlines [Falik-Zaccai et al 2010, Besio et al 2015]. See Figure 2.

Skin

The hallmark of prolidase deficiency is severe, chronic, recalcitrant, and painful skin ulcers (see Figure 1). The ulcers are located mainly on the lower extremities, particularly the feet. However, a few individuals have been reported with upper extremity involvement [Sheffield et al 1977, Cantatore et al 1993, El-Darouti 2013] or, rarely, facial involvement [Isik et al 2008].

- Skin ulcers can begin as early as age six months or as late as age 30 years. Half of affected individuals have ulcers by age 12 years and around 75% by age 18 years (see also Genotype-Phenotype Correlations).
- Ulceration is recurrent, and individual ulcers can take months to heal.
- Typically, no precipitating factors are identified with the appearance of an ulcer, although trauma has been reported as a triggering factor.

A variety of skin findings can precede the appearance of ulcers by many years, including:

- Telangiectasias of the face, shoulders, and hands
- Scaly, erythematous, maculopapular lesions

- Purpuric lesions in the absence of hematologic abnormalities
- Premature graying of the hair

Occasional skin findings may also include:

- Lymphedema
- Hyperkeratosis of the elbows and knees
- Hirsutism
- Perioral pitted scars or radial scars

As prolidase deficiency is associated with chronic recalcitrant lower extremity ulcers, an increased risk of squamous cell carcinoma of the skin could be expected, and indeed has been reported in one individual [Fimiani et al 1999].

Developmental Delay (DD) and Intellectual Disability (ID)

DD of variable degree has been described in approximately 60% of individuals with prolidase deficiency [Rossignol et al 2021].

- The reported spectrum varies widely, from normal development to mild-to-moderate DD or, less frequently, severe ID [Falik-Zaccai et al 2010, Besio et al 2015].
- Reported IQ values (n=18) ranged from 30 to 90.

Other Neurologic/Brain Findings

Seizures have been described in rare affected individuals [De Rijcke et al 1989, Wang et al 2006, Butbul Aviel et al 2012].

Microcephaly has been reported in a few affected children and adults [Butbul Aviel et al 2012, Besio et al 2015, Hintze et al 2016].

Abnormal brain MRI findings

- Multiple microthromboses bilaterally in the cerebral white matter [Arata et al 1991]
- Multiple bilateral subcortical white matter lesions (mainly in the parieto-occipital area), accompanied by leptomeningeal enhancement (one affected individual) [Butbul Aviel et al 2012]
- Findings compatible with vasculitis [Falik-Zaccai et al 2010]

Rarely, an axonal neuropathy can occur [Marotte et al 2010, Cottin et al 2020].

Organomegaly

Splenomegaly is common and variable in severity; in one instance massive splenomegaly (spleen measuring 35 cm) was reported [Nasser et al 2015]. Splenomegaly is sometimes accompanied by hepatomegaly.

- Liver enzymes may be mildly elevated [Butbul Aviel et al 2012].
- Only a few individuals have progressed to more severe liver disease, including cirrhosis or hepatitis, sometimes in the context of autoimmune disease [Kelly et al 2010, Kuloglu et al 2015, Cottin et al 2020].

Hematologic Manifestations

Anemia is present in around 30% of affected individuals and can be either mild microcytic hypochromic anemia or normocytic normochromic anemia [Dunn et al 2011].

Hemolysis has been described, with reticulocytosis varying from 5.9% [Powell et al 1977] to 8.6% [Powell et al 1974].

Thrombocytopenia is present in around 18% of affected individuals, but recurrent bleeding episodes or easy bruising has been rarely reported in the literature.

Immunologic Manifestations

Recurrent episodes of otitis media, sinusitis, pneumonia, and gastroenteritis are common. A few affected individuals have been reported with hemophagocytic lymphohistiocytosis / macrophage activation syndrome, which required emergent management (see Management) [Chidambaram et al 2021, Rossignol et al 2021].

Immunologic studies may reveal the following (see also Suggestive Findings):

- Elevated levels of IgG, IgA, and IgM
- Hypocomplementemia
- Decreased neutrophil chemotaxis
- Increased serum IgE levels, ranging from 20,000 IU/mL to 77,600 IU/mL
- Grimbacher scores for hyper IgE syndrome were 34 (possible) for one affected individual [Lopes et al 2002] and 41 (probable) in another [Hershkovitz et al 2006].

Pulmonary Manifestations

Asthma-like chronic reactive airway disease has been described in approximately 7% of affected individuals.

Other forms of chronic pulmonary disease occasionally seen:

- Bronchiectasis, chronic lipoid pneumonia, and a cystic fibrosis-like phenotype with elevated sweat chloride and transepithelial potential difference. One man developed severe progressive restrictive lung disease at age 45 years [Luder et al 2007].
- Progressive lung disease with chest CT findings of mainly cystic lung lesions and ground glass opacity in a Druze woman age 24 years [Butbul Aviel et al 2012]. She experienced further deterioration in her pulmonary function and secondary pulmonary hypertension and became oxygen dependent.
- Pulmonary hypertension requiring supplemental oxygen in an Amish child age six years [Kelly et al 2010]
- Pulmonary fibrosis with pulmonary capillaritis and cystic lung changes in two individuals age five years [Rayment et al 2019] and 22 years, respectively. The latter individual required oxygen therapy by age 33 years [Cottin et al 2020].

Autoimmune Disorders and Systemic Lupus Erythematosus-Like Findings

About one fifth of individuals with prolidase deficiency develop an autoimmune disorder. Various manifestations of these disorders may comprise arthritis, nephritis, pericarditis, cytopenias, mouth ulcers, malar rash, and hypocomplementemia (low C3, C4, and CH50 levels).

The most common autoimmune disorder associated with prolidase deficiency is systemic lupus erythematosus (SLE), although not all individuals fulfill the American College of Rheumatology criteria for a diagnosis of SLE.

- Reported positive markers include rheumatoid factor, antinuclear antibodies, ANCA, anti-dsDNA, anti-cardiolipin, anti-SSA/Ro, anti-SSB/La, anti-chromatin, anti-RNP, and/or anti-Sm antibodies.
- A couple of cases of cryoglobulinemia have been reported [Marotte et al 2010, Cottin et al 2020].
- Sometimes, these antibodies have been reported in the absence of SLE-like clinical findings [Kurien et al 2013].

Other autoimmune conditions may include:

- Autoimmune arthritis, including psoriatic arthritis or juvenile idiopathic arthritis
- Vasculitis, including central nervous system vasculitis

- Rhupus (a condition in which individuals have features of both rheumatoid arthritis and SLE, often in a sequential manner)
- Coombs-positive hemolytic anemia
- Crohn-like disease
- Autoimmune adrenal failure (in one affected individual) [Luder et al 2007]

Bone/Limb Manifestations

Among 12 affected individuals reported by Besio et al [2015], short stature was described in seven, osteopenia in six, and genu valgum in four. Joint laxity has been described in more than a dozen affected individuals. Some limb deformities have been reported to be secondary to complications of severe ulceration, particularly in the lower limbs. Talipes equinovarus was noted in early reported cases and may be a secondary finding. Digital clubbing, in the presence or absence of pulmonary abnormalities, has been reported in up to 7% of affected individuals [Luder et al 2007, Kelly et al 2010].

Other primary bone/limb findings (reported in a few cases each) include:

- Spina bifida of C3 and 13 thoracic vertebrae [Freij et al 1984]
- Fusion of C2 and C3 [Lacarbonara et al 2014]
- Delayed bone age [Pedersen at al 1983, Lacarbonara et al 2014]
- Syndactyly of the hands and/or feet
- Pes planus
- Pes cavus
- Short fingers / brachydactyly
- Arachnodactyly

Other Manifestations

Ocular abnormalities have been found in approximately 15% of affected individuals and include varied phenomena including optic and chorioretinal atrophy in two individuals [Ogata et al 1981] and keratitis [Ogata et al 1981, Freij et al 1984, Andry et al 1992].

Dental abnormalities were present in more than 20 affected individuals. Dental findings have included multiple caries with or without enamel hypoplasia, misaligned teeth, and hypodontia.

Diarrhea has been reported in 19 affected individuals, even in the absence of Crohn-like inflammatory bowel disease (reported in only 5 individuals).

Both poor weight gain (14%) and short stature (12%) as well as overweight/obesity (9%) have been reported.

Prognosis

The severity of prolidase deficiency is quite variable: in some individuals skin ulcerations lead to amputation of one or all toes, whereas others remain entirely asymptomatic [Isemura et al 1979, Hechtman 2001, Lupi et al 2006]. Most individuals will have developed some symptoms (albeit sometimes mild) of prolidase deficiency by age four years and 90% by age 14 years.

In many instances, however, individuals with prolidase deficiency experience severe morbidity and sometimes early death, usually as a result of infection or respiratory failure. The youngest reported death was at age three months [Shrinath et al 1997]. A review by Rossignol et al [2021] estimated a survival of 90% by age 20 years and 82% by age 40 years.

Genotype-Phenotype Correlations

In general, individuals with biallelic loss-of-function pathogenic variants in *PEPD* are more likely to develop ulcers and have an earlier age of onset than individuals with biallelic pathogenic missense variants [Rossignol et al 2021].

- By age 20 years, 100% of individuals with loss-of-function pathogenic variants reported ulcers, whereas fewer than 50% of individuals with biallelic pathogenic missense variants reported having ulcers by this age.
- However, marked phenotypic variability has been found among affected individuals even from the same family (who have the same pathogenic variants) [Falik-Zaccai et al 2010].

Nomenclature

Prolidase deficiency was also known as hyperimidodipeptiduria, although increased excretion of imidodipeptides is not exclusive to prolidase deficiency. Other names used in the past include imidodipeptidase deficiency and peptidase D deficiency.

Prevalence

Approximately 175 affected individuals have been reported in the literature; however, prolidase deficiency likely remains underdiagnosed as a result of underrecognition by physicians.

The Québec Newborn Urine Screening Program (Programme québécois de dépistage neonatal urinaire, PQDNU) identified two affected infants out of 2,469,929 screened between 1973 and 2006, for an incidence of 1:1,235,000 [Renaud & Dagenais 2009]. Thus, a few thousand cases would be predicted to exist worldwide, as opposed to only about 175 cases reported to date.

Prolidase deficiency has been diagnosed throughout the world [Lupi et al 2008].

A founder variant has been described in the Geauga County Amish settlement in Ohio [Wang et al 2006], as well as in the Druze (carrier frequency 1:21) and Arab Muslim populations in northern Israel [Falik-Zaccai et al 2008] (see Molecular Genetics).

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PEPD*.

Differential Diagnosis

Disorders with imidodipeptiduria. Imidodipeptiduria has been described in bone disorders, presumably originating from collagen under conditions of high bone turnover [Seakins 1963, Scriver 1964, Alderman et al 1969, Cahill et al 1970].

Genetic disorders with skin ulcers and/or hyper IgE. See Table 3.

Table 3. Genetic Disorders with Skin Ulcers and/or Immune Deficiency in the Differential Diagnosis of Prolidase Deficiency

Gene	DiffDx Disorder	MOI	Key Features of DiffDx Disorder	Distinguishing Features
DOCK8	DOCK8 deficiency (*DOCK8* AR HIES) (OMIM 243700)	AR	Primary immune deficiency syndrome characterized by ↑ serum concentration of IgE, severe eczema, & recurrent skin & lung infections, all of which can also be seen in prolidase deficiency.	In *DOCK8*-HIES: ↑ incidence of neurologic abnormalities, ↑ occurrence of viral infections of skin (e.g., *Molluscum contagiosum*, warts) & virus-driven malignancies. Note: Nonimmunologic findings of *STAT3*-HIES (e.g., connective tissue, skeletal, & dental involvement) are absent in *DOCK8*-HIES. [1]
HBB	Sickle cell disease (SCD)	AR	Intermittent vaso-occlusive events & chronic hemolytic anemia. Persons w/highest rates of hemolysis are predisposed to leg ulcers.	In SCD: While urinary excretion of hydroxyproline has been significantly ↑ in persons w/SCD compared to controls [2] (presumably due to bone involvement), glycylprolinuria has not been reported. More importantly, although persons w/ prolidase deficiency can have mild findings of hemolysis, they do not have veno-occlusive episodes.
HBB	Beta-thalassemia	AR	↓ synthesis of hemoglobin subunit beta that → ↓ amounts of hemoglobin A, microcytic hypochromic anemia, & abnormal peripheral blood smear w/nucleated red blood cells. Leg ulcers are reported in untreated or poorly transfused persons w/beta-thalassemia.	Imidopeptiduria is not known to occur in beta-thalassemia. Persons w/prolidase deficiency should have normal hemoglobin electrophoretic pattern.
STAT3	*STAT3* hyper IgE syndrome (*STAT3*-HIES)	AD	Primary immune deficiency syndrome characterized by ↑ serum IgE, eczema, & recurrent skin & respiratory tract infections, together w/nonimmune features. *STAT3*-HIES typically manifests in newborn period w/rash (often diagnosed as eosinophilic pustulosis) that subsequently evolves into eczematoid dermatitis.	Mucocutaneous candidiasis is frequent in *STAT3*-HIES, but not commonly reported in prolidase deficiency. Retention of primary teeth & bone fractures following minimal trauma are also distinguishing features of *STAT3*-HIES.
WRN	Werner syndrome	AR	Cancer predisposition & premature appearance of features assoc w/normal aging. Findings shared by prolidase deficiency & Werner syndrome: chronic lower-extremity ulcers, premature graying of hair, & "bird-like" facial appearance.	Imidodipeptiduria has not been reported in Werner syndrome.

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; HIES = hyper IgE syndrome; MOI = mode of inheritance

1. Renner et al [2004]

2. Mohammed et al [1991]

Acquired causes of lower-extremity ulcers include arterial insufficiency, venous insufficiency, pressure ulcers, vasculitis, systemic lupus erythematosus, and infectious etiologies, among others. Although glycineprolinuria could be anticipated in cases of secondary skin ulcers given the high content of collagen in the dermis, a number of individuals with extensive skin ulceration have been tested, and imidodipeptiduria was only found when accompanied by severe concurrent bone disease (e.g., multiple fractures) [Sheffield et al 1977].

Management

No clinical practice guidelines for prolidase deficiency have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with prolidase deficiency, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Prolidase Deficiency

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	To assess for abnormal growth, short stature, & microcephaly
Skin	Full skin exam	Consider consultation w/wound care specialist.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurologic	Neurologic eval	• Consider brain MRI if clinically indicated. • Consider EEG if seizures are a concern.
Gastrointestinal	Physical exam to assess for hepatosplenomegaly	If present, perform abdominal ultrasound to assess extent.
	Measurement of liver enzymes (AST/ALT)	To assess for elevation
Hematologic	Complete blood count	To assess for anemia & thrombocytopenia
Immunologic	Quantitative immunoglobulins	To assess for hyperimmunoglobulinemia
	Consider eval for autoimmune condition in presence of consistent clinical signs/ symptoms.	Consider referral to rheumatologist.
Pulmonary/ Cardiac	Assess for any pulmonary issues.	If present, consider: • Chest imaging, including chest x-ray; • Pulmonary function tests; • Echocardiogram to assess for pulmonary hypertension.
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
	Bone health assessment should be considered on individual basis.	May incl lab studies (e.g., serum calcium, phosphorus, alkaline phosphatase, vitamin D levels) &/or imaging (e.g., DXA scan)
Eyes	Ophthalmologic eval	To assess for BCVA, refractive errors, optic nerve abnormalities, & more complex findings that may require subspecialty referral.
ENT/Mouth	Dental eval	For dental anomalies (in those whose teeth have erupted)
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of prolidase deficiency to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ALT = alanine transaminase; AST = aspartate aminotransferase; BCVA = best corrected visual acuity; DXA = dual-energy x-ray absorptiometry; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Care is preferably provided by a multidisciplinary team.

Table 5. Treatment of Manifestations in Individuals with Prolidase Deficiency

Manifestation/Concern	Treatment	Considerations/Other
Skin ulcers [1]	Standard treatment by wound care specialist	
	Topical proline (often 5%) ointment w/liquid paraffin applied w/dressing changes	Treatment successful in some affected persons [2]
	Topical 5% proline-5% glycine ointment applied thickly 1x/day w/dressing gauze & bandage	Treatment successful in some affected persons [3]
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	No ASM has been demonstrated effective specifically for this disorder.
Hepatosplenomegaly	No specific treatment is typically available.	Avoid contact sports.
Anemia/ Thrombocytopenia	Given mild nature of these findings, treatment is rarely required.	• Consider PRBC transfusion in those w/ severe anemia. • Consider platelet transfusion in those w/severe thrombocytopenia or low platelet counts who require any (incl dental) surgical procedures.
Infections	Standard therapy depending on type & degree of infection	Infections should be treated aggressively, as they can be fulminant & fatal.
Reactive airway disease / Restrictive lung disease	Standard treatment per pulmonologist	
Pulmonary hypertension		
SLE / SLE-like symptoms	Standard treatment per rheumatologist	Treatment of underlying autoimmune disorders has anecdotally been reported to improve ulcer healing. [4]
HLH	Standard treatment per hematologist	See also Familial Hemophagocytic Lymphohistiocytosis.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Mast cell activation	Standard treatment per allergist/ immunologist	
Osteopenia	Standard treatment per endocrinologist	
Ophthalmologic involvement	Standard treatment per ophthalmologist	Treatment of refractive errors
Dental anomalies	Standard treatment per dentist/orthodontist	
Family/Community	• Ensure appropriate social work involvement to connect families w/ local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	Ongoing assessment of need for palliative care involvement &/or home nursing

ASM = anti-seizure medication, DD = developmental delay; HLH = hemophagocytic lymphohistiocytosis; ID = intellectual disability; SLE = systemic lupus erythematosus
1. Many therapies have been tried but few are successful. Oral proline supplementation has not been successful. For a full list of treatments that have been trialed (with partial success in some), click here (pdf).
2. Jemec & Moe [1996], Dunn & Dolianitis [2008], Karthikeyan et al [2019]
3. Arata et al [1986], Jemec & Moe [1996]
4. Razmi et al [2020], Sato et al [2020]

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected

individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Prevention of Secondary Complications

Those who have undergone splenectomy should be appropriately immunized and treated promptly with antibiotics at the first sign of infection.

Antibiotic prophylaxis should also be considered in the appropriate setting.

Surveillance

Table 6. Recommended Surveillance for Individuals with Prolidase Deficiency

System/Concern	Evaluation	Frequency
Constitutional	Measurement of growth parameters	At each visit
Development	Monitor developmental progress & educational needs.	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations incl seizures, changes in tone, & mvmt disorders.	
Pulmonary	Monitor for evidence of respiratory insufficiency.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
ENT/Mouth	Dental eval	Every 6 mos after tooth eruption

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Gastrointestinal	• Liver function tests • Abdominal ultrasound exam to assess liver & spleen size	Annually
Skin	Skin exam for evidence of malignant transformation in persons w/chronic recalcitrant skin ulcers	
Hematologic/ Immunologic	Complete blood count	
Eyes	Ophthalmology eval	Annually or as clinically indicated
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Individuals with prolidase deficiency who have splenomegaly should avoid contact sports given the increased risk for splenic rupture.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Adenovirus-mediated gene transfer. Ikeda et al [1997] performed transfer of the human prolidase cDNA into fibroblasts from individuals with prolidase deficiency. This increased the fibroblast prolidase activity up to 75 times normal.

Intracellular delivery of liposome-encapsulated prolidase. Perugini et al [2005] showed that active prolidase encapsulated in liposomes was completely transported via endocytosis into fibroblasts six days after incubation.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Prolidase deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *PEPD* pathogenic variant.

- If a molecular diagnosis has been established in the proband, genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *PEPD* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *PEPD* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of inheriting neither of the familial *PEPD* pathogenic variants.
- Significant clinical variability may be observed between sibs with the same *PEPD* pathogenic variants (see Genotype-Phenotype Correlations).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has prolidase deficiency or is a carrier (see Related Genetic Counseling Issues, **Family planning**), offspring will be obligate heterozygotes for a pathogenic variant in *PEPD*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *PEPD* pathogenic variant.

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *PEPD* pathogenic variants in the family.

Note: Urine amino acid analysis of carriers for detection of imidodipeptiduria is uninformative.

Related Genetic Counseling Issues

Family planning

- A high carrier rate for prolidase deficiency exists in certain populations, increasing the risk that an affected individual may have a reproductive partner who is heterozygous (see Prevalence). The offspring of such an individual and a proband are at 50% risk of being affected and 50% risk of being obligate heterozygotes.
- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from

probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *PEPD* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for prolidase deficiency are possible.

Biochemical genetic testing. Measurement of prolidase activity in amniocytes has been used for prenatal diagnosis [Mandel et al 2000]; however, molecular genetic testing is the preferred method if both *PEPD* pathogenic variants in an affected family member are known.

Note: Results of prenatal testing cannot be used to predict age of onset or clinical course. Severity of the condition can vary among affected individuals within the same family.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Prolidase deficiency
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  www.metabolicsupportuk.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Prolidase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
PEPD	19q13.11	Xaa-Pro dipeptidase	PEPD	PEPD

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Prolidase Deficiency (View All in OMIM)

170100	PROLIDASE DEFICIENCY
613230	PEPTIDASE D; PEPD

Molecular Pathogenesis

Prolidase contains 493 amino acids. It is a homodimer, with each subunit binding two manganese ions that are required for full enzymatic activity. The enzyme is required in the final catabolic steps of endogenous and dietary proteins, as it cleaves proline or hydroxyproline when these amino acids are in the C-terminal position. It is thus particularly important in the metabolism of proteins rich in proline and hydroxyproline, such as collagen. The deficiency of prolidase leads to accumulation of imidodipeptides, or peptides with two amino acids, with a C-terminal proline or hydroxyproline.

Several pathophysiologic hypotheses have been proposed, many involving abnormal collagen recycling or complement abnormalities. Prolidase is released from damaged cells and has some roles in the regulation of transforming growth factor beta, hypoxia-induced factor 1-alpha, and epidermal growth factor receptor. Both the imidodipeptidase activity and non-enzymatic roles of prolidase may be responsible for the findings.

Mechanism of disease causation. Loss of function

Table 7. Notable *PEPD* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_000285.4 NP_000276.2	c.605C>T	p.Ser202Phe	Most common pathogenic variant in Druze & Arab Muslim persons from northern Israel [Falik-Zaccai et al 2010]
	c.793C>T	p.Arg265Ter	Founder variant in Amish from Geauga County, OH [Wang et al 2006]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Revision History

- 7 July 2022 (ma) Comprehensive update posted live
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