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X-Linked Protoporphyria

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Summary

Clinical characteristics

X-linked protoporphyria (XLP) is characterized in affected males by cutaneous photosensitivity (usually beginning in infancy or childhood) that results in tingling, burning, pain, and itching within minutes of sun/light exposure and may be accompanied by swelling and redness. Blistering lesions are uncommon. Pain, which may seem out of proportion to the visible skin lesions, may persist for hours or days after the initial phototoxic reaction. Photosensitivity is lifelong. Multiple episodes of acute photosensitivity may lead to chronic changes of sun-exposed skin (lichenification, leathery pseudovesicles, grooving around the lips) and loss of lunulae of the nails. An unknown proportion of individuals with XLP develop liver disease. Except for those with advanced liver disease, life expectancy is not reduced. The phenotype in heterozygous females ranges from asymptomatic to as severe as in affected males.

Diagnosis/testing

The diagnosis of XLP is established in a male proband with markedly increased free erythrocyte protoporphyrin and zinc-chelated erythrocyte protoporphyrin by identification of a hemizygous pathogenic gain-of-function variant in *ALAS2* on molecular genetic testing.

The diagnosis of XLP is established in a female proband with increased free erythrocyte protoporphyrin and zinc-chelated erythrocyte protoporphyrin by identification of a heterozygous pathogenic gain-of-function variant in *ALAS2* on molecular genetic testing.

Management

Treatment of manifestations: The phototoxicity and subsequent pain can be reduced by the administration of afamelanotide, an α-melanocyte-stimulating hormone analog. Otherwise, the only effective treatment is

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prevention of the painful attacks by avoidance of sun/light (including the long-wave ultraviolet light that passes through window glass) through use of protective clothing (e.g., long sleeves, gloves, wide-brimmed hats, protective tinted glass for cars and windows). Although topical sunscreens are typically not useful, some tanning products containing creams that cause increased pigmentation may be helpful. Oral Lumitene™ (β-carotene) has been used to improve tolerance to sunlight by causing mild skin discoloration due to carotenemia; however, a systematic review of treatment options showed no evidence of efficacy. Vitamin D supplementation is recommended to prevent vitamin D insufficiency resulting from sun avoidance.

Severe liver complications are difficult to treat: cholestyramine and other porphyrin absorbents (to interrupt the enterohepatic circulation of protoporphyrin and promote its fecal excretion) and plasmapheresis and intravenous hemin are sometimes beneficial. Liver transplantation can be a lifesaving measure in individuals with severe protoporphyric liver disease; combined bone marrow and liver transplantation is indicated in those with liver failure to prevent future damage to the allografts.

Surveillance: Monitoring of: hepatic function every 6-12 months and hepatic imaging if cholelithiasis is suspected; erythrocyte protoporphyrin levels (free and zinc-chelated), hematologic indices, and iron profile annually; vitamin D 25-OH levels.

Agents/circumstances to avoid: Sunlight and UV light; for those with hepatic dysfunction, drugs that may induce cholestasis (e.g., estrogens). For those with cholestatic liver failure, protective filters should be used for the operating room lights for liver transplant surgery to avoid phototoxic damage.

Evaluation of relatives at risk: If the *ALAS2* pathogenic variant has been identified in an affected family member, at-risk relatives can be tested as newborns or infants so that those with the pathogenic variant can benefit from early intervention (sun protection) and future monitoring for signs of liver dysfunction.

Genetic counseling

By definition, XLP is inherited in an X-linked manner. Affected males transmit the pathogenic variant to all of their daughters and none of their sons. Women with an *ALAS2* pathogenic variant have a 50% chance of transmitting the variant to each child. Once the *ALAS2* pathogenic variant has been identified in an affected family member, heterozygote testing for at-risk female relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

There are no established guidelines or diagnostic algorithms.

Suggestive Findings

X-linked protoporphyria (XLP) should be suspected in individuals with the following clinical findings and initial laboratory findings.

Clinical findings

- Cutaneous photosensitivity, usually beginning in childhood
- Burning, tingling, pain, and itching of the skin (the most common findings); may occur within minutes of sun/light exposure, followed later by erythema and swelling
- Painful symptoms; may occur without obvious skin damage
- Absent or sparse blisters and bullae

Note: The absence of skin damage (e.g., scarring), vesicles, and bullae often make it difficult to suspect the diagnosis.

- Hepatic complications, particularly cholestatic liver disease, may develop in fewer than 5% of affected individuals.

Initial laboratory findings. Detection of markedly increased free erythrocyte protoporphyrin and zinc-chelated erythrocyte protoporphyrin is the most sensitive biochemical diagnostic test for XLP (Table 1).

Note: It is essential to use an assay for erythrocyte protoporphyrin that distinguishes between free protoporphyrin and zinc-chelated protoporphyrin to differentiate XLP from erythropoietic protoporphyria (EPP-AR) and several other conditions that may lead to elevation of erythrocyte protoporphyrins (see Table 1, footnotes 3 and 4).

Table 1. Biochemical Characteristics of X-Linked Protoporphyria (XLP)

Enzyme Defect	Enzyme Activity	Erythrocytes	Urine	Stool	Other
Erythroid-specific 5-aminolevulinate synthase 2 (ALAS2)	>100% of normal [1]	Free protoporphyrin/ zinc-chelated protoporphyrin ratio 90:10 to 50:50 [2, 3, 4]	Protoporphyrins not detectable	Protoporphyrin normal or ↑	Plasma porphyrins ↑ [5]

1. Increased enzyme activity is due to *ALAS2* pathogenic gain-of-function variants in exon 11. Note: Lymphocyte ferrochelatase activity is normal.
2. Many assays for erythrocyte protoporphyrin or "free erythrocyte protoporphyrin" measure both zinc-chelated protoporphyrin and free protoporphyrin. Free protoporphyrin is distinguished from zinc-chelated protoporphyrin by ethanol extraction or HPLC.
3. Protoporphyrins (usually zinc-chelated protoporphyrin) are also increased in lead poisoning, iron deficiency, anemia of chronic disease, and various hemolytic disorders, as well as in those porphyrias caused by biallelic pathogenic variants (e.g., harderoporphyria).
4. In erythropoietic protoporphyria, free protoporphyrin levels are elevated significantly as compared to zinc-chelated protoporphyrin (see Differential Diagnosis).
5. Plasma total porphyrins are increased in porphyrias with cutaneous manifestations including XLP. If plasma porphyrins are increased, the fluorescence emission spectrum of plasma porphyrins at neutral pH can be characteristic and can distinguish XLP and EPP-AR from other porphyrias. The emission maximum in XLP and EPP-AR occurs at 634 nm.

Establishing the Diagnosis

Male proband. The diagnosis of X-linked protoporphyria (XLP) **is established** in a male proband with markedly increased free erythrocyte protoporphyrin and zinc-chelated erythrocyte protoporphyrin by identification of a hemizygous pathogenic (or likely pathogenic) gain-of-function variant in *ALAS2* (encoding erythroid specific 5-aminolevulinate synthase 2) on molecular genetic testing (see Table 2).

Female proband. The diagnosis of X-linked protoporphyria (XLP) **is established** in a female proband with increased free erythrocyte protoporphyrin and zinc-chelated erythrocyte protoporphyrin by identification of a heterozygous pathogenic (or likely pathogenic) gain-of-function variant in *ALAS2* on 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 hemizygous/heterozygous *ALAS2* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular Genetic Testing

Molecular genetic testing approaches include **gene-targeted testing** (single-gene testing).

Single-gene testing. Sequence analysis of *ALAS2* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants.

Note: All *ALAS2* pathogenic variants associated with XLP reported to date are gain-of-function missense, nonsense, or deletion variants in the last exon (exon 11; see Molecular Genetics). Therefore, sequence analysis of all other exons, as well as testing for haploinsufficiency or duplication (overexpression) is not indicated based on current knowledge.

Table 2. Molecular Genetic Testing Used in X-Linked Protoporphyria

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ALAS2	Sequence analysis [3]	All variants reported to date [4]
	Gene-targeted deletion/duplication analysis [5]	See footnote 6.

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. Balwani [2019]
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.
6. All *ALAS2* pathogenic variants reported to date are gain-of-function missense variants; thus, testing for deletion (haploinsufficiency) or duplication (overexpression) is not indicated.

Clinical Characteristics

Clinical Description

The natural history of X-linked protoporphyria (XLP) is not as well characterized as that of the autosomal recessive type of erythropoietic protoporphyria (EPP-AR) (see Differential Diagnosis). A natural history study from the US described 22 individuals with XLP from seven unrelated families [Balwani et al 2017].

XLP in Males

While the cutaneous manifestations in males with XLP are similar to those of EPP, Balwani et al [2017] suggest that males with XLP have significantly higher protoporphyrin levels and increased risk of liver dysfunction.

Photosensitivity. Onset of photosensitivity is typically in infancy or childhood (with the first exposure to sun); in most individuals with XLP the photosensitivity is lifelong.

Most males with XLP develop acute cutaneous photosensitivity within five to 30 minutes following exposure to sun or ultraviolet light. Photosensitivity symptoms are provoked mainly by visible blue-violet light in the Soret band, to a lesser degree in the long-wave UV region.

The initial symptoms reported are tingling, burning, and/or itching that may be accompanied by swelling and redness. Symptoms vary based on the intensity and duration of sun exposure; pain may be severe and refractory to narcotic analgesics, persisting for hours or days after the initial phototoxic reaction. Symptoms may seem out of proportion to the visible skin lesions. Blistering lesions are uncommon.

Affected males are also sensitive to sunlight that passes through window glass, which does not block long-wave UVA or visible light.

Cutaneous manifestations. Multiple episodes of acute photosensitivity may lead to chronic changes of sun-exposed skin (lichenification, leathery pseudovesicles, grooving around the lips) and loss of lunulae of the nails. The dorsum of the hands is most notably affected.

Severe scarring is rare, as are hyper- or hypopigmentation, skin friability, and hirsutism.

Unlike in other cutaneous porphyrias, blistering and scarring rarely occur.

Hepatobiliary manifestations. Protoporphyrin is not excreted in the urine by the kidneys, but is taken up by the liver and excreted in the bile. Accumulated protoporphyrin in the bile can form stones, reduce bile flow, and damage the liver. Protoporphyric liver disease may cause back pain and severe abdominal pain (especially in the right upper quadrant).

The information on XLP and liver disease is limited. The risk for liver dysfunction in XLP (observed in 5/31 affected individuals) is higher than the risk in EPP-AR [Whatley et al 2008]. A natural history study in the US showed that 40% of males with XLP had a history of abnormal liver enzymes compared to 33% of persons with EPP-AR. Gallstones were seen in 40% of males with XLP and 33.3% of females with XLP compared to 22.1% of individuals with EPP-AR.

Note that the information on liver involvement presented below is based on experience with liver disease in autosomal recessive EPP. Gallstones composed in part of protoporphyrin may be symptomatic in individuals with XLP and need to be excluded as a cause of biliary obstruction in persons with hepatic decompensation.

Life-threatening hepatic complications are preceded by increased levels of plasma and erythrocyte protoporphyrins, worsening hepatic function tests, increased photosensitivity, and increased deposition of protoporphyrins in hepatic cells and bile canaliculi. End-stage liver disease may be accompanied by motor neuropathy, similar to that seen in acute porphyrias. Comorbid conditions, such as viral hepatitis, alcohol abuse, and use of oral contraceptives, which may impair hepatic function or protoporphyrin metabolism, may contribute to hepatic disease in some [McGuire et al 2005].

Hematologic. Anemia and abnormal iron metabolism can occur in XLP. Mild anemia with microcytosis and hypochromia or occasionally reticulocytosis can be seen; however, hemolysis is absent or mild. In a recent series, 30% of males with XLP and 75% of females with XLP were anemic [Balwani et al 2017]

Vitamin D deficiency. Persons with XLP who avoid sun/light are at risk for vitamin D deficiency [Holme et al 2008, Spelt et al 2010, Wahlin et al 2011a].

Precipitating factors. Unlike the precipitating factors for acute hepatic porphyrias, the only known precipitating factor for XLP is sunlight.

XLP in Females

The phenotype of XLP in heterozygous females, the consequence of random X-chromosome inactivation, ranges from as severe as in affected males to asymptomatic. The median age of symptom onset for females with XLP was 11 years. Following sun exposure, symptom onset ranged from within ten minutes to none [Balwani et al 2017].

Pathophysiology

Bone marrow reticulocytes are thought to be the primary source of the accumulated protoporphyrin that is excreted in bile and feces. Most of the excess protoporphyrin in circulating erythrocytes is found in a small percentage of cells, and the rate of protoporphyrin leakage from these cells is proportional to their protoporphyrin content.

The skin of persons with XLP is maximally sensitive to visible blue-violet light near 400 nm, which corresponds to the so-called "Soret band" (the narrow peak absorption maximum that is characteristic for protoporphyrin and other porphyrins). When porphyrins absorb light they enter an excited energy state. This energy is presumably released as fluorescence and by formation of singlet oxygen and other oxygen radicals that can produce tissue and vessel damage. This may involve lipid peroxidation, oxidation of amino acids, and cross-linking of proteins in cell membranes.

Photoactivation of the complement system and release of histamine, kinins, and chemotactic factors may mediate skin damage. Histologic changes occur predominantly in the upper dermis and include deposition of amorphous material containing immunoglobulin, complement components, glycoproteins, glycosaminoglycans, and lipids around blood vessels. Damage to capillary endothelial cells in the upper dermis has been demonstrated immediately after light exposure in this disease [Schneider-Yin et al 2000].

Long-term observations of individuals with protoporphyria generally show little change in protoporphyrin levels in erythrocytes, plasma, and feces [Gou et al 2018]. In contrast, severe hepatic complications, when they occur, often follow increasing accumulation of protoporphyrin in erythrocytes, plasma, and liver. Iron deficiency and factors that impair liver function sometimes contribute. Enterohepatic circulation of protoporphyrin may favor its return and retention in the liver, especially when liver function is impaired. Liver damage probably results at least in part from protoporphyrin accumulation itself. As this porphyrin is insoluble, it tends to form crystalline structures in liver cells, can impair mitochondrial functions in liver cells, and can decrease hepatic bile formation and flow [Anderson et al 2001].

Genotype-Phenotype Correlations

Because of the limited number of families known to have XLP, no genotype-phenotype correlations have been identified.

Penetrance

XLP appears to be 100% penetrant in males.

In heterozygous females, clinical variability is attributed to random X-chromosome inactivation. Symptomatic females have been reported [Whatley et al 2008, Di Pierro et al 2009].

Nomenclature

Although sometimes considered a synonym for XLP, the term "erythropoietic protoporphyria, X-linked dominant" is incorrect and should not be used: in all X-linked metabolic disorders the phenotype in heterozygous females can range from asymptomatic to as severe as that seen in affected male relatives.

Prevalence

The prevalence of XLP is unknown.

- Based on studies from the UK, XLP appears to account for about 2% of individuals with the erythropoietic protoporphyria phenotype [Whatley et al 2010].
- In the US, XLP accounts for about 10% of individuals with the erythropoietic protoporphyria phenotype [Balwani et al 2017].

Genetically Related (Allelic) Disorders

X-linked sideroblastic anemia, the only other phenotype known to be associated with pathogenic variants in *ALAS2*, is caused by pathogenic loss-of-function variants throughout *ALAS2*.

Differential Diagnosis

Other causes of the X-linked protoporphyria (XLP) phenotype include the following:

- Polymorphous light eruption
- Solar urticaria
- Drug-induced photosensitivity

The phenotype of acquired late-onset cutaneous photosensitivity and elevated erythrocyte protoporphyrins, observed on occasion in myelodysplastic syndrome, is caused by somatic pathogenic variant(s) or chromosome 18 deletions that decrease ferrochelatase activity, presumably resulting from the genomic instability associated with this syndrome [Aplin et al 2001, Sarkany et al 2006, Blagojevic et al 2010].

Late-onset XLP with photosensitivity and elevated protoporphyrin levels has been reported in an instance of emerging myelodysplastic syndrome with somatic mosaicism of a nonsense *ALAS2* variant in the bone marrow [Livideanu et al 2013].

Erythropoietic protoporphyria, autosomal recessive (EPP-AR) is caused by biallelic pathogenic variants in *FECH* (encoding ferrochelatase). The photosensitivity and cutaneous manifestations are clinically indistinguishable from those seen in males with XLP. The only significant phenotypic difference is that only about 20%-30% of individuals with EPP-AR have some degree of liver dysfunction, which is typically mild with slight elevations of the liver enzymes; however, up to 5% may develop more advanced liver disease.

In EPP-AR free protoporphyrin levels are elevated significantly as compared to zinc-chelated protoporphyrin (Table 3).

Table 3. Biochemical Characteristics of Autosomal Recessive Erythropoietic Protoporphyria (EPP-AR)

Deficient Enzyme	Enzyme Activity	Erythrocytes	Urine	Stool	Other
Ferro-chelatase	~10%-30% of normal	Free protoporphyrin ↑: >90% free, <10% zinc-chelated	Protoporphyrins normal	Protoporphyrin normal or ↑	Plasma porphyrins ↑

Possible additional genetic loci. It is presumed that additional loci may be responsible for the EPP phenotype (i.e., cutaneous photosensitivity and elevated erythrocyte protoporphyrins). Molecular epidemiology studies in the UK have identified biallelic *FECH* pathogenic variants or an *ALAS2* pathogenic variant in only 94% of individuals with the EPP phenotype [Whatley et al 2010]. Studies in the North American population showed that 4% of persons with the EPP phenotype and elevated protoporphyrin levels did not have a detectable *FECH* or *ALAS2* pathogenic variant.

Recently a heterozygous pathogenic variant was identified in CLPX, a heme biosynthesis modulator, in a family with elevated protoporphyrin levels and the EPP phenotype inherited in an autosomal dominant manner [Yien et al 2017].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with X-linked protoporphyria (XLP), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended [Balwani 2019]:

- Comprehensive medical history including history of phototoxicity
- Complete physical examination, including thorough skin examination

- Assessment of erythrocyte protoporphyrin levels (free and zinc-chelated), complete blood count with indices to evaluate for anemia, and iron profile (including ferritin) to monitor iron stores
- Assessment for liver disease:
  - Hepatic function panel (including serum aminotransferases)
  - Imaging studies such as abdominal ultrasound examination if cholelithiasis is suspected
  - Newer imaging modalities such as Fibroscan® may be useful in evaluating liver fibrosis; however, this has not been validated in erythropoietic protoporphyria, autosomal recessive (EPP-AR) or XLP.
  - A liver biopsy may be indicated to evaluate for protoporphyric liver disease.
- Vitamin D studies to evaluate for deficiency as affected individuals are predisposed to vitamin D insufficiency resulting from sun avoidance
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Acute photosensitivity. Although several treatments have been proposed, most have been tried only in a single individual or a small number of patients.

- Use of protective clothing including long sleeves, gloves, and wide-brimmed hats is indicated.
- Protective tinted glass for cars and windows prevents exposure to UV light. Gray or smoke-colored filters provide only partial protection.
- Topical sunscreens are typically not useful; however, some tanning products containing creams that cause increased pigmentation may be helpful. Sun creams containing a physical reflecting agent (e.g., zinc oxide) are often effective but are not cosmetically acceptable to all.
- Oral Lumitene™ (β-carotene) (120–180 mg/dL) has been used to improve tolerance to sunlight if the dose is adjusted to maintain serum carotene levels in the range of 10-15 µmol/L (600–800 µg/dL), causing mild skin discoloration due to carotenemia. The beneficial effects of β-carotene may involve quenching of singlet oxygen or free radicals. However, a systematic review of about 25 studies showed that the available data are unable to prove efficacy of treatments including beta-carotene, N-acetyl cysteine, and vitamin C [Minder et al 2009].
- Afamelanotide (Scenesse®), a controlled-release, long-acting, α-melanocyte-stimulating hormone analogue, increases eumelanin by binding to the melanocortin-1 receptor and provides photoprotection by increasing pigmentation and antioxidant properties [Harms et al 2009, Minder 2010].

Afamelanotide showed positive results in Phase III clinical trials in the US and Europe [Langendonk et al 2015]. Long-term studies in Europe show good compliance, clinical effectiveness, and improved quality of life [Biolcati et al 2015]. It was approved for patients with the EPP phenotype by the European Medicines Agency in 2014, and by the FDA in October 2019.

Hepatic disease. Treatment of hepatic complications, which may be accompanied by motor neuropathy, is difficult.

- Cholestyramine and other porphyrin absorbents, such as activated charcoal, may interrupt the enterohepatic circulation of protoporphyrin and promote its fecal excretion, leading to some improvement [McCullough et al 1988].
- Plasmapheresis and intravenous hemin are sometimes beneficial [Do et al 2002].
- Liver transplantation has been performed as a lifesaving measure in individuals with severe protoporphyric liver disease [McGuire et al 2005, Wahlin et al 2011b]. However, many transplant recipients experience a recurrence of the protoporphyric liver disease in the transplanted liver. Combined bone marrow and liver transplantation is indicated in patients with liver failure to prevent future damage to the allografts [Rand et al 2006], and sequential liver and bone marrow transplantation has been successful in curing protoporphyric liver disease [Wahlin & Harper 2010].

- Bone marrow transplantation has also been attempted without liver transplantation in some instances. A child age two years with XLP and stage IV hepatic fibrosis was treated with a hematopoietic progenitor cell transplantation that stabilized his liver disease, thus avoiding liver transplantation [Butler et al 2015].

Other

- Vitamin D supplementation is advised as patients are predisposed to vitamin D insufficiency resulting from sun avoidance.
- Immunization for hepatitis A and B is recommended.
- Iron supplementation may be attempted in persons with XLP who have anemia and low ferritin levels.

  Whatley et al [2008] reported some evidence of diminished iron stores in males with XLP; in one patient with iron deficiency, iron repletion decreased protoporphyrin accumulation and corrected the anemia. Subsequent reports indicate that iron supplementation can improve protoporphyrin levels, liver damage, and anemia in XLP [Landefeld et al 2016]. A pilot study using oral iron supplementation in persons with XLP showed a reduction in protoporphyrin levels [Balwani 2019].

Surveillance

Table 4. Recommended Surveillance for Individuals with X-Linked Protoporphyria

System/Concern	Evaluation	Frequency
Erythrocyte protoporphyrin levels & plasma total porphyrins	Both free & zinc-chelated	Annually
Anemia	Complete blood count w/indices	
Iron store depletion	Serum ferritin levels	
Hepatic involvement	Hepatic function (liver transaminases)	
	US exam (if cholelithiasis is suspected)	As indicated
	Fibroscan® to evaluate for hepatic fibrosis	
Vitamin D deficiency	Vitamin D 25-OH levels whether or not receiving supplements	Annually

US = ultrasound

Agents/Circumstances to Avoid

The following are appropriate:

- Avoidance of sunlight and UV light
- In patients with hepatic dysfunction, avoidance of alcohol and drugs that may induce cholestasis (e.g., estrogens)
- In patients with cholestatic liver failure, use of protective filters for artificial lights in the operating room to prevent phototoxic damage during procedures such as endoscopy and surgery [Wahlin et al 2008]

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of at-risk newborn or infant family members in order to identify as early as possible those who would benefit from early intervention (sun protection) and routine monitoring (Table 4).

Evaluations include:

- Targeted molecular genetic testing if the *ALAS2* pathogenic variant has been identified in an affected family member;
- Detection of markedly elevated erythrocyte protoporphyrin levels with a predominance of metal-free protoporphyrin if the pathogenic variant in the family is not known.

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

Pregnancy Management

There is no information on pregnancy management in XLP. Based on experience with autosomal recessive EPP, pregnancy is unlikely to be complicated by XLP [Poh-Fitzpatrick 1997].

Therapies Under Investigation

A Phase II clinical trial with MT-7117, an oral small molecule that works as a melanocortin 1 receptor agonist and increases skin pigmentation, has been completed. A Phase III clinical trial for adults and children is planned for MT-7117.

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

By definition, X-linked protoporphyria is inherited in an X-linked manner.

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 *ALAS2* 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 *ALAS2* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism. No data on the frequency of germline mosaicism in XLP are available.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have a *de novo ALAS2* pathogenic variant, in which case the mother is not heterozygous. No data on the frequency of *de novo* pathogenic variants in XLP are available.

Parents of a female proband

- A female proband may have inherited the *ALAS2* pathogenic variant from either her mother or her father, or the pathogenic variant may be *de novo*.
- Detailed evaluation of the parents and review of the extended family history may help to distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant. Molecular

genetic testing of the mother (and possibly the father, or subsequently the father) can determine if the *ALAS2* pathogenic variant was inherited.

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

- If the mother of the proband has an *ALAS2* 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 may be asymptomatic or have clinical manifestations of the disorder ranging from mild to severe depending on favorable vs nonfavorable X-chromosome inactivation (see Penetrance).
- If a male proband represents a simplex case and if the *ALAS2* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of maternal germline mosaicism.

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

- If the mother of the proband has an *ALAS2* 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 (see **Sibs of a male proband**).
- If the father of the proband has an *ALAS2* pathogenic variant, he will transmit the variant to all of his daughters and none of his sons.
- If a female proband represents a simplex case and if the *ALAS2* pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of parental germline mosaicism.

Offspring of a male proband. Affected males transmit the *ALAS2* pathogenic variant to:

- All of their daughters, who will be heterozygotes and may be asymptomatic or have clinical manifestations of the disorder ranging from mild to severe depending on favorable vs nonfavorable X-chromosome inactivation (see Penetrance);
- None of their sons.

Offspring of a female proband. Women with an *ALAS2* pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child:

- Males who inherit the pathogenic variant will be affected. Note: Asymptomatic or mildly symptomatic females are at risk for having affected male children who may have early-onset, more severe symptoms.
- Females who inherit the pathogenic variant will be heterozygotes (see **Offspring of a male proband**).

Other family members

- The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.
- 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.

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 or at risk of having the *ALAS2* pathogenic variant.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ALAS2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

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

- **MedlinePlus**
  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
- **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. X-Linked Protoporphyria: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

ALAS2	Xp11.21	5-aminolevulinate synthase, erythroid-specific, mitochondrial	ALAS2 database	ALAS2	ALAS2

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 X-Linked Protoporphyria (View All in OMIM)

300752	PROTOPORPHYRIA, ERYTHROPOIETIC, X-LINKED; XLEPP
301300	DELTA-AMINOLEVULINATE SYNTHASE 2; ALAS2

Molecular Pathogenesis

ALAS2 encodes an erythroid-specific 5-aminolevulinate synthase; the normal isoform (NP_000023.2) has 587 amino acid residues, including a 49-amino acid transit peptide. The C-terminal amino acids encoded by exon 11 interact with the active site or other cofactors in a manner that regulates the activity of the enzyme.

Disease-associated alteration of erythroid-specific 5-aminolevulinate synthase C-terminal amino acids results in increased ALAS2 enzyme activity [Whatley et al 2008, Balwani et al 2013, Bishop et al 2013] and systemic accumulation of free and zinc-chelated protoporphyrins, particularly in erythroid and hepatic cells. The rate of 5-aminolevulinic acid formation is increased to such an extent that insertion of iron into protoporphyrin becomes rate limiting for heme synthesis, resulting in the accumulation of protoporphyrins [Whatley et al 2008].

Mechanism of disease causation. All *ALAS2* pathogenic variants associated with XLP are located in the last exon (exon 11 of NM_000032.4) and result in a gain-of-function effect. Reported disease-associated variants to date include missense, nonsense, and several small deletion variants (Table 5).

***ALAS2*-specific laboratory technical considerations.** Variants causing XLP have only been observed in exon 11 (NM_000032.4), which encodes the C terminus of the protein [Balwani 2019].

Table 5. Notable *ALAS2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_000032.4 NP_000023.2	c.1642C>T	p.Glu548Ter	XLP disease-assoc variants in exon 11 that have a gain-of-function effect
	c.1651_1676del	p. Ser551ProfsTer6	
	c.1699_1700delAT	p.Met567GlufsTer2	
	c.1706_1709delAGTG	p.Glu569GlyfsTer24	
	c.1736delG	p.Gln581SerfsTer13	

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

Chapter Notes

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