U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Erwin A, Balwani M, Desnick RJ; Porphyrias Consortium of the NIH-Sponsored Rare Diseases Clinical Research Network. Congenital Erythropoietic Porphyria. 2013 Sep 12 [Updated 2021 Apr 15]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Congenital Erythropoietic Porphyria

Synonym: Günther Disease

Angelika Erwin, MD, PhD,[1] Manisha Balwani, MD, MS,[2] and Robert J Desnick, MD, PhD, FACMG;[2] Porphyrias Consortium of the NIH-Sponsored Rare Diseases Clinical Research Network*

Created: September 12, 2013; Updated: April 15, 2021.

Summary

Clinical characteristics

Congenital erythropoietic porphyria (CEP) is characterized in most individuals by severe cutaneous photosensitivity with blistering and increased friability of the skin over light-exposed areas. Onset in most affected individuals occurs at birth or early infancy. The first manifestation is often pink-to-dark red discoloration of the urine. Hemolytic anemia is common and can range from mild to severe, with some affected individuals requiring chronic blood transfusions. Porphyrin deposition may lead to corneal ulcers and scarring, reddish-brown discoloration of the teeth (erythrodontia), and bone loss and/or expansion of the bone marrow. The phenotypic spectrum, however, is broad and ranges from nonimmune hydrops fetalis in utero to late-onset disease with only mild cutaneous manifestations in adulthood.

Diagnosis/testing

The diagnosis of CEP in a proband with suggestive clinical and biochemical findings is most commonly established by identification of biallelic pathogenic variants in *UROS*, and – on rare occasion – by identification of a hemizygous pathogenic variant in the X-linked gene *GATA1*.

Management

Treatment of manifestations: There is no FDA-approved treatment for CEP or specific treatment for the photosensitivity. Currently, the only effective management is prevention of blistering by avoidance of sun and light exposure, including the long-wave ultraviolet light that passes through window glass or is emitted from artificial light sources. Therefore, the use of protective clothing, wraparound sunglasses, protective window films, reddish incandescent bulbs, filtering screens for fluorescent lights, and opaque sunscreens containing zinc oxide

Author Affiliations: 1 Cleveland Clinic Cleveland, Ohio; Email: erwina@ccf.org. 2 Icahn School of Medicine at Mount Sinai New York, New York; Email: manisha.balwani@mssm.edu; Email: robert.desnick@mssm.edu.

* See Chapter Notes, Acknowledgments.

or titanium oxide is recommended. Wound care is necessary to prevent infection of opened blisters; surgical intervention may be necessary; blood transfusions are necessary when hemolysis is significant. Bone marrow transplantation (BMT) is the only cure for CEP and should be considered in children with severe cutaneous and hematologic involvement.

Surveillance: Monitor hematologic indices to assess hemolysis every six months. In those receiving transfusions, monitor for hemolysis more frequently and for iron overload. Monitor hepatic function and vitamin D 25-OH every six to twelve months in all affected individuals.

Agents/circumstances to avoid: All affected individuals: avoid sunlight and UV light. In those with hepatic dysfunction: avoid drugs that may induce cholestasis.

Evaluation of relatives at risk: It is appropriate to evaluate at-risk sibs as newborns or infants in order to identify as early as possible those who would benefit from early intervention (no phototherapy, strict sun protection) and future monitoring for signs of hemolytic anemia.

Pregnancy management: Protective filters for artificial lights should be used in the delivery/operating room to prevent phototoxic damage to a mother with CEP during delivery.

Genetic counseling

CEP caused by biallelic *UROS* pathogenic variants is inherited in an autosomal recessive (AR) manner. CEP caused by a hemizygous *GATA1* pathogenic variant is inherited in an X-linked (XL) manner.

- **AR CEP.** 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. Heterozygotes (carriers) are asymptomatic.
- **XL CEP.** If the mother of an affected male is heterozygous for a *GATA1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and can be either asymptomatic or have a milder phenotype.
- **Both AR and XL CEP.** Once the pathogenic variant(s) in the family have been identified, carrier testing for at-risk family members, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for congenital erythropoietic porphyria (CEP) have been published.

Suggestive Findings

Congenital erythropoietic porphyria (CEP) **should be suspected** in individuals with the following clinical and laboratory findings and family history.

Clinical findings

- Nonimmune hydrops fetalis
- Signs of congenital erythropoietic porphyria
  - Pink-to-dark red discoloration of the urine (pink or dark red urine-stained diapers are often the first sign in infants)
  - Hemolytic anemia
  - Severe cutaneous photosensitivity with onset usually in infancy or early childhood
  - Blisters and vesicles in light-exposed areas, which are prone to rupture and infection

- Scarring and deformities (photomutilation) of digits and facial features, caused by recurrent blistering, infections, and bone resorption
- In light-exposed areas: friable skin, skin thickening, hypo- and hyperpigmentation
- Reddish-brown discoloration of teeth (fluoresce on exposure to long-wave ultraviolet light), also called erythrodontia
- Corneal ulcers and scarring
- Hypertrichosis of the face and extremities

Laboratory findings include markedly increased levels of uroporphyrin I and coproporphyrin I isomers in erythrocytes, urine, or amniotic fluid as well as coproporphyrin I in stool (see Table 1).

Table 1. Biochemical Characteristics of Congenital Erythropoietic Porphyria

Enzyme Defect	Enzyme Activity [1]	Tissue	Uroporphyrin [1]	Coproporphyrin [1]
Uroporphyrinogen III synthase (URO-synthase) [2]	Undetectable to ~10% of normal mean activity in erythrocytes	Erythrocytes	↑	↑
		Urine	↑	↑
		Stool		↑
		Amniotic fluid [3]	↑	↑

↑ = markedly elevated

1. The deficient activity of uroporphyrinogen III synthase EC 4.2.1.75, encoded by *UROS*, results in non-enzymatic conversion of hydroxymethylbilane to uroporphyrinogen I, which is then metabolized to coproporphyrinogen I. Coproporphyrinogen I cannot be metabolized further. These metabolites are then oxidized to uroporphyrin I and coproporphyrin I, respectively, which are non-physiologic and pathogenic.

2. The assay for the enzyme uroporphyrinogen III synthase is available on a clinical basis and can be used to establish the diagnosis of congenital erythropoietic porphyria.

3. Amniotic fluid appears red to dark brown. Prenatal diagnosis is also possible by demonstrating markedly deficient URO-synthase activity in cultured amniotic cells or chorionic villi cells [Daïkha-Dahmane et al 2001].

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity) or, rarely, X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of CEP **is established** by biochemical testing, which shows marked elevation of the uroporphyrin and coproporphyrin I isomers (see Table 1), and should be confirmed by molecular genetic testing for biallelic *UROS* pathogenic variants. On rare occasion, a hemizygous pathogenic variant in the X-linked gene *GATA1* can be identified [Phillips et al 2007] (see Table 2).

Note:

- In the absence of biochemical or enzymatic testing results, identification of biallelic *UROS* variants of uncertain significance (or identification of one known *UROS* pathogenic variant and one *UROS* variant of uncertain significance) does not establish or rule out a diagnosis autosomal recessive CEP.
- If the diagnosis cannot be established by molecular genetic testing, the findings of reduced URO-synthase activity in erythrocytes and markedly elevated urinary or erythrocyte uroporphyrin and coproporphyrin I isomers (Table 1) confirm the diagnosis and indicate that the variants of uncertain significance may be pathogenic.
- Identification of a hemizygous *GATA1* variant of uncertain significance does not establish or rule out a diagnosis of X-linked CEP.

Molecular genetic testing approaches can include **gene-targeted testing** (single gene or multigene panel) or **comprehensive genomic testing** (exome sequencing, genome sequencing).

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 CEP has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

A multigene panel such as a comprehensive porphyrias panel that includes *UROS*, *GATA1*, and other genes of interest (see Differential Diagnosis) may be considered. 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*; thus, clinicians need to determine which multigene panel 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. (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

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 2. Molecular Genetic Testing Used in Congenital Erythropoietic Porphyria

Gene [1]	Proportion of CEP Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detected by Method	
		Sequence analysis [3]	Gene-targeted deletion/duplication analysis [4]
UROS	>98% [5]	~90% [5]	~10% [6]
GATA1	~1% [7]	100%	None reported

CEP = congenital erythropoietic porphyria

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in these genes.

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. 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.

5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

6. Two gross deletions, two gross duplications, and one complex rearrangement have been reported [Boulechfar et al 1992, Shady et al 2002, Katugampola et al 2012a].

7. A *GATA1* pathogenic variant (c.646C>T [p.Arg216Trp]) was identified in three unrelated individuals with CEP and hematologic abnormalities [Phillips et al 2007, Di Pierro et al 2015].

Clinical Characteristics

Clinical Description

Most individuals with congenital erythropoietic porphyria (CEP) experience severe cutaneous photosensitivity in early infancy; the first manifestation is often pink-to-dark red discoloration of the urine. Hemolytic anemia is common and can be mild to severe, requiring chronic erythrocyte transfusions in some. The phenotypic spectrum ranges from severe (nonimmune hydrops fetalis) to milder disease (adult-onset with isolated cutaneous manifestations) [Warner et al 1992]. (See Genotype-Phenotype Correlations for variants that correlate with disease severity.)

Skin. Cutaneous photosensitivity is present at birth or in early infancy and is characterized by blistering and increased friability of the skin over light-exposed areas. Bullae and vesicles are filled with serous fluid and are prone to rupture. Secondary infections with scarring and bone resorption (photomutilation) may lead to deformity and disfigurement of fingers, toes, and facial features including the nose, ears, and eyelids. Skin thickening, focal hyper- or hypopigmentation, and hypertrichosis of face and extremities may occur [Poh-Fitzpatrick 1986].

Photosensitivity symptoms are provoked mainly by visible light (400-410 nm Soret wavelength) and to a lesser degree by wavelengths in the long-wave UV region. Affected individuals are also sensitive to sunlight that passes through window glass that does not filter long-wave UVA or visible light as well as to light from artificial light sources.

Unlike the cutaneous manifestations in erythropoietic protoporphyria (EPP), manifestations such as tingling, burning, itching, or swelling usually do not occur in persons with CEP after light exposure.

Hemolytic anemia. Mild-to-severe hemolytic anemia with anisocytosis, poikilocytosis, polychromasia, basophilic stippling, and reticulocytosis is common in CEP. Findings also include the absence of haptoglobin, increased unconjugated bilirubin, and increased fecal urobilinogen [Schmid et al 1955]. Hemolysis presumably results from the accumulation of uroporphyrinogen I in the erythrocytes [Bishop et al 2006].

Those with severe hemolytic anemia often require chronic erythrocyte transfusions, which decrease porphyrin production by suppressing erythropoiesis, but can lead to iron overload and other complications [Piomelli et al 1986].

Secondary splenomegaly may develop as a consequence of hemolytic anemia. In addition to worsening the anemia, it can also result in leukopenia and thrombocytopenia, which may be associated with significant bleeding [Pain et al 1975, Weston et al 1978, Phillips et al 2007].

Ophthalmologic involvement. Deposition of porphyrins may lead to corneal ulcers and scarring, which can ultimately lead to blindness. Other ocular manifestations can include scleral necrosis, necrotizing scleritis, seborrheic blepharitis, keratoconjunctivitis, sclerokeratitis, and ectropion [Oguz et al 1993, Venkatesh et al 2000, Siddique et al 2011].

Erythrodontia. Porphyrin deposition in the teeth produces a reddish-brown color, termed erythrodontia. The teeth may fluoresce on exposure to long-wave ultraviolet light.

Bone involvement. Deposition of porphyrins in bone causes bone loss (osteopenia on x-ray) due to demineralization [Piomelli et al 1986, Laorr & Greenspan 1994, Fritsch et al 1997, Kontos et al 2003]. It can also cause expansion of the bone marrow, which can lead to hyperplastic bone marrow observed on biopsy [Poh-Fitzpatrick 1986, Anderson et al 2001].

Vitamin D deficiency. Individuals with CEP who avoid sunlight are at risk for vitamin D deficiency.

Genotype-Phenotype Correlations

The genotype-phenotype correlations that have been established in CEP are largely determined by the amount of residual enzyme activity encoded by the specific pathogenic variants (Table 5).

UROS. The most common *UROS* pathogenic variant, c.217T>C (p.Cys73Arg), is observed in about one third of individuals with CEP.

- Homozygosity for the c.217T>C (p.Cys73Arg) variant results in less than 1% of normal URO-synthase activity and a severe phenotype that may manifest as nonimmune hydrops fetalis [Frank et al 1998, Desnick & Astrin 2002].
- Compound heterozygosity for the c.217T>C (p.Cys73Arg) variant and a pathogenic variant that expresses a very low level of residual activity results in a severe or moderately severe phenotype.

In contrast, individuals with pathogenic variants expressing higher residual activities such as c.244G>T (p.Val82Phe) (35% of normal activity in vitro), c.311C>T (p.Ala104Val) (7.7% of normal activity in vitro), and c.197C>T (p.Ala66Val) (14.5% of normal activity in vitro) have milder phenotypes even if heteroallelic for c.217T>C (p.Cys73Arg) or another pathogenic variant with very low or almost absent residual enzyme activity [Desnick & Astrin 2002].

Determination of genotype-phenotype correlations for erythroid-specific promoter pathogenic variants showed the following:

- Compound heterozygotes with the c.-203T>C variant (2.9% of normal activity in vitro) in combination with the c.217T>C (p.Cys73Arg)table4 variant led to nonimmune hydrops fetalis [Solis et al 2001].
- The c.-223C>A variant (8.3% of normal activity in vitro) when in compound heterozygosity with another variant with low residual enzyme activity (c.673G>A [p.Gly225Ser]), 1.2% of normal activity in vitro) led to a moderately severe phenotype in one individual [Solis et al 2001].
- The two other known erythrocyte-specific promoter pathogenic variants, c.-209G>A and c.-219C>A, with high residual activities (53.9% and 43.4% of normal in vitro, respectively) in individuals in whom the second variant was c.217T>C (p.Cys73Arg), led to mild cutaneous disease [Desnick & Astrin 2002].

GATA1. The c.646C>T (p.Arg216Trp) pathogenic variant is predicted to dramatically alter the binding of GATA1 to URO-synthase, resulting in significantly reduced (~20% of normal) URO-synthase activity [Phillips et al 2007].

Nomenclature

Obsolete terms for CEP are erythropoietic porphyria, congenital porphyria, congenital hematoporphyria, and erythropoietic uroporphyria.

Prevalence

CEP is an ultra-rare disorder. To date, about 220 affected individuals have been reported.

Genetically Related (Allelic) Disorders

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

GATA1. Pathogenic variants in this gene are also observed in:

- *GATA1*-related X-linked cytopenia;
- Diamond-Blackfan anemia.

Differential Diagnosis

See Table 3 for other disorders that present with a congenital erythropoietic porphyria (CEP)-like phenotype.

Table 3. Disorders to Consider in the Differential Diagnosis of Congenital Erythropoietic Porphyria

Disease Name	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
Porphyria cutanea tarda (PCT) type I (OMIM 176090)	See footnote 1.		• Cutaneous photosensitivity w/blistering & friability of skin in sun-exposed areas • Facial hypertrichosis • Discolored urine	• Usually manifests in adulthood • Distinct biochemical porphyrin profile
Porphyria cutanea tarda (PCT) type II	*UROD*	AD		
Hepato-erythropoietic porphyria	*UROD*	AR	• Phenotype similar to PCT • Manifests in early childhood • Discolored urine • Photosensitivity	• Distinct biochemical porphyrin profile • Developmental delay (in some)
Hereditary coproporphyria	*CPOX*	AD	20% of affected persons experience photosensitivity w/skin blistering in sun-exposed areas.	• Acute (hepatic) porphyria • Acute attacks of abdominal or generalized pain; can be assoc w/ neurologic symptoms • Incompletely penetrant in absence of environmental inducers • Usually manifests after puberty
Variegate porphyria	*PPOX*	AD		
Myeloid malignancy			Elderly adults w/myelodysplastic syndrome may exhibit features of CEP. [2, 3]	
Epidermolysis bullosa simplex (EBS)	*KRT5* *KRT14*	AD [4]	• Fragility of skin → nonscarring blisters caused by little/no trauma • Major & minor subtypes share common feature of blistering above dermal-epidermal junction at the ultrastructural level.	
Junctional epidermolysis bullosa (JEB)	*LAMA3* *LAMB3* *LAMC2* *COL17A1*	AR	• Fragility of skin & mucous membranes, manifest by blistering w/little or no trauma • Herlitz JEB (classic severe form): blisters present at birth or become apparent in neonatal period • Non-Herlitz JEB: may be mild w/blistering localized to hands, feet, knees, elbows	

Table 3. continued from previous page.

Disease Name	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
Dystrophic epidermolysis bullosa	*COL7A1*	AR	• Blisters affecting whole body may be present in neonatal period. • Oral involvement • Corneal erosions	• Esophageal erosions • Severe nutritional deficiency & secondary problems • "Mitten" hands & feet • >90% lifetime risk of aggressive squamous cell carcinoma
		AD	Blistering, often mild & limited to hands, feet, knees, elbows; heals w/ scarring	Dystrophic nails possibly the only manifestation

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance

1. 80% of persons with porphyria cutanea tarda (PCT) have type I PCT (also referred to as acquired or "sporadic" PCT because it is not known to be associated with an inherited genetic alteration). Type I PCT is characterized by normal URO-decarboxylase activity systemically when affected individuals are asymptomatic. Inhibition of the enzyme activity resulting in PCT can be caused by excessive alcohol intake, hemochromatosis, viral hepatitis (mostly hepatitis C), HIV infection, certain medications, and environmental exposures such as aromatic polyhalogenated hepatotoxins. Treatment consists of eliminating or treating the underlying cause and, if symptoms persist, frequent phlebotomies or therapy with oral low-dose hydroxychloroquine.

2. Fritsch et al [1997], Kontos et al [2003], Sarkany et al [2011]

3. Affected individuals had normal erythrocyte URO-synthase activity. Presumably, the CEP-like manifestations resulted from genetic or functional changes associated with the bone marrow disorder.

4. EBS caused by pathogenic variants in *KRT5* or *KRT14* is usually inherited in an autosomal dominant manner; in rare families, especially those with consanguinity, it can be inherited in an autosomal recessive manner.

Management

A management algorithm for congenital erythropoietic porphyria (CEP) has been published [Katugampola et al 2012a].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with congenital erythropoietic porphyria (CEP), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Hematologic indices including reticulocytes and bilirubin (to assess hemolysis) and iron profile (to assess iron storage)
- Serum calcium and vitamin D concentrations; bone densitometry
- Hepatic function tests, especially in transfusion-dependent individuals given the risk for liver disease due to iron storage
- Dermatologic evaluation to assess photosensitivity, photomutilation, and secondary skin changes (thickening, hyper- or hypopigmentation, hypertrichosis)
- Ophthalmologic evaluation for corneal ulcers and scarring and other ocular manifestations
- Dental assessment for erythrodontia (reddish-brown color from porphyrin deposition)
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse to inform affected individuals and their families about the nature, mode of inheritance, and implications of CEP in order to facilitate medical and personal decision making

Treatment of Manifestations

Cutaneous photosensitivity. There is no FDA-approved treatment for this disease or specific treatment for the photosensitivity.

Currently the only effective treatment is prevention of blistering by avoidance of light exposure, including the long-wave ultraviolet sunlight that passes through window glass or light emitted by fluorescent sources:

- Sun protection using protective clothing including long sleeves, gloves, and wide-brimmed hats
- Protective window films for cars and windows at home as well as at school/work to prevent exposure to UV light
- Replacement of LED and fluorescent lights with reddish incandescent bulbs or installation of filtering screens
- Reflectant sunscreens containing zinc oxide or titanium dioxide. Note, however, that these may be cosmetically unacceptable and, in any case, do not replace strict avoidance of sun/light exposure.

Skin trauma should be avoided.

Wound care is essential to prevent infection of opened blisters. Antiseptic and topical/oral antibiotic treatment may be indicated to avoid progression to osteomyelitis and bone resorption with subsequent mutilation.

Surgical intervention may be indicated for severe mutilation (repair of microstomia, correction of ectropion, reconstruction of the nose).

Laser hair removal can be used to treat facial hypertrichosis.

Vitamin D supplementation is advised as affected individuals are predisposed to vitamin D insufficiency due to sun avoidance.

Immunization for hepatitis A and B is recommended.

Note: (1) Beta-carotene has been tried in some individuals but without significant benefit. (2) Phototherapy with narrowband ultraviolet B radiation did not show any benefit.

Ocular manifestations

- Avoidance of damage to the eyelids and cornea by wearing wraparound sunglasses
- Topical antibiotics for corneal ulcers, scleritis, and blepharitis
- Artificial tears and lubricants to help prevent dry eyes in those with ectropion
- Corrective surgery of eyelids to help protect the cornea from injury in those with ectropion [Katugampola et al 2012a]

Bone manifestations. Bisphosphonates can be considered in individuals with osteoporosis [Katugampola et al 2012a].

Hemolytic anemia

- Consider frozen matched-erythrocyte transfusions when hemolysis is significant, or bone marrow transplantation
- Chronic transfusions (every 2-4 weeks) with a target hematocrit greater than 35% can suppress erythropoiesis and decrease porphyrin production, which reduces porphyrin levels and photosensitivity [Piomelli et al 1986].
- Note: In those who receive frequent transfusions, the body iron burden can be reduced with parenteral or oral chelators [Poh-Fitzpatrick et al 1988].

- Experimental induction of iron deficiency either using treatment with iron chelators or via phlebotomies improved photosensitivity and hemolysis in a few affected individuals [Egan at al 2015, Blouin et al 2020, Blouin et al 2021, Mirmiran et al 2021].

Note: Although oral charcoal and cholestyramine were thought to increase fecal loss of porphyrins, a clear clinical benefit has not been shown [Tishler & Winston 1990].

Successful bone marrow transplantation (BMT) is an effective cure for CEP and should be considered in children with severe cutaneous and hematologic involvement. Autologous as well as allogeneic stem cell transplants have been performed successfully [Thomas et al 1996, Tezcan et al 1998, Harada et al 2001, Shaw et al 2001, Dupuis-Girod et al 2005, Taibjee et al 2007, Faraci et al 2008]. Urine and erythrocyte porphyrins can be measured periodically after bone marrow transplantation to monitor engraftment.

The age of children with CEP receiving BMT ranges from younger than one year to 13 years [Katugampola et al 2012b]. Some of the first individuals with CEP to successfully undergo BMT in childhood are now in their 20s [Thomas et al 1996, Zix-Kieffer et al 1996]. Although there is limited information available regarding their long-term outcome post BMT, experts have learned that individuals successfully transplanted have essentially no photosensitivity to artificial light sources or sunlight.

Surveillance

Monitor the following:

- Hematologic indices including iron profile, reticulocyte count, and bilirubin to assess hemolysis every six months

  Note: Individuals receiving transfusion therapy need closer monitoring.
- Iron profile on a regular basis to assess for iron overload for those who are transfusion dependent
- Hepatic function every six to twelve months
- Vitamin D 25-OH levels in all individuals whether or not they are receiving vitamin D supplements

Agents/Circumstances to Avoid

The following are appropriate:

- Avoidance of sunlight and UV light
- In individuals with hepatic dysfunction, avoidance of drugs that may induce cholestasis (e.g., estrogens)
- In individuals undergoing surgeries, use of protective filters for artificial lights in the operating room to prevent phototoxic damage [Wahlin et al 2008]

Evaluation of Relatives at Risk

It is appropriate to evaluate at-risk sibs as newborns or infants in order to identify as early as possible those who would benefit from early intervention (no phototherapy, strict sun protection) and future monitoring for signs of hemolytic anemia. Evaluations include:

- Molecular genetic testing if the pathogenic variant(s) in the family are known;
- Biochemical testing for urinary or erythrocyte uroporphyrin I and coproporphyrin I isomer elevation if the pathogenic variants in the family are not known.

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

Pregnancy Management

Successful pregnancies in women with CEP resulting in healthy and unaffected children have been described [Hallai et al 2007, Katugampola et al 2012b].

Protective filters for artificial lights should be used in the delivery/operating room to prevent phototoxic damage to the mother during delivery [Wahlin et al 2008].

Therapies Under Investigation

Although there are no clinical trials at the present time, therapeutic approaches under investigation include phlebotomy or iron chelation strategies to reduce the hemolysis and decrease the accumulated porphyrins and, thus, photosensitivity [Egan at al 2015, Blouin et al 2020, Blouin et al 2021, Mirmiran et al 2021].

A murine CEP model is being used to investigate pharmacologic chaperone therapy (i.e., administration of small-molecule drugs to enhance the residual activity of mutated enzymes that have low activities or are unstable). Specifically, use of the antimicrobial agent ciclopirox as a chaperone-stabilized UROIII-synthase and reversed CEP-related findings such as abnormal URO I levels in the blood, splenomegaly, and liver porphyrins [Urquiza et al 2018]. Studies involving use of this medication in humans have not yet been performed.

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

Congenital erythropoietic porphyria (CEP) caused by biallelic *UROS* pathogenic variants is inherited in an autosomal recessive manner.

CEP caused by a hemizygous *GATA1* pathogenic variant is inherited in an X-linked manner. To date only three such individuals have been identified [Phillips et al 2007, Di Pierro et al 2015].

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., presumed to be carriers of one *UROS* pathogenic variant based on family history).
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *UROS* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband.
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant 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 *UROS* 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 being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an individual with congenital erythropoietic porphyria has children with an affected individual or a carrier, the offspring of a proband will be obligate heterozygotes (carriers) for a pathogenic variant in *UROS*.

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

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *UROS* pathogenic variants in the family.

X-Linked Inheritance – Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *GATA1* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote. Note: If a woman has more than one affected child and no other affected relatives and if the *GATA1* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a carrier, the affected male may have a *de novo GATA1* pathogenic variant (in which case the mother is not a carrier), or the mother may have somatic/germline mosaicism.

  The frequency of *de novo GATA1* pathogenic variants is unknown.
- Molecular genetic testing of the mother is recommended to confirm her genetic status and to allow reliable recurrence risk assessment.

Sibs of a male proband. The risk to sibs of a male proband depends on the genetic status of the mother:

- If the mother of the proband has a *GATA1* pathogenic variant, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the pathogenic variant will be affected;
  - Females who inherit the pathogenic variant will be heterozygotes and can be either asymptomatic or have a milder phenotype with predominantly hematologic and/or cutaneous abnormalities due to skewed X-chromosome inactivation [Phillips et al 2007, Di Pierro et al 2015].
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *GATA1* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is presumed to be low but slightly greater than that of the general population because of the theoretic possibility of maternal germline mosaicism.

Offspring of a male proband. Affected males transmit the *GATA1* pathogenic variant to all of their daughters and none of their sons.

Other family members. The proband's maternal aunts may be at risk of being carriers and the aunts' offspring, depending on their sex, may be at risk of being carriers or of being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

Heterozygote Detection

Identification of female heterozygotes requires either prior identification of the *GATA1* pathogenic variant in the family or, if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

Note: Females who are heterozygous for this X-linked disorder will be either asymptomatic or have a milder phenotype with predominantly hematologic abnormalities due to skewed X-chromosome inactivation [Phillips et al 2007, Di Pierro et al 2015].

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- 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).

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the *UROS* pathogenic variants or the *GATA1* pathogenic variant have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Biochemical genetic testing. Prenatal diagnosis is also possible by demonstrating markedly deficient UROsynthase activity in cultured amniotic cells or chorionic villi cells, and/or markedly elevated uroporphyrin I and coproporphyrin I concentrations in amniotic fluid (see Table 1).

Note: It is assumed that an elevation of uroporphyrin I and coproporphyrin I concentrations in amniotic fluid is also present in *GATA1*-related CEP; however, at this time data are insufficient to confirm this hypothesis.

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.

- **American Porphyria Foundation (APF)**
  Phone: 866-APF-3635
  Email: general@porphyriafoundation.org
  www.porphyriafoundation.org
- **MedlinePlus**
  Porphyria
- **United Porphyrias Association**
  Phone: 800-868-1292
  Email: info@porphyria.org
  www.porphyria.org
- **Canadian Association for Porphyria/Association Canadienne de Porphyrie**
  Canada
  www.canadianassociationforporphyria.ca
- **Find a Porphyria Expert**
  American Porphyria Foundation
  www.porphyriafoundation.org/for-patients/porphyria-experts
- **Global Porphyria Advocacy Coalition**
  GPAC
- **International Porphyria Network**
  Email: contact@porphyria.eu
  porphyria.eu
- **Porphyria South Africa**
  South Africa
  Phone: +27 21-4066332
  Fax: +27 21-4066061
  Email: Peter.Meissner@uct.ac.za
  Porphyria for Patients
- **Swedish Porphyria Association**
  Sweden
  Phone: +46730803820
  Email: porfyrisjukdomar@gmail.com
  www.porfyri.se

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. Congenital Erythropoietic Porphyria: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GATA1	Xp11.23	Erythroid transcription factor	GATA1 @ LOVD	GATA1	GATA1

Table A. continued from previous page.

UROS	10q26.2	Uroporphyrinogen-III synthase	UROS database	UROS	UROS

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 Congenital Erythropoietic Porphyria (View All in OMIM)

263700	PORPHYRIA, CONGENITAL ERYTHROPOIETIC; CEP
305371	GATA-BINDING PROTEIN 1; GATA1
606938	UROPORPHYRINOGEN III SYNTHASE; UROS

Molecular Pathogenesis

CEP results from markedly decreased (but not absent) URO-synthase activity (<1% to ~10% of normal). When expressed in vitro, the residual enzyme activity of individual pathogenic variants ranges from less than 1.0% to approximately 35% [Desnick & Astrin 2002].

URO-synthase, the fourth enzyme in the heme biosynthesis pathway, normally converts hydroxymethylbilane (HMB) to uroporphyrinogen III. When URO-synthase activity is deficient, HMB accumulates primarily in the erythron and is non-enzymatically converted to uroporphyrinogen I. Decarboxylation of uroporphyrinogen I by URO-decarboxylase leads to formation of hepta-, hexa-, and pentacarboxyl porphyrinogen I isomers, with coproporphyrinogen I being the final product. Since coproporphyrinogen oxidase is specific for the III isomer, coproporphyrinogen I cannot be further metabolized to heme and is therefore non-physiologic. Isomer I porphyrinogens are pathogenic when they accumulate in large amounts and are auto-oxidized to their corresponding porphyrins [Piomelli et al 1986, Poh-Fitzpatrick et al 1988].

Porphyrinogen I isomers accumulate in bone marrow erythroid precursors; erythrocytes undergo auto-oxidation, which causes damage of the erythrocytes and hemolysis. Porphyrin I isomers are released into the circulation and deposited in skin, bone, and other tissues as well as excreted in urine and feces [Desnick et al 1998].

Urinary porphyrin excretion is markedly increased (100-1,000x normal) and consists mainly of uroporphyrin I and coproporphyrin I, with lesser increases in hepta-, hexa-, and pentacarboxyl porphyrin isomers [Fritsch et al 1997]. While isomer I porphyrins are predominant, isomer III porphyrins are also increased.

Cutaneous photosensitivity with blistering and increased friability occurs because the porphyrins deposited in the skin are photocatalytic and cytotoxic compounds [Poh-Fitzpatrick 1985]. Presumably, exposure of the skin to sunlight or other sources of visible light in the Soret band (400-410 nm) and to a lesser extent long-wave ultraviolet light leads to a phototoxic excitation of the accumulated uroporphyrin I and coproporphyrin I isomers. This results in formation of singlet oxygen and other oxygen radicals, which presumably produce tissue and vessel damage [Kaufman et al 1967, Bickers 1987, Dawe et al 2002].

The bone marrow contains much larger amounts of porphyrins (mostly uroporphyrin I and coproporphyrin I) than other tissues and hemolysis is almost always present in persons with CEP. Whether it is accompanied by anemia depends on whether erythroid hyperplasia is sufficient to compensate for the increased rate of erythrocyte destruction, which may vary over time. More severely affected individuals are transfusion dependent.

Splenomegaly usually develops secondary to hemolysis and can also lead to thrombocytopenia and leukopenia. In addition, porphyrin deposition also occurs in the spleen and to a lesser degree in the liver.

Mechanism of disease causation

- *UROS* pathogenic variants result in either absent or reduced UROS enzymatic activity.
- *GATA1* pathogenic variants alter the binding of GATA1 to URO-synthase, resulting in significantly reduced (~20% of normal) URO-synthase activity [Phillips et al 2007].

Table 4. Congenital Erythropoietic Porphyria: Gene-Specific Laboratory Considerations

Gene	Special Consideration
UROS	Regulatory pathogenic variants, located in the erythroid-specific promoter region (intron 1 upstream of the exon 2 ATG), can be detected by sequence analysis when this DNA region is included in the analysis. See Table 5.
GATA1	To date, only one *GATA1* variant (c.646C>T [p.Arg216Trp]) has been described as causative of CEP.

Disease modifiers. The CEP phenotype may be modulated by sequence variants in *ALAS2*, mutation of which typically causes X-linked protoporphyria (XLP). A novel c.1757A>T (p.Tyr586Phe) variant in exon 11 of *ALAS2* was identified in a girl with severe CEP who had biallelic *UROS* pathogenic variants [To-Figueras et al 2011].

Table 5. Congenital Erythropoietic Porphyria: Notable Pathogenic Variants by Gene

Gene	Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
UROS	NM_000375.2 NP_000366.1	c.139T>C	p.Ser47Pro	Assoc w/a severe CEP phenotype; however, in 1 family w/5 children homozygous for this variant, 4 children had severe clinical findings while 1 had very mild cutaneous findings [Ged et al 2004].
		c.197C>T	p.Ala66Val	See Genotype-Phenotype Correlations.
		c.217T>C	p.Cys73Arg	Most common *UROS* pathogenic variant observed in ~1/3 of affected persons [2]
		c.244G>T	p.Val82Phe	See Genotype-Phenotype Correlations.
		c.311C>T	p.Ala104Val	
		c.673G>A	p.Gly225Ser	
		c.-203T>C (-70T>C)	NA	Pathogenic variants in the erythroid-specific promoter region [2]
		c.-209G>A (-76G>A)	NA	
		c.-219C>A (-86C>A)	NA	
		c.-223C>A (-90C>A)	NA	
GATA1	NM_002049.3 NP_002040.1	c.646C>T	p.Arg216Trp	See Genotype-Phenotype Correlations.

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.
1. Variant designation that does not conform to current naming conventions
2. See Genotype-Phenotype Correlations.

Chapter Notes

Acknowledgments

The *GeneReview* "Congenital Erythropoietic Porphyria" was supported in part by the Porphyrias Consortium of the NIH-supported Rare Diseases Clinical Research Network (NIH grant: 5 U54 DK083909).

Revision History

- 15 April 2021 (bp) Comprehensive update posted live
- 7 April 2016 (bp) Comprehensive update posted live
- 12 September 2013 (me) Review posted live
- 5 March 2013 (ae) Original submission

References

Literature Cited

Anderson KE, Sassa S, Bishop DF, Desnick RJ. Disorders of heme biosynthesis: X-linked sideroblastic anemias and the porphyrias. In: Scriver CR, Beaudet AL, Sly WS, eds. *The Metabolic and Molecular Basis of Inherited Disease.* 8 ed. New York, NY: McGraw-Hill; 2001:2991.

Bickers DR. The dermatologic manifestations of human porphyria. Ann N Y Acad Sci. 1987;514:261–7. PubMed PMID: 3327430.

Bishop DF, Johansson A, Phelps R, Shady AA, Ramirez MC, Yasuda M, Caro A, Desnick RJ. Uroporphyrinogen III synthase knock-in mice have the human congenital erythropoietic porphyria phenotype, including the characteristic light-induced cutaneous lesions. Am J Hum Genet. 2006;78:645–58. PubMed PMID: 16532394.

Blouin JM, Ged C, Bernardo-Seisdedos G, Cabantous T, Pinson B, Poli A, Puy H, Millet O, Gouya L, Morice-Picard F, Richard E. Identification of novel UROS mutations in a patient with congenital erythropoietic porphyria and efficient treatment by phlebotomy. Mol Genet Metab Rep. 2021;27:100722. PubMed PMID: 33659185.

Blouin JM, Ged C, Lalanne M, Lamrissi-Garcia I, Morice-Picard F, Costet P, Daher R, Moreau-Gaudry F, Bedel A, Puy H, Gouya L, Karim Z, Richard E. Iron chelation rescues hemolytic anemia and skin photosensitivity in congenital erythropoietic porphyria. Blood. 2020;136:2457–68. PubMed PMID: 32678895.

Boulechfar S, Da Silva V, Deybach JC, Nordmann Y, Grandchamp B, de Verneuil H. Heterogeneity of mutations in the uroporphyrinogen III synthase gene in congenital erythropoietic porphyria. Hum Genet. 1992;88:320–4. PubMed PMID: 1733834.

Daïkha-Dahmane F, Dommergues M, Narcy F, Gubler MC, Dumez Y, Gauthier E, Nordmann Y, Nessmann C, Terrasse G, Muller F. Congenital erythropoietic porphyria: prenatal diagnosis and autopsy findings in two sibling fetuses. Pediatr Dev Pathol. 2001;4:180–4. PubMed PMID: 11178635.

Dawe SA, Peters TJ, Du Vivier A, Creamer JD. Congenital erythropoietic porphyria: dilemmas in present day management. Clin Exp Dermatol. 2002;27:680–3. PubMed PMID: 12472546.

Desnick RJ, Astrin KH. Congenital erythropoietic porphyria: advances in pathogenesis and treatment. Br J Haematol. 2002;117:779–95. PubMed PMID: 12060112.

Desnick RJ, Glass IA, Xu W, Solis C, Astrin KH. Molecular genetics of congenital erythropoietic porphyria. Semin Liver Dis. 1998;18:77–84. PubMed PMID: 9516681.

Di Pierro E, Russo R, Karakas Z, Brancaleoni V, Gambale A, Kurt I, Winter SS, Granata F, Czuchlewski DR, Langella C, Iolascon A, Cappellini MD. Congenital erythropoietic porphyria linked to GATA1-R216W mutation: challenges for diagnosis. Eur J Haematol. 2015;94:491–7. PubMed PMID: 25251786.

Dupuis-Girod S, Akkari V, Ged C, Galambrun C, Kebaïli K, Deybach JC, Claudy A, Geburher L, Philippe N, de Verneuil H, Bertrand Y. Successful match-unrelated donor bone marrow transplantation for congenital erythropoietic porphyria (Günther disease). Eur J Pediatr. 2005;164:104–7. PubMed PMID: 15703981.

Egan DN, Yang Z, Phillips J, Abkowitz JL. Inducing iron deficiency improves erythropoiesis and photosensitivity in congenital erythropoietic porphyria. Blood. 2015;126:257–61. PubMed PMID: 25972160.

Faraci M, Morreale G, Boeri E, Lanino E, Dallorso S, Dini G, Scuderi F, Cohen A, Cappelli B. Unrelated HSCT in an adolescent affected by congenital erythropoietic porphyria. Pediatr Transplant. 2008;12:117–20. PubMed PMID: 18186900.

Frank J, Wang X, Lam HM, Aita VM, Jugert FK, Goerz G, Merk HF, Poh-Fitzpatrick MB, Christiano AM. C73R is a hotspot mutation in the uroporphyrinogen III synthase gene in congenital erythropoietic porphyria. Ann Hum Genet. 1998;62:225–30. PubMed PMID: 9803266.

Fritsch C, Bolsen K, Ruzicka T, Goerz G. Congenital erythropoietic porphyria. J Am Acad Dermatol. 1997;36:594–610. PubMed PMID: 9092747.

Ged C, Mégarbané H, Chouery E, Lalanne M, Mégarbané A, de Verneuil H. Congenital erythropoietic porphyria: report of a novel mutation with absence of clinical manifestations in a homozygous mutant sibling. J Invest Dermatol. 2004;123:589–91. PubMed PMID: 15304101.

Hallai N, Anstey A, Mendelsohn S, Williams J, Evans-Jones G, Malick S, Badminton MN. Pregnancy in a patient with congenital erythropoietic porphyria. N Engl J Med. 2007;357:622–3. PubMed PMID: 17687144.

Harada FA, Shwayder TA, Desnick RJ, Lim HW. Treatment of severe congenital erythropoietic porphyria by bone marrow transplantation. J Am Acad Dermatol. 2001;45:279–82. PubMed PMID: 11464191.

Katugampola RP, Anstey AV, Finlay AY, Whatley S, Woolf J, Mason N, Deybach JC, Puy H, Ged C, de Verneuil H, Hanneken S, Minder E, Schneider-Yin X, Badminton MN. A management algorithm for congenital erythropoietic porphyria derived from a study of 29 cases. Br J Dermatol. 2012a;167:888–900. PubMed PMID: 22804244.

Katugampola RP, Badminton MN, Finlay AY, Whatley S, Woolf J, Mason N, Deybach JC, Puy H, Ged C, de Verneuil H, Hanneken S, Minder E, Schneider-Yin X, Anstey AV. Congenital erythropoietic porphyria: a single-observer clinical study of 29 cases. Br J Dermatol. 2012b;167:901–13. PubMed PMID: 22816431.

Kaufman BM, Vickers HR, Rayne J, Ryan TJ. Congenital erythropoietic porphyria. Report of a case. Br J Dermatol. 1967;79:210–20. PubMed PMID: 6024737.

Kontos AP, Ozog D, Bichakjian C, Lim HW. Congenital erythropoietic porphyria associated with myelodysplasia presenting in a 72-year-old man: report of a case and review of the literature. Br J Dermatol. 2003;148:160–4. PubMed PMID: 12534613.

Laorr A, Greenspan A. Severe osteopenia in congenital erythropoietic porphyria. Can Assoc Radiol J. 1994;45:307–9. PubMed PMID: 8062123.

Mirmiran A, Poli A, Ged C, Schmitt C, Lefebvre T, Manceau H, Daher R, Moulouel B, Peoc'h K, Simonin S, Blouin JM, Deybach JC, Nicolas G, Puy H, Richard E, Gouya L. Phlebotomy as an efficient long-term treatment of congenital erythropoietic porphyria. Haematologica. 2021;106:913–7. PubMed PMID: 31919078.

Oguz F, Sidal M, Bayram C, Sansoy N, Hekim N. Ocular involvement in two symptomatic congenital erythropoietic porphyria. Eur J Pediatr. 1993;152:671–3. PubMed PMID: 8404971.

Pain RW, Welch FW, Woodroffe AJ, Handley DA, Lockwood WH. Erythropoietic uroporphyria of Gunther first presenting at 58 years with positive family studies. Br Med J. 1975;3:621–3. PubMed PMID: 1164638.

Phillips JD, Steensma DP, Pulsipher MA, Spangrude GJ, Kushner JP. Congenital erythropoietic porphyria due to a mutation in GATA1: the first trans-acting mutation causative for a human porphyria. Blood. 2007;109:2618–21. PubMed PMID: 17148589.

Piomelli S, Poh-Fitzpatrick MB, Seaman C, Skolnick LM, Berdon WE. Complete suppression of the symptoms of congenital erythropoietic porphyria by long-term treatment with high-level transfusions. N Engl J Med. 1986;314:1029–31. PubMed PMID: 3960070.

Poh-Fitzpatrick MB, Piomelli S, Seaman C, Skolnick LM. Congenital erythropoietic porphyria: complete suppression of symptoms by long-term high-level transfusion with deferoxamine infusion iron rescue. In: Orfanos CE, Stadler R, Gollnick H, eds. *Dermatology in Five Continents*. Berlin, Germany: Springer Verlag; 1988:876-9.

Poh-Fitzpatrick MB. Porphyrin sensitized cutaneous photosensitivity - pathogenesis and treatment. In: Disler PB, Moore MR, eds. *Porphyria-Clinics in Dermatology*. Philadelphia, PA: Lippincott; 1985:41-82.

Poh-Fitzpatrick MB. The erythropoietic porphyrias. Dermatol Clin. 1986;4:291–6. PubMed PMID: 3955899.

Sarkany RP, Ibbotson SH, Whatley SD, Lawrence CM, Gover P, Mufti GJ, Murphy GM, Masters GS, Badminton MN, Elder GH. Erythropoietic uroporphyria associated with myeloid malignancy is likely distinct from autosomal recessive congenital erythropoietic porphyria. J Invest Dermatol. 2011;131:1172–5. PubMed PMID: 21326293.

Schmid R, Schwartz S, Sundberg RD. Erythropoietic (congenital) porphyria: a rare abnormality of the normoblasts. Blood. 1955;10:416–28. PubMed PMID: 14363322.

Shady AA, Colby BR, Cunha LF, Astrin KH, Bishop DF, Desnick RJ. Congenital erythropoietic porphyria: identification and expression of eight novel mutations in the uroporphyrinogen III synthase gene. Br J Haematol. 2002;117:980–7. PubMed PMID: 12060141.

Shaw PH, Mancini AJ, McConnell JP, Brown D, Kletzel M. Treatment of congenital erythropoietic porphyria in children by allogeneic stem cell transplantation: a case report and review of the literature. Bone Marrow Transplant. 2001;27:101–5. PubMed PMID: 11244446.

Siddique SS, Gonzalez-Gonzalez LA, Thakuria P, Chang PY, Foster CS. Scleral necrosis in a patient with congenital erythropoietic porphyria. Cornea. 2011;30:97–9. PubMed PMID: 20847674.

Solis C, Aizencang GI, Astrin KH, Bishop DF, Desnick RJ. Uroporphyrinogen III synthase erythroid promoter mutations in adjacent GATA1 and CP2 elements cause congenital erythropoietic porphyria. J Clin Invest. 2001 Mar;107:753–62. PubMed PMID: 11254675.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

Taibjee SM, Stevenson OE, Abdullah A, Tan CY, Darbyshire P, Moss C, Goodyear H, Heagerty A, Whatley S, Badminton MN. Allogeneic bone marrow transplantation in a 7-year-old girl with congenital erythropoietic porphyria: a treatment dilemma. Br J Dermatol. 2007;156:567–71. PubMed PMID: 17300251.

Tezcan I, Xu W, Gurgey A, Tuncer M, Cetin M, Oner C, Yetgin S, Ersoy F, Aizencang G, Astrin KH, Desnick RJ. Congenital erythropoietic porphyria successfully treated by allogeneic bone marrow transplantation. Blood. 1998;92:4053–8. PubMed PMID: 9834209.

Thomas C, Ged C, Nordmann Y, de Verneuil H, Pellier I, Fischer A, Blanche S. Correction of congenital erythropoietic porphyria by bone marrow transplantation. J Pediatr. 1996;129:453–6. PubMed PMID: 8804339.

Tishler PV, Winston SH. Rapid improvement in the chemical pathology of congenital erythropoietic porphyria with treatment with superactivated charcoal. Methods Find Exp Clin Pharmacol. 1990;12:645–8. PubMed PMID: 2084460.

To-Figueras J, Ducamp S, Clayton J, Badenas C, Delaby C, Ged C, Lyoumi S, Gouya L, de Verneuil H, Beaumont C, Ferreira GC, Deybach JC, Herrero C, Puy H. ALAS2 acts as a modifier gene in patients with congenital erythropoietic porphyria. Blood. 2011;118:1443–51. PubMed PMID: 21653323.

Urquiza P, Lain A, Sanz-Parra A, Moreno J, Bernardo-Seisdedos G, Dubus P, González E, Gutiérrez-de-Juan V, García S, Eraña H, San Juan I, Macías I, Ben Bdira F, Pluta P, Ortega G, Oyarzábal J, González-Muñiz R, Rodríguez-Cuesta J, Anguita J, Díez E, Blouin JM, de Verneuil H, Mato JM, Richard E, Falcón-Pérez JM, Castilla J, Millet O. Repurposing ciclopirox as a pharmacological chaperone in a model of congenital erythropoietic porphyria. Sci Transl Med. 2018;10:eaat7467. PubMed PMID: 30232228.

Venkatesh P, Garg SP, Kumaran E, Tewari HK. Congenital porphyria with necrotizing scleritis in a 9-year-old child. Clin Experiment Ophthalmol. 2000;28:314–8. PubMed PMID: 11021563.

Wahlin S, Srikanthan N, Hamre B, Harper P, Brun A. Protection from phototoxic injury during surgery and endoscopy in erythropoietic protoporphyria. Liver Transpl. 2008;14:1340–6. PubMed PMID: 18756472.

Warner CA, Yoo HW, Roberts AG, Desnick RJ. Congenital erythropoietic porphyria: identification and expression of exonic mutations in the uroporphyrinogen III synthase gene. J Clin Invest. 1992;89:693–700. PubMed PMID: 1737856.

Weston MJ, Nicholson DC, Lim CK, Clark KG, Macdonald A, Henderson MA, Williams R. Congenital erythropoietic uroporphyria (Günther's disease) presenting in a middle aged man. Int J Biochem. 1978;9:921–6. PubMed PMID: 744297.

Zix-Kieffer I, Langer B, Eyer D, Acar G, Racadot E, Schlaeder G, Oberlin F, Lutz P. Successful cord blood stem cell transplantation for congenital erythropoietic porphyria (Gunther's disease). Bone Marrow Transplant. 1996;18:217–20. PubMed PMID: 8832020.

License