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Familial Porphyria Cutanea Tarda

Synonyms: Familial PCT (F-PCT); Porphyria Cutanea Tarda, Type II (Type II PCT); *UROD*-Related Porphyria Cutanea Tarda

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Summary

Clinical characteristics

Familial porphyria cutanea tarda (F-PCT) is characterized by: skin findings including blistering over the dorsal aspects of the hands and other sun-exposed areas of skin, skin friability after minor trauma, facial hypertrichosis and hyperpigmentation, and severe thickening of affected skin areas (pseudoscleroderma); and an increased risk for hepatocellular carcinoma (HCC).

Diagnosis/testing

The diagnosis of F-PCT is established in a proband with elevated porphyrins in the urine (predominantly uroporphyrin and heptacarboxylporphyrin) and a heterozygous pathogenic variant in *UROD* identified by molecular genetic testing.

Management

Treatment of manifestations: No treatment regimens can restore UROD enzyme levels in individuals with F-PCT. The mainstays of therapy are reduction of body iron stores and liver iron content, and use of low-dose antimalarial agents (hydroxychloroquine). In addition, modifiable risk factors can be addressed by ceasing alcohol/tobacco use, modifying estrogen use, and treating hepatitis C infection (if present).

Surveillance: Monitor urinary porphyrin levels annually. For those who have been treated by phlebotomy, resume iron reduction by therapeutic phlebotomies if and when urinary uroporphyrins and heptacarboxylporphyrins increase to greater than 400 µg/g creatinine. Monitor for diabetes mellitus annually

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with fasting glucose, particularly in individuals with hypertension. Monitor for HCC annually with serum AFP concentration and hepatic ultrasonography; monitor every six months in those with cirrhosis.

Agents/circumstances to avoid: Susceptibility factors (e.g., iron supplements, alcohol consumption, smoking, estrogen use, and hepatotoxins); exposure to sunlight in the symptomatic phase.

Evaluation of relatives at risk: If the family-specific *UROD* pathogenic variant is known, it is reasonable to clarify the genetic status of at-risk relatives so that those with a *UROD* pathogenic variant can avoid known susceptibility factors.

Genetic counseling

F-PCT is inherited in an autosomal dominant manner with reduced penetrance. Most individuals diagnosed with F-PCT inherited a *UROD* pathogenic variant from a heterozygous, asymptomatic parent. Each child of an individual with F-PCT has a 50% chance of inheriting the *UROD* pathogenic variant; because the penetrance of F-PCT is low, the likelihood of offspring developing signs and symptoms of PCT is small. Once the *UROD* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. However, because of the low penetrance of F-PCT, the results of prenatal testing are not useful in accurately predicting whether an individual with one *UROD* pathogenic variant will develop clinical manifestations of PCT.

Diagnosis

Suggestive Findings

Familial porphyria cutanea tarda (F-PCT) **should be suspected** in a proband with the following clinical findings and suggestive biochemical findings. In some, there may also be a family history of PCT, although this is far from universal.

Clinical features (typically developing in the 5th-6th decade):

- Photosensitivity resulting in fluid-filled vesicles, bullae, blisters, and sores developing over the dorsal aspects of the hands and other sun-exposed areas of skin (e.g., forearms, face and scalp, ears, neck, legs, and feet). Because the blister fluid is high in porphyrin content, it may appear pink to red. Upon rupturing, these lesions can crust over, heal slowly, and result in secondary infection.
- Skin fragility after minor trauma (which may occur over the same areas where the blisters develop)
- Facial hypertrichosis and hyperpigmentation
- Severe thickening of the affected skin areas (pseudoscleroderma) that resembles progressive systemic sclerosis

Biochemical findings

- Increased urine or plasma total porphyrins (first-line testing; sensitive, not specific)
- Fractionate urine porphyrins showing a predominance of uroporphyrin & heptacarboxylporphyrin (second-line testing)

  See Table 1 for the complete biochemical profile of F-PCT.
- Normal or minimally increased urine delta-aminolevulinic acid levels
- In some persons with severe F-PCT, pink-appearing urine that fluoresces bright pink when excited by long UV-blue light

Table 1. Complete Biochemical Features of Familial Porphyria Cutanea Tarda

Feature	Biochemical Finding
Deficient enzyme	Uroporphyrinogen decarboxylase
Enzyme activity	<~20% of normal (hepatic); ~50% of normal (red blood cell)
Plasma	↑ uroporphyrin, heptacarboxylporphyrin (peak fluorescence emission ~620 nm) [1]
Urine	↑ uroporphyrin, heptacarboxylporphyrin
Stool	Mild ↑ in heptacarboxylporphyrin, isocoproporphyrins, & pentacarboxylporphyrins

1. Fluorescence emission peak of diluted plasma at neutral pH, following excitation at 400-410 nm

Family history may suggest autosomal dominant inheritance (e.g., an affected parent) or may not reveal other affected family members because of the low penetrance of clinical manifestations of PCT that result in a significant proportion of heterozygotes remaining asymptomatic (see Penetrance).

Establishing the Diagnosis

The diagnosis of familial porphyria cutanea tarda (F-PCT) **is established** in a proband with elevated porphyrins in the urine (predominantly uroporphyrin and heptacarboxylporphyrin) (see Table 1) and a heterozygous pathogenic (or likely pathogenic) variant in *UROD* identified by molecular genetic testing (see Table 2).

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 a heterozygous *UROD* variant of uncertain significance does not establish or rule out the diagnosis of the disorder.

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 (Option 1), whereas genomic testing does not (Option 2).

Option 1

Single-gene testing. Sequence analysis of *UROD* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If 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.

A porphyria or heme biosynthesis multigene panel that includes *UROD* 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

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 Familial Porphyria Cutanea Tarda

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
UROD	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [5]	<5% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. 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.

Clinical Characteristics

Clinical Description

Familial porphyria cutanea tarda (F-PCT) is characterized by cutaneous findings including skin friability and chronic blistering over sun-exposed areas (classically the dorsal aspects of the hands). In contrast to the acute hepatic porphyrias or erythropoietic cutaneous porphyrias, F-PCT does not manifest as acute episodes of pain or acute/painful skin changes upon sun exposure, respectively. Hepatic involvement of F-PCT is characterized by elevation in aminotransferases, increased iron stores, and varying degrees of fibrosis accompanied by an increased risk for hepatocellular carcinoma.

Skin findings include photosensitivity resulting in the formation of blisters over the dorsal aspects of the hands and other sun-exposed areas of skin (e.g., forearms, face and scalp, ears, neck, legs, and feet), skin friability after minor trauma, which can occur over the same areas where the blisters develop, secondary infection of ruptured blisters, facial hypertrichosis and hyperpigmentation, and severe thickening of the affected skin areas (pseudoscleroderma) that resembles systemic scleroderma.

Histopathology of the skin in F-PCT demonstrates subepidermal fluid collections (blistering), hyperkeratosis, and lipid proteinosis. Additional findings can include deposition of PAS-positive material around blood vessels and fine fibrillar material in the upper dermis, as well as splitting of the lamina lucida of the basement membrane at the dermoepithelial junction [Dabski & Beutner 1991]. These findings are not diagnostic of F-PCT and can be found in other cutaneous porphyrias, pseudoporphyria, and other disorders.

Hepatic involvement commonly manifests as elevated serum aminotransferase levels and gamma glutamyl transpeptidase.

Some affected individuals will demonstrate evidence of hepatic iron overload, suggested by elevated serum ferritin concentration and elevated transferrin saturation.

While cirrhosis may develop in 30%-40% of individuals, predisposing factors are concomitant infection with hepatitis C virus and use of alcohol.

The risk for hepatocellular carcinoma is increased in individuals with F-PCT, especially in those with other risk factors predisposing to advanced liver disease (see Pathophysiology) [Cassiman et al 2008, Baravelli et al 2019].

Pathophysiology

Development of clinical manifestations of familial porphyria cutanea tarda (F-PCT) requires **both** heterozygosity for a *UROD* pathogenic variant that results in approximately 50% reduction of the activity of the enzyme uroporphyrinogen decarboxylase (UROD) **and** the presence of other susceptibility factors that generate an inhibitor that reduces UROD activity to less than 20% of normal. When the hepatic enzyme UROD is significantly inhibited, oxidized porphyrins (mostly uroporphyrin and heptacarboxylporphyrin) that accumulate in the liver are transported from the hepatocytes into the plasma and eventually into the urine. These excess plasma porphyrins may also be deposited in the skin and other tissues.

Susceptibility Factors

Inherited, environmental, medical, and infectious factors that are known or suspected to influence disease susceptibility in F-PTC include the following [Jalil et al 2010, Smith & Elder 2010]:

- *HFE* pathogenic variants that lead to increased intestinal iron absorption (See *HFE* Hemochromatosis.)
- Secondary iron overload. Some degree of hepatic siderosis (mild-to-moderate iron overload) is seen in most individuals with F-PCT. Conversely, iron deficiency is protective.
- Excessive alcohol consumption
- Tobacco use
- Oral estrogen use
- Estrogen mimetics/antagonists (e.g., tamoxifen)
- Exposure to toxins such as polychlorinated biphenyls, hexochlorobenzene, and other polyhalogenated hydrocarbons that significantly induce cytochrome P450 enzymes
- End-stage kidney disease (ESKD) can lead to manifestations of F-PCT that are often more severe than usual because the lack of urinary porphyrin excretion results in much higher porphyrin plasma concentrations (which are poorly dialyzable). In addition, the blood transfusions necessary to treat the anemia that often accompanies ESKD can result in secondary iron overload.
- Hepatitis C infection is a modifiable risk factor for PCT, the prevalence of which has ranged from 21% to 92% in various countries [Ryan Caballes et al 2012]. Note that hepatitis C infection is seen more frequently in type I PCT (sporadic) than in F-PCT [Muñoz-Santos et al 2010].
- Human immunodeficiency virus (HIV) infection
- Factors that substantially reduce plasma levels of ascorbate and carotenoids [Sinclair et al 1997, Rocchi et al 1999]

Genotype-Phenotype Correlations

No *UROD* genotype-phenotype correlations are known.

Presence of biallelic null variants is lethal [Phillips et al 2007].

Nomenclature

Porphyria cutanea tarda (PCT) that is not associated with a *UROD* pathogenic variant is referred to as type I PCT or sporadic PCT [Bonkovsky et al 2013] (see Differential Diagnosis).

F-PCT (i.e., porphyria cutanea tarda caused by a heterozygous pathogenic variant in *UROD*) may also be referred to as "*UROD*-related porphyria cutanea tarda" based on the naming approach proposed by Biesecker et al [2021] to delineate mendelian genetic disorders.

Table 3. Porphyria Classification Systems

Hereditary Porphyria	Primary Symptom-Based Porphyria Classification	Organ-Based Porphyria Classification
Acute intermittent porphyria (AIP)	Neurologic	Hepatic
ALA dehydratase deficiency porphyria (ADP)	Neurologic	Hepatic
Congenital erythropoietic porphyria (CEP)	Cutaneous	Erythropoietic
Erythropoietic protoporphyria (EPP)	Cutaneous	Erythropoietic
Hepatoerythropoietic porphyria (HEP)	Cutaneous	Hepatic/erythropoietic
Hereditary coproporphyria (HCP)	Neurologic (cutaneous possible but rare)	Hepatic
Porphyria cutanea tarda (PCT)	Cutaneous	Hepatic
Variegate porphyria (VP)	Cutaneous & neurologic	Hepatic
X-linked protoporphyria (XLP)	Cutaneous	Erythropoietic

ALA = aminolevulinic acid
See also The Porphyrias Consortium: Disorder Definitions.

Penetrance

The penetrance of F-PCT is low, given that in addition to heterozygosity for a *UROD* pathogenic variant, other susceptibility factors need to be present (see Pathophysiology, Susceptibility Factors).

Prevalence

The prevalence of F-PCT is approximately 8:1,000,000 (based on the estimated prevalence of PCT as 40:1,000,000 and of F-PCT as ~20% of PCT) [Merk 2016].

Genetically Related (Allelic) Disorders

Hepatoerythropoietic porphyria (HEP). Individuals with biallelic pathogenic variants in *UROD* – with at least one of the pathogenic variants preserving some degree of catalytic activity – have HEP. The clinical features of HEP and porphyria cutanea tarda (PCT) are indistinguishable. However, the skin lesions of HEP are typically more severe and start during infancy or childhood (see Differential Diagnosis). Although several *UROD* pathogenic variants have been described in HEP, data are insufficient to identify variants that are more common in HEP.

Differential Diagnosis

Porphyria cutanea tarda (PCT) is the most common type of porphyria and encompasses both familial *UROD*-related porphyria cutanea tarda (~20% of all PCT) and type I sporadic PCT [Weiss et al 2019].

Sporadic PCT (i.e., PCT that is not associated with a *UROD* pathogenic variant) is clinically indistinguishable from F-PCT and, like F-PCT, is highly influenced by susceptibility factors associated with PCT (see Pathophysiology).

Other types of hereditary porphyria in the differential diagnosis of F-PCT are summarized in Table 4.

Table 4. Other Types of Porphyria in the Differential Diagnosis of Familial Porphyria Cutanea Tarda

Gene	Disorder	MOI	Skin Lesions	Distinguishing Features / Comment
CPOX	Hereditary coproporphyria (HCP)	AD	Blistering skin lesions in HCP, which occur only occasionally, are nearly identical to those in PCT.	Neurovisceral features of HCP are not seen in PCT. Urine & fecal porphyrin profiles are different.
PPOX	Variegate porphyria (VP)	AD	Blistering skin lesions in VP are nearly identical to those in PCT.	VP is both a cutaneous & a neurovisceral porphyria & can present w/chronic blistering cutaneous manifestations &/or acute neurovisceral attacks similar to those of AIP.
UROD	Hepatoerythropoietic porphyria (HEP)	AR	Although they resemble those of PCT, skin lesions in HEP are usually more severe & mutilating & appear early in life (e.g., infancy & childhood); in PCT the lesions generally appear in the 5th & 6th decades.	Because lab findings in F-PCT & HEP can be clinically indistinguishable at time of diagnosis, molecular genetic testing is needed to differentiate the disorders. Measurement of UROD enzyme activity is not an accurate method to distinguish between F-PCT & HEP.
UROS [1]	Congenital erythropoietic porphyria (CEP)	AR	Blistering skin lesions resemble those of PCT, but are more severe (i.e., appear in infancy & childhood, & disfigure & mutilate the skin).	CEP, a cutaneous porphyria, can be mistaken for HEP or PCT, but urine porphyrin analysis (demonstrating uroporphyrin I & coproporphyrin I) rules out HEP & PCT. Fecal analysis may be necessary in persons w/later onset. Severe anemia (may be transfusion dependent) can occur.

AD = autosomal dominant; AIP = acute intermittent porphyria; AR = autosomal recessive; MOI = mode of inheritance; PCT = porphyria cutanea tarda

1. A pathogenic variant in *GATA1* (an X-linked gene) was identified in three unrelated individuals with CEP and hematologic abnormalities (see Congenital Erythropoietic Porphyria).

Other Disorders in the Differential Diagnosis of F-PCT

African iron overload (OMIM 601195) results from a predisposition to iron overload that is exacerbated by excessive intake of dietary iron. It is particularly prevalent among Africans who drink a traditional beer brewed in nongalvanized steel drums.

Pseudoporphyria. Although the skin histopathologic findings of pseudoporphyria are indistinguishable from those of PCT, pseudoporphyria is not associated with porphyrin biochemical abnormalities. Drugs implicated in the pathogenesis of this immune-mediated condition include photosensitizing agents such as nonsteroidal anti-inflammatory drugs, tetracycline, voriconazole, loop/thiazide diuretics, retinoids, imatinib, and simvastatin [Gil-Lianes et al 2022]. Host genetic factors are likely also involved. The cause(s) of pseudoporphyria can be difficult to ascertain, and the disease can be long-lasting.

Management

No clinical practice guidelines for familial porphyria cutanea tarda (F-PCT) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with familial porphyria cutanea tarda (F-PCT), the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Evaluation of skin findings, including blistering over the dorsal aspects of the hands and other sun-exposed areas of skin, skin friability after minor trauma, facial hypertrichosis and hyperpigmentation, and severe thickening of affected skin areas (pseudoscleroderma)
- Medical history regarding susceptibility factors that are known to influence the presence and/or severity of clinical manifestations (see Pathophysiology, Susceptibility Factors). When warranted, evaluation for medical findings that could influence occurrence and severity of cutaneous manifestations, including the following:
  - Presence of *HFE* pathogenic variants that lead to iron loading (identified by molecular genetic testing; see *HFE* Hemochromatosis.)
  - Excess iron based on iron indices: serum ferritin level; serum iron concentration, total iron binding capacity, and percent iron saturation
  - Alcohol consumption
  - Tobacco use
  - Oral estrogen use
  - Chronic kidney disease / end-stage kidney disease
  - Presence of hepatitis C and/or human immunodeficiency virus infection
- 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 F-PCT in order to facilitate medical and personal decision making

Treatment of Manifestations

There are no effective treatment regimens to restore UROD enzyme levels in individuals with F-PCT.

The mainstays of therapy for PCT that are highly effective in individuals with F-PCT are:

- Reduction of body iron stores and liver iron content;
- Use of low-dose antimalarial agents (hydroxychloroquine).

In addition, addressing modifiable risk factors such as ceasing alcohol/tobacco use, modifying estrogen use, and treatment of hepatitis C infection, if present, is warranted.

Reduction of Body Iron Stores and Liver Iron Content

Serial phlebotomy. In most centers, serial phlebotomy is the preferred mode of reducing body iron stores and liver iron content. Serum ferritin concentration should be measured before initiating phlebotomy therapy. Typically, approximately 450 mL of blood is removed during a therapeutic phlebotomy, usually initially at two-week intervals. Hemoglobin levels (which are generally >10-11 g/dL) are followed as safety (not therapeutic) targets to prevent symptomatic anemia. The therapeutic target is to reduce the serum ferritin concentration to the low-normal range (15-25 ng/mL), which is associated with tissue iron depletion but usually not anemia.

Phlebotomy therapy is also guided by plasma (or serum) porphyrin levels, which can more easily be measured repeatedly than urine porphyrins, and which decrease more slowly than the serum ferritin concentration. Plasma porphyrin levels usually decline from initial concentrations of 10-25 µg/dL to below the upper limit of normal (~1 µg/dL) within three to six weeks after phlebotomies are completed [Rocchi et al 1986, Ratnaike et al 1988].

Development of new skin lesions generally ceases as plasma porphyrin levels normalize; however, therapy should be continued until the serum ferritin concentration has reached the low end of normal. The chronic skin lesions of PCT are slow to resolve, and some chronic scarring may remain indefinitely.

After remission has been achieved, continued phlebotomies are generally not needed unless initial evaluation has determined the presence of *HFE* hemochromatosis (or, rarely, other inborn errors that lead to iron overload). For persons with the *HFE* genotypes p.Cys282Tyr/p.Cys282Tyr or p.Cys282Tyr/p.His63Asp, management guidelines for *HFE* hemochromatosis should be followed.

Note: Treatment of PCT in persons with ESRD is more difficult because the option for phlebotomy is often limited by anemia. However, in several instances erythropoietin therapy has been shown to improve anemia, mobilize iron, and support phlebotomy [Shieh et al 2000]. Such individuals may also be considered for iron chelation therapy.

Iron chelation therapy (e.g., deferasirox, deferiprone, or desferrioxamine) is less efficient and more costly than therapeutic phlebotomies in reducing iron, but may be considered if the latter is contraindicated [Rodrigues et al 2017].

Low-iron diet. Although not essential, adherence to a low-iron diet, especially with restriction of intake of red meat and liver (rich sources of heme iron, which is absorbed better than iron from vegetable sources) is reasonable, especially in individuals with *HFE* pathogenic variants.

In addition, the ingestion of tea with lunch or dinner further reduces the gastrointestinal absorption of iron.

Low-Dose Antimalarial Agents

A low-dose regimen of twice-weekly hydroxychloroquine (100 mg) or chloroquine (125 mg) is also effective and most appropriate when phlebotomy is contraindicated or poorly tolerated. Note: Chloroquine is not recommended in persons with increased serum ferritin concentration [Singal et al 2012].

Although the use of low-dose antimalarial agents is preferred at some centers because they are less costly and more convenient, these agents do not deplete hepatic iron, and the mechanism of their action in the treatment of PCT is not fully understood. Combining both treatment modalities (i.e., antimalarial agent therapy and phlebotomy) may be beneficial if the individual is unable to tolerate full courses of phlebotomy.

Other

Individuals are advised to stop drinking alcohol and smoking and to discontinue further oral estrogen use. If hormone replacement therapy is indicated, switching to a transdermal alternative is recommended.

Manifestations of F-PCT may also improve after treatment of coexisting hepatitis C. F-PCT should be treated first in most individuals.

- F-PCT generally causes more symptoms and can be treated more quickly and effectively than hepatitis C.
- Some evidence shows that hepatitis C treatment with interferon-based therapies is more effective after iron reduction [Ryan Caballes et al 2012, Desai et al 2012]. However, the highly active direct-acting antivirals now available to cure hepatitis C infection have obviated the need for iron reduction.
- Attainment and maintenance of an iron-reduced state decreases the severity and progression of chronic hepatitis C and may also reduce the risk of developing hepatocellular carcinoma [Ryan Caballes et al 2012].

Vaccination against hepatitis A and B is appropriate.

Although adequate intake of ascorbic acid and other nutrients may be recommended, this is not considered a primary therapy.

Surveillance

Monitor urinary porphyrin levels annually. For those who have been treated by phlebotomy, resume iron reduction by therapeutic phlebotomies if and when urinary uroporphyrins and heptacarboxylporphyrins increase to greater than 400 µg/g creatinine (see Treatment of Manifestations) to prevent recurrence of cutaneous signs. Note: Increase in urinary total porphyrins may also be caused by an increase in coproporphyrin (which is not relevant to F-PCT); thus, when urinary porphyrin levels are only moderately increased, urinary porphyrin fractionation should be performed.

Because of reports of an association between diabetes mellitus and PCT [Muñoz-Santos et al 2011], annual screening with a fasting glucose level is recommended, particularly in those with hypertension (blood pressure >135/80 mm Hg).

Hepatocellular cancer (HCC) surveillance relies on a combination of serum alpha-fetoprotein determinations and hepatic ultrasonography or cross-sectional imaging (CT or MRI). No guidelines as to the frequency of these tests are currently available because of the rarity of F-PCT and even rarer occurrence of HCC. Surveillance is usually performed annually; however, in those with cirrhosis, hepatologists generally agree that surveillance for HCC should be at least every six months.

Agents/Circumstances to Avoid

Avoid the following:

- Susceptibility factors (if known) (e.g., iron supplements, alcohol consumption, smoking, estrogen use, and hepatotoxins such as hexachlorobenzene) (See Pathophysiology, Susceptibility Factors.)
- Exposure to sunlight in symptomatic phase (i.e., when new skin changes appear)

Evaluation of Relatives at Risk

Testing at-risk relatives of an individual with F-PCT to identify those with a *UROD* pathogenic variant is not expected to alter their management because of the low penetrance, and hence low risk of development of the signs and symptoms of F-PCT. Nevertheless, if the family-specific *UROD* pathogenic variant is known, it is reasonable to clarify the genetic status of at-risk relatives so that those with a *UROD* pathogenic variant can avoid known susceptibility factors (see Pathophysiology, Susceptibility Factors).

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

Pregnancy Management

Women with active F-PCT should be able to carry pregnancies to term, though the pregnancy should be considered "high risk" and followed by an appropriately qualified obstetrician [Aziz Ibrahim & Esen 2004, Tollånes et al 2011].

It is recommended that women with F-PCT and iron overload (which is rather unusual in women during their child-bearing years) be treated to reduce body iron stores prior to the onset of planned pregnancies (see Treatment of Manifestations).

The use of hydroxychloroquine during human pregnancy is not thought to lead to adverse fetal effects.

The use of chloroquine at higher doses has produced adverse embryonic effects in animal pregnancies; however, case reports of low doses of chloroquine used in human pregnancy for rheumatic disease have not been associated with adverse fetal outcomes. The US FDA recommends that chloroquine or hydroxychloroquine not be used in pregnant or lactating women unless the expected benefit outweighs the possible risks. No formal grade for use in such women has been assigned.

While iron chelation therapy is not a treatment of choice, some pregnant women may be taking an iron chelator at the time of conception or during pregnancy.

- Data on the use of deferoxamine during human pregnancy suggest that it is not likely to cause adverse fetal effects.
- Data on use of deferasirox during human pregnancy are more limited, although reassuring.
- Data on the use of deferiprone during human pregnancy are very limited.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

A Phase II open-label trial (NCT03118674) is studying the effect of treating individuals with porphyria cutanea tarda (PCT) and hepatitis C with direct-acting antiviral agents as the sole therapy (i.e., no phlebotomy or low-dose hydroxychloroquine). However, it is noted that the effect of this approach on the disease course of F-PCT is less clear.

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

Familial porphyria cutanea tarda (F-PCT) is inherited in an autosomal dominant manner with reduced penetrance.

Note: The penetrance of F-PCT is low, given that in addition to heterozygosity for a *UROD* pathogenic variant, other susceptibility factors need to be present (see Pathophysiology, Susceptibility Factors).

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with F-PCT inherited a *UROD* pathogenic variant from a heterozygous, asymptomatic parent. Few individuals diagnosed with F-PCT have a clinically affected parent because penetrance is low.
- Some individuals diagnosed with F-PCT have the disorder as the result of a *de novo* pathogenic variant; however, the proportion of probands who have a *de novo* pathogenic variant is unknown.
- Molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

- The family history of some individuals diagnosed may appear to be negative because of the low penetrance F-PCT in heterozygous individuals. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *UROD* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%. Because development of clinical manifestations of F-PCT requires both heterozygosity for a *UROD* pathogenic variant and the presence of other susceptibility factors, the likelihood that a sib who inherits a *UROD* pathogenic will develop signs and symptoms of PCT is small (see Pathophysiology).
- If the proband has a known *UROD* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with F-PCT has a 50% chance of inheriting the *UROD* pathogenic variant. (Because the penetrance of F-PCT is low, the likelihood of offspring developing signs and symptoms of PCT is small.)

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent is affected and/or has a *UROD* pathogenic variant, members of the parent's family may be at risk.

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 with F-PCT.

Prenatal Testing and Preimplantation Genetic Testing

Once the *UROD* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. However, because of the low penetrance of F-PCT, the results of prenatal testing are not useful in accurately predicting whether an individual with one *UROD* pathogenic variant will develop clinical manifestations of PCT.

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.

- **British Porphyria Association**
  United Kingdom
  Phone: 0300 30 200 30
  Email: helpline@porphyria.org.uk
  www.porphyria.org.uk
- **MedlinePlus**
  Porphyria
- **United Porphyrias Association**
  Phone: 800-868-1292
  Email: info@porphyria.org
  www.porphyria.org
- **American Porphyria Foundation (APF)**
  Phone: 866-APF-3635
  Email: general@porphyriafoundation.org
  www.porphyriafoundation.org
- **Global Porphyria Advocacy Coalition**
  GPAC
- **International Porphyria Network**
  Email: contact@porphyria.eu
  porphyria.eu
- **Porphyrias Consortium**
  Together with the American Porphyria Foundation, the Porphyrias Consortium enables a large-scale collaborative effort to develop new strategies and methods for diagnosis, treatment, and prevention of illness and disability resulting from these rare disorders.
  www1.rarediseasesnetwork.org/cms/porphyrias
- **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. Familial Porphyria Cutanea Tarda: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

UROD	1p34.1	Uroporphyrinogen decarboxylase	UROD database	UROD	UROD

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 Familial Porphyria Cutanea Tarda (View All in OMIM)

176100	PORPHYRIA CUTANEA TARDA
613521	UROPORPHYRINOGEN DECARBOXYLASE; UROD

Molecular Pathogenesis

UROD encodes the enzyme uroporphyrinogen decarboxylase (UROD). Although persons with familial porphyria cutanea tarda (F-PCT) are heterozygous for a pathogenic variant that reduces UROD activity in all tissues to approximately 50% of normal, they remain asymptomatic until exposure to one or more susceptibility factors that generate an inhibitor reduces UROD activity to less than 20% of normal (see Pathophysiology). Hepatic enzyme activity below a certain critical threshold results in accumulation of highly carboxylated porphyrins (mostly uroporphyrin and heptacarboxylporphyrin) in the liver, which are then transported out of hepatocytes and appear in the plasma, urine, and feces. These excess plasma porphyrins are deposited in the skin and other tissues. Porphyrins in the skin and microcapillaries of the skin are activated when exposed to light, releasing reactive oxygen species that further damage the surrounding tissue, resulting in the observed cutaneous manifestations.

Mechanism of disease causation. Loss of function

Chapter Notes

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References

Literature Cited

Aziz Ibrahim A, Esen UI. Porphyria cutanea tarda in pregnancy: a case report. J Obstet Gynaecol. 2004;24:574–5. PubMed PMID: 15369945.

Baravelli CM, Sandberg S, Aarsand A, Tollanes M. Porphyria cutanea tarda increases risk of hepatocellular carcinoma and premature death: a nationwide cohort study. Orphanet J Rare Dis. 2019;14:77. PubMed PMID: 30944007.

Biesecker LG, Adam MP, Alkuraya FS, Amemiya AR, Bamshad MJ, Beck AE, Bennett JT, Bird LM, Carey JC, Chung B, Clark RD, Cox TC, Curry C, Dinulos MBP, Dobyns WB, Giampietro PF, Girisha KM, Glass IA, Graham JM Jr, Gripp KW, Haldeman-Englert CR, Hall BD, Innes AM, Kalish JM, Keppler-Noreuil KM, Kosaki K, Kozel BA, Mirzaa GM, Mulvihill JJ, Nowaczyk MJM, Pagon RA, Retterer K, Rope AF, Sanchez-Lara PA, Seaver LH, Shieh JT, Slavotinek AM, Sobering AK, Stevens CA, Stevenson DA, Tan TY, Tan WH, Tsai AC, Weaver DD, Williams MS, Zackai E, Zarate YA. A dyadic approach to the delineation of diagnostic entities in clinical genomics. Am J Hum Genet. 2021;108:8–15. PubMed PMID: 33417889.

Bonkovsky HL, Hou W, Li T, Guo J-T, Narang T, Thapar M. Porphyrin and heme metabolism and the porphyrias. Compr Physiol. 2013;3:365–401. PubMed PMID: 23720291.

Cassiman D, Vannoote J, Roelandts R, Libbrecht L, Roskams T, Van den Oord J, Fevery J, Garmyn M, Nevens F. Porphyria cutanea tarda and liver disease: A retrospective analysis of 17 cases from a single centre and review of the literature. Acta Gastroenterol Belg. 2008;71:237–42. PubMed PMID: 18720935.

Dabski C, Beutner EH. Studies of laminin and type IV collagen in blisters of porphyria cutanea tarda and drug-induced pseudoporphyria. J Am Acad Dermatol. 1991;25:28–32. PubMed PMID: 1880250.

Desai T, Bortman J, Al-Sibae R, Bonkovsky HL. The role of iron in hepatitis C infection. Curr Hepat Rep. 2012;11:41–7.

Gil-Lianes J, Luque-Luna M, Morgado-Carrasco D, Aguilera-Peiró P. Pseudoporphyria-a diagnostic challenge: a case series and a proposed diagnostic algorithm. Photodermatol Photoimmunol Photomed. 2022. Epub ahead of print.

Jalil S, Grady JJ, Lee C, Anderson KE. Associations among behavior-related susceptibility factors in porphyria cutanea tarda. Clin Gastroenterol Hepatol. 2010;8:297–302. PubMed PMID: 19948245.

Merk HF. Porphyria cutanea tarda. Hautarzt. 2016;67:207–10. PubMed PMID: 26743054.

Muñoz-Santos C, Guilabert A, Moreno N, Gimenez M, Darwich E, To-Figueras J, Herrero C. The association between porphyria cutanea tarda and diabetes mellitus: analysis of a long-term follow-up cohort. Br J Dermatol. 2011;165:486–91. PubMed PMID: 21564073.

Muñoz-Santos C, Guilabert A, Moreno N, To-Figueras J, Badenas C, Darwich E, Herrero C. Familial and sporadic porphyria cutanea tarda: clinical and biochemical features and risk factors in 152 patients. Medicine (Baltimore). 2010;89:69–74. PubMed PMID: 20517178.

Phillips JD, Bergonia HA, Reilly CA, Franklin MR, Kushner JP. A porphomethene inhibitor of uroporphyrinogen decarboxylase causes porphyria cutanea tarda. Proc Natl Acad Sci U S A. 2007;104:5079–84. PubMed PMID: 17360334.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126–33. PubMed PMID: 26656846.

Ratnaike S, Blake D, Campbell D, Cowen P, Varigos G. Plasma ferritin levels as a guide to the treatment of porphyria cutanea tarda by venesection. Australas J Dermatol. 1988;29:3–8. PubMed PMID: 3250437.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Rocchi E, Casalgrandi G, Masini A, Giovannini F, Ceccarelli D, Ferrali M, Marchini S, Ventura E. Circulating pro- and antioxidant factors in iron and porphyrin metabolism disorders. Ital J Gastroenterol Hepatol. 1999;31:861–7. PubMed PMID: 10669994.

Rocchi E, Gibertini P, Cassanelli M, Pietrangelo A, Borghi A, Ventura E. Serum ferritin in the assessment of liver iron overload and iron removal therapy in porphyria cutanea tarda. J Lab Clin Med. 1986;107:36–42. PubMed PMID: 3941293.

Rodrigues N, Caeiro F, Santana A, Mendes T, Lopes L. Porphyria cutanea tarda in a patient with end-stage renal disease: A case of successful treatment with deferoxamine and ferric carboxymaltose. Case Rep Nephrol. 2017;2017:4591871. PubMed PMID: 28210512.

Ryan Caballes F, Sendi H, Bonkovsky HL. Hepatitis C, porphyria cutanea tarda and liver iron: an update. Liver Int. 2012;32:880–93. PubMed PMID: 22510500.

Shieh S, Cohen JL, Lim HW. Management of porphyria cutanea tarda in the setting of chronic renal failure: a case report and review. J Am Acad Dermatol. 2000;42:645–52. PubMed PMID: 10727312.

Sinclair PR, Gorman N, Shedlofsky SI, Honsinger CP, Sinclair JF, Karagas MR, Anderson KE. Ascorbic acid deficiency in porphyria cutanea tarda. J Lab Clin Med. 1997;130:197–201. PubMed PMID: 9280147.

Singal AK, Kormos-Hallberg C, Lee C, Sadagoparamanujam VM, Grady JJ, Freeman DH Jr, Anderson KE. Low-dose hydroxychloroquine is as effective as phlebotomy in treatment of patients with porphyria cutanea tarda. Clin Gastroenterol Hepatol. 2012;10:1402–9. PubMed PMID: 22985607.

Smith AG, Elder GH. Complex gene-chemical interactions: hepatic uroporphyria as a paradigm. Chem Res Toxicol. 2010;23:712–23. PubMed PMID: 20099833.

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.

Tollånes MC, Aarsand AK, Sandberg S. Excess risk of adverse pregnancy outcomes in women with porphyria: a population-based cohort study. J Inherit Metab Dis. 2011;34:217–23. PubMed PMID: 20978938.

Weiss Y, Chen B, Yasuda M, Nazarenko I, Anderson KE, Desnick RJ. Porphyria cutanea tarda and hepatoerythropoietic porphyria: identification of 19 novel uroporphyrinogen III decarboxylase mutations. Mol Genet Metab. 2019;128:363–6. PubMed PMID: 30514647.

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