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

NLM Citation: Balwani M, Bloomer J, Desnick R; Porphyrias Consortium of the NIH-Sponsored Rare Diseases Clinical Research Network. Erythropoietic Protoporphyria, Autosomal Recessive. 2012 Sep 27 [Updated 2017 Sep 7]. 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/

Erythropoietic Protoporphyria, Autosomal Recessive

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

Created: September 27, 2012; Updated: September 7, 2017.

Summary

Clinical characteristics

Erythropoietic protoporphyria (EPP) is characterized by cutaneous photosensitivity (usually beginning in infancy or childhood) that results in tingling, burning, pain, and itching within 30 minutes after exposure to sun or ultraviolet light and may be accompanied by swelling and redness. Symptoms (which may seem out of proportion to the visible skin lesions) may persist for hours or days after the initial phototoxic reaction. Photosensitivity remains for life. 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. Approximately 20%-30% of individuals with EPP have some degree of liver dysfunction, which is typically mild with slight elevations of the liver enzymes. Up to 5% may develop more advanced liver disease which may be accompanied by motor neuropathy similar to that seen in the acute porphyrias.

Diagnosis/testing

The diagnosis of EPP is established by detection of markedly increased free erythrocyte protoporphyrin and/or by the identification of biallelic pathogenic variants in *FECH* on molecular genetic testing.

Management

Treatment of manifestations: Afamelanotide (Scenesse®), a synthetic α-melanocyte stimulating hormone analog was approved for treatment of EPP by the European Medicines Agency in 2014 and is awaiting approval in the US by the FDA. This medication increases pain-free sun exposure and has improved quality of life in those with EPP. The phototoxic pain is not responsive to narcotic analgesics. Current management centers on prevention of the painful attacks by avoidance of sun/light (including the long-wave ultraviolet light sunlight that passes

Author Affiliations: 1 Icahn School of Medicine at Mount Sinai New York, New York; Email: manisha.balwani@mssm.edu; Email: robert.desnick@mssm.edu. 2 University of Alabama at Birmingham Birmingham, Alabama; Email: jbloomer@uab.edu.

* See Chapter Notes, Acknowledgments.

Copyright © 1993-2024, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

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.

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 may be required.

Prevention of primary manifestations. Sun avoidance.

Prevention of secondary complications: Vitamin D supplementation to prevent vitamin D insufficiency due to sun avoidance. Immunization for hepatitis A and B.

Surveillance: Monitoring of: hepatic function every six to 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: Avoid: sunlight and UV light; for those with hepatic dysfunction, drugs that may induce cholestasis (e.g., estrogens). For those with cholestatic liver failure, use of protective filters for artificial lights in the operating room to avoid phototoxic damage.

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

Genetic counseling

EPP is inherited in an autosomal recessive manner. In about 96% of cases an affected individual inherits a loss-of-function *FECH* allele from one parent and a low-expression *FECH* allele from the other parent. In about 4% of cases, an affected individual has two loss-of-function *FECH* alleles. 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) and individuals who inherit two low-expression alleles are asymptomatic. Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk are possible if the pathogenic variants in the family have been identified.

Diagnosis

Suggestive Findings

Erythropoietic protoporphyria (EPP) **should be suspected** in individuals with the following clinical features and suggestive laboratory findings.

Clinical features

- Cutaneous photosensitivity, usually beginning in childhood
- Burning, tingling, and itching (the most common findings); may occur within minutes of sun/light exposure, followed later by erythema and swelling
- Burning, itching, and intense pain; 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 establish the diagnosis.)
- Hepatic dysfunction; may occur in 20%-30% of individuals (~2%-5% have severe liver disease that may be life threatening, necessitating liver transplantation.)

Suggestive biochemical laboratory findings. Detection of markedly increased free erythrocyte protoporphyrin is the most sensitive and specific biochemical diagnostic test for EPP (see Table 1).

Note: It is important to evaluate by using an assay that distinguishes free protoporphyrin from zinc-chelated protoporphyrin, as several other conditions may lead to elevation of erythrocyte protoporphyrins (see Table 1, footnote 5).

Table 1. Biochemical Characteristics of Erythropoietic Protoporphyria (EPP)

Deficient Enzyme	Enzyme Activity	Erythrocytes	Urine	Stool	Other
Ferrochelatase [1]	~10%-30% of normal [2]	Free protoporphyrin: increased [3, 4, 5, 6]	Protoporphyrins: normal	Protoporphyrin: normal or increased	Plasma porphyrins: increased [7, 8]

1. Deficient activity of ferrochelatase (EC 4.99.1.1), encoded by *FECH*, leads to the systemic accumulation of free protoporphyrin and a markedly lesser amount of zinc-chelated protoporphyrin, particularly in erythroid and hepatic cells.
2. The assay for the enzyme ferrochelatase is not widely available and is not used for diagnostic purposes.
3. In EPP, free protoporphyrin levels are elevated significantly as compared to zinc-chelated protoporphyrin.
4. 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.
5. 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), which are more severe than the acute autosomal dominant porphyrias (e.g., hereditary coproporphyria) caused by a heterozygous variant of the same gene (e.g., *CPOX*).
6. In X-linked protoporphyria (XLP), resulting from pathogenic gain-of-function variants in exon 11 of *ALAS2*, both free and zinc-chelated protoporphyrins are increased (see Differential Diagnosis).
7. Plasma porphyrins of the III-isomer series are usually increased.
8. Plasma total porphyrins are increased in porphyrias with cutaneous manifestations including EPP. If plasma porphyrins are increased, the fluorescence emission spectrum of plasma porphyrins at neutral pH can be characteristic and can distinguish EPP from other porphyrias. The emission maximum in EPP occurs at 632-634 nm.

Establishing the Diagnosis

The diagnosis of EPP **is established** in a proband who has markedly increased free erythrocyte protoporphyrin and/or by the identification of biallelic pathogenic variants in *FECH* on molecular genetic testing (see Table 2).

Molecular genetic testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *FECH* is performed first, and followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
- **A multigene panel** that includes *FECH* 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.

- **More comprehensive genomic testing** (when available) including exome sequencing and genome sequencing may be considered if single-gene testing (and/or use of a multigene panel that includes *FECH*) fails to confirm a diagnosis in an individual with features of EPP and a significantly elevated erythrocyte protoporphyrin level. Such testing may provide or suggest a diagnosis not previously considered (e.g., mutation of a different gene or genes that results in a similar clinical presentation). 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 Erythropoietic Protoporphyria

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
FECH	Sequence analysis [3]	~91.5% [4]
	Gene-targeted deletion/duplication analysis [5]	~8.5% [6]
Unknown [7]	NA	

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. In addition to flanking intronic regions, sequence analysis must include deep regions of at least some introns to detect splicing or other pathogenic variant alleles (in particular, the common c.315-48T>C variant).
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include 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. Whatley et al [2007], Balwani et al [2013]
7. In males the phenotype of EPP is clinically indistinguishable from that of X-linked protoporphyria (XLP). Based on reported and unreported information, individuals with an EPP or XLP phenotype and with significantly elevated erythrocyte protoporphyrin levels who do not have *FECH* or *ALAS2* pathogenic variants have (rarely) been noted in the European Union [Whatley et al 2010] as well as in the US (9 individuals) [Balwani et al 2017].

Note: Individuals with EPP have pathogenic variants in both *FECH* alleles.

- About 96% of affected individuals are compound heterozygotes for a pathogenic variant resulting in markedly decreased ferrochelatase activity and a second low-expression pathogenic variant (c.315-48T>C; also known as IVS3-48T>C) resulting in residual ferrochelatase activity.

  In populations in which a low-expression allele is quite common (see Prevalence), the disorder may appear to be "pseudodominant" – that is, an autosomal recessive condition present in individuals in two or more generations of a family, thereby appearing to follow a dominant inheritance pattern. An example is the low-expression allele resulting from the cryptic splicing variant c.315-48T>C that has an allele frequency of about 10% in healthy individuals of European descent [Gouya et al 1999, Gouya et al 2002].

- In about 4% of families with EPP, two pathogenic loss-of-function *FECH* variants are inherited, resulting in very low levels of functional ferrochelatase [Whatley et al 2010].

Clinical Characteristics

Clinical Description

Photosensitivity. Onset of photosensitivity is typically in infancy or childhood (with the first exposure to sun) and the photosensitivity remains for life.

- Most individuals with EPP develop acute cutaneous photosensitivity within 30 minutes after exposure to sun or ultraviolet light.
- Photosensitivity symptoms are provoked mainly by visible blue-violet light in the Soret band and to a lesser degree in the long-wave UV region.
- Affected individuals are also sensitive to sunlight that passes through window glass that does not block long-wave UVA or visible light.
- 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.
- Pregnancy has been associated with decreased protoporphyrin levels and increased tolerance to sun exposure [Anderson et al 2001, Wahlin et al 2011a].

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 pigment changes, friability, and hirsutism.
- Blistering was reported in 26% of individuals in one large series [Balwani et al 2017].
- Palmar keratoderma has been observed in some individuals with two loss-of-function *FECH* alleles (in contrast to one severe loss-of-function allele and the low-expression allele) [Holme et al 2009, Méndez et al 2009, Minder et al 2010].

Hepatobiliary manifestations. Protoporphyrin is not excreted 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 severe abdominal pain (especially in the right upper quadrant) and back pain.
- Gallstones composed in part of protoporphyrin may be symptomatic in individuals with EPP and need to be excluded as a cause of biliary obstruction in persons with hepatic decompensation.
- About 20%-30% of individuals with EPP have some degree of liver dysfunction.
- In most cases, the hepatic manifestations are mild with slight elevations of the liver enzymes.
- However, up to 5% of affected individuals may develop more advanced liver disease, most notably cholestatic liver failure. In most of these individuals, underlying liver cirrhosis is already present; however, some may present with rapidly progressive cholestatic liver failure.
- 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 including 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].
- The risk of liver disease appears to be related to higher protoporphyrin levels.

Hematologic manifestations. Anemia and abnormal iron metabolism can occur in EPP. Mild anemia with microcytosis and hypochromia or occasionally reticulocytosis can be seen; however, hemolysis is absent or mild.

Vitamin D deficiency. Persons with EPP 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 acute hepatic porphyrias, the only known precipitating factor for EPP is sun/light.

Pathophysiology

The deficient activity (<30% of normal) of ferrochelatase results in EPP.

Bone marrow reticulocytes are thought to be the primary source of the accumulated protoporphyrin that is excreted in bile and feces. At times, the liver may be an important source of excess protoporphyrin, but measuring its contribution relative to that of the erythron has not been possible.

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. Erythrocyte protoporphyrin in EPP is more than 90% free and not complexed with zinc. The content of free protoporphyrin in these cells declines much more rapidly when red cells age than it does in conditions in which erythrocyte zinc-chelated protoporphyrin is increased. Moreover, ultraviolet light may cause free protoporphyrin to be released from the red cell even without disruption of the red cell membrane. In this manner, free protoporphyrin may then diffuse into the plasma (where it is bound to albumin) and be taken up by the endothelium of blood vessels.

The skin of persons with EPP 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, acid 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].

As noted, individuals with EPP appear to be predisposed to developing gallstones that are fluorescent and contain large quantities of protoporphyrin. In one series, approximately 22% of individuals with EPP had a known history of gallstones [Balwani et al 2017]. This and other hepatobiliary complications relate to uptake and excretion of protoporphyrin by the liver [Bloomer 1988]. This dicarboxyl porphyrin is not soluble in aqueous solution and is therefore not excreted in urine.

Long-term observations of patients with protoporphyria generally show little change in protoporphyrin levels in erythrocytes, plasma, and feces. On the other hand, severe hepatic complications, when they do 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, tends to form crystalline structures in liver cells, can impair mitochondrial functions in liver cells, and can decrease hepatic bile formation and flow [Bloomer 1988, Anderson et al 2001].

Genotype-Phenotype Correlations

About 96% of affected individuals are compound heterozygotes for a loss-of-function variant that markedly decreases ferrochelatase (FECH) activity and a second low-expression pathogenic variant which also decreases the FECH activity by about 50%.

Persons with low residual activity may have a more severe clinical presentation. Palmar keratoderma was reported in persons with two loss-of-function *FECH* variants [Holme et al 2009, Méndez et al 2009, Minder et al 2010]. Some reports have indicated that null variants in *FECH* may be associated with liver complications [Minder et al 2002],

Individuals with EPP with pathogenic missense variants have significantly lower median erythrocyte protoporphyrin levels than those with deletions or nonsense or consensus splice site variants. The greater the level of erythrocyte protoporphyrin, the more likely that the patient will be more severely affected, characterized by decreased sun tolerance and increased risk of liver dysfunction [Balwani et al 2017].

Penetrance

EPP appears to be 100% penetrant when there are biallelic *FECH* loss-of-function variants or compound heterozygosity for a *FECH* loss-of-function variant and a variant that causes low expression of the other *FECH* allele.

Nomenclature

Obsolete terms for EPP are: erythrohepatic protoporphyria, heme synthetase deficiency, and ferrochelatase deficiency

Prevalence

EPP is the third most common porphyria, with an estimated incidence of two to five in 1,000,000; it is the most common porphyria in children.

EPP is equally common in women and men. The prevalence ranges from 1:75,000 in the Netherlands (as the result of a founder effect) to 1:200,000 reported in Wales [Holme et al 2006].

EPP has been described worldwide. The prevalence of EPP may vary based on the population allele frequency of the low-expression c.315-48T>C allele, which ranges from approximately 1%-3% in Africans to approximately 43% in Japanese.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Other causes of the erythropoietic protoporphyria (EPP) phenotype include the following.

Acquired causes

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

Acquired late-onset EPP phenotype has been described in rare instances secondary to myelodysplastic syndrome caused by somatic pathogenic variant(s) that decrease ferrochelatase activity, presumably a result of the genomic instability associated with myelodysplasia [Aplin et al 2001, Sarkany et al 2006, Blagojevic et al 2010].

X-linked protoporphyria (XLP) (also known as EPP, X-linked) is caused by pathogenic gain-of-function variants in exon 11 of *ALAS2* (the gene encoding erythroid-specific 5-aminolevulinate synthase). In males the phenotype is clinically indistinguishable from that of EPP caused by two *FECH* pathogenic variants; in female heterozygotes the phenotype is more variable, depending primarily on random X-chromosome inactivation [Brancaleoni et al 2016]. A higher percentage of persons with liver dysfunction have been reported with XLP [Whatley et al 2008].

Recent natural history studies showed that 37.5% of males with XLP and 22.2% of females with XLP had abnormal serum aminotransferases compared to 13.7% of individuals with EPP [Balwani et al 2017].

In XLP, the ratio of free protoporphyrin to zinc-chelated protoporphyrin may range from 90:30 to 50:50 (Table 3). Plasma levels of protoporphyrin are elevated.

Table 3. Biochemical Characteristics of X-Linked Protoporphyria (XLP)

Enzyme	Enzyme Activity	Erythrocytes	Urine	Stool	Other
Erythroid-specific 5-aminolevulinate synthase	>100% [1] of normal	Free protoporphyrin / zinc-chelated protoporphyrin: ratio 90:30 to 50:50	Protoporphyrins: not detectable	Protoporphyrin: normal or increased	Plasma porphyrins: increased

1. Increased activity due to pathogenic "gain-of-function" variants in *ALAS2* exon 11

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

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with erythropoietic protoporphyria (EPP), the following evaluations are recommended:

- Assessment of erythrocyte protoporphyrin levels (free and zinc-chelated), hematologic indices, and iron profile if not performed as part of diagnostic testing
- Assessment of hepatic function as well as imaging studies such as abdominal sonogram if cholelithiasis is suspected
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Acute photosensitivity. Afamelanotide (Scenesse®), a synthetic α-melanocyte-stimulating hormone analog was approved for treatment of EPP by the European Medicines Agency in 2014. The drug is administered through a subcutaneously inserted bioresorbable implant which results in increased pigmentation due to an increase in

eumelanin. Phase III clinical trials in the US and Europe showed an increase in pain-free sun exposure and improved quality of life in individuals with EPP. In the United States, the drug is pending FDA approval.

The phototoxic pain is not responsive to narcotic analgesics.

Current management centers on prevention of the painful attacks by avoidance of sun/light, including the long-wave ultraviolet light sunlight that passes through window glass:

- Sun protection using protective clothing including long sleeves, gloves, and wide-brimmed hats
- Protective tinted glass for cars and windows to prevent exposure to UV light. Grey or smoke-colored filters provide only partial protection.
- Tanning products. Some tanning creams which cause increased pigmentation may be helpful. Sun creams containing a physical reflecting agent are often effective but are not cosmetically acceptable to all. Topical sunscreens are typically not useful.
- β-carotene. Oral Lumitene™ (120-180 mg/dL) may improve tolerance to sunlight in some patients 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 dose of Lumitene depends on age, ranging from two to ten 30-mg capsules per day and usually started six to eight weeks before summer. The beneficial effects of β-carotene may involve quenching of singlet oxygen or free radicals. However, there are currently no data to support its efficacy [Minder et al 2009].

Hepatic disease. Some affected individuals develop severe liver complications that are difficult to treat, often requiring liver transplantation [Anderson et al 2001]. Hepatic complications may be accompanied by motor neuropathy.

- 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 life-saving measure in individuals with severe protoporphyric liver disease [McGuire et al 2005, Wahlin et al 2011b]. However, transplant recipients may experience a recurrence of 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].

Other. Iron supplementation may be attempted in persons with anemia and abnormal iron metabolism; close monitoring is warranted. Both clinical improvement and increased photosensitivity have been reported during iron replacement therapy [Holme et al 2007, Lyoumi et al 2007].

Prevention of Primary Manifestations

Sun avoidance is the only effective means of preventing primary manifestations.

Prevention of Secondary Complications

Vitamin D supplementation is advised as patients are predisposed to vitamin D insufficiency as a result of to sun avoidance.

Immunization for hepatitis A and B is recommended.

Surveillance

Annual assessment of erythrocyte protoporphyrin levels (free and zinc-chelated), hematologic indices, and iron profile is appropriate.

Hepatic function should be monitored every six to 12 months. Hepatic imaging studies including abdominal sonogram are indicated if cholelithiasis is suspected.

Vitamin D 25-OH levels should be monitored in all patients whether or not they are receiving supplements.

Agents/Circumstances to Avoid

The following are appropriate:

- Avoidance of sunlight and UV light
- In patients with hepatic dysfunction, avoidance of 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 evaluate at-risk family members as newborns or infants in order to identify as early as possible those who would benefit from early intervention (sun protection) and future monitoring for signs of liver dysfunction.

Evaluations can include the following:

- Molecular genetic testing if both *FECH* pathogenic variants in the family are known
- Biochemical testing to detect markedly increased free erythrocyte protoporphyrin 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

Pregnancy is not complicated by EPP. There may be some improvement in photosensitivity during pregnancy as well as a reduction in protoporphyrin levels [Poh-Fitzpatrick 1997, Heerfordt & Wulf 2016].

Therapies Under Investigation

Phase III clinical trials from the US and Europe with a subcutaneous insertion of a biodegradable, slow-released α-melanocyte-stimulating hormone analog, afamelanotide (Scenesse®), which increases pigmentation by increasing melanin, showed increased pain-free sun exposure and improved quality of life in those with EPP [Harms et al 2009, Minder et al 2009, Minder 2010, Langendonk et al 2015]. A long-term observational study of 115 individuals receiving Scenesse® for up to eight years showed improved quality of life and high compliance with the drug [Biolcati et al 2015].

- Scenesse® is currently approved for use in patients with EPP in the European Union.
- In the United States, the drug is pending FDA review.

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

Erythropoietic protoporphyria (EPP) is inherited in an autosomal recessive manner.

Note: Because of the relatively high carrier frequency of a low-expression *FECH* allele in some populations, and the observation of two-generation occurrence in some families, EPP was initially thought to be inherited in an autosomal dominant manner. However, molecular genetic studies have determined that the inheritance pattern is autosomal recessive.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers) for either a *FECH* loss-of-function allele or the common low-expression *FECH* allele.
  - Most often one parent transmits the loss-of-function *FECH* allele and the other transmits the common low-expression *FECH* allele to their affected child.
  - In about 4% of couples, both parents transmit a loss-of-function *FECH* allele to their affected child.
- Heterozygotes (carriers) and individuals who inherit two low-expression alleles are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- 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) and sibs who inherit two low-expression alleles are asymptomatic.

Offspring of a proband

- The offspring of an individual with EPP are obligate heterozygotes (carriers) for a loss-of-function *FECH* allele or the low-expression *FECH* allele.
- Unless an individual with EPP has children with an affected individual or a carrier of a loss-of-function *FECH* allele or low-expression *FECH* allele, his/her offspring will be obligate heterozygotes (carriers) for a loss-of-function *FECH* allele or the low-expression *FECH* allele. Note: An individual who inherits two copies of the common low-expression *FECH* allele does not manifest EPP.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a loss of function *FECH* allele or low-expression *FECH* allele.

Carrier Detection

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

Biochemical testing is not used for carrier detection.

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, clarification of carrier status, 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

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

Biochemical testing is not used for prenatal diagnosis.

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
- **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
- **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. Erythropoietic Protoporphyria, Autosomal Recessive: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
FECH	18q21.31	Ferrochelatase, mitochondrial	FECH database	FECH	FECH

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 Erythropoietic Protoporphyria, Autosomal Recessive (View All in OMIM)

177000	PROTOPORPHYRIA, ERYTHROPOIETIC, 1; EPP1
612386	FERROCHELATASE; FECH

Gene structure. Two transcript variants encoding different isoforms have been found for *FECH*. The transcript variant NM_000140.3 has 11 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Nearly 200 pathogenic variants [Stenson et al 2020, HGMD] have been identified in *FECH*, many of which result in an unstable or absent enzyme. Loss-of-function variants include missense and nonsense variants, small deletions, and insertions. The common low-expression allele c.315-48T>C creates a cryptic splice acceptor site and decreases the abundance of the normal transcript to about 25% of normal levels. The aberrantly spliced mRNA is degraded by a nonsense-mediated decay mechanism. This variant has an allele frequency of about 10% in healthy individuals of European descent [Gouya et al 1999, Gouya et al 2002].

Table 4. Selected *FECH* Pathogenic Variants

DNA Nucleotide Change (Conventional Nomenclature [1])	Predicted Protein Change	Reference Sequences
c.315-48T>C [2] (IVS3-48T>C)	Aberrant splicing of exon 4	NM_000140.3 NP_000131.2

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. Conventional variant nomenclature: Human Genome Variation Society (varnomen.hgvs.org)
2. Variant designation that does not conform to current naming conventions

Normal gene product. The normal gene encodes an enzyme of 423 amino acids (NP_000131.2), including a 54-residue polypeptide for localization in the mitochondrion.

Abnormal gene product. Pathogenic variants in *FECH* result in either a nonfunctional or a partially functional enzyme.

About 96% of affected individuals are compound heterozygotes for a pathogenic variant resulting in markedly decreased ferrochelatase activity and a second low-expression mutated allele (c.315-48T>C) resulting in residual ferrochelatase activity. In about 4% of families with EPP, two pathogenic loss-of-function *FECH* variants are inherited, resulting in very low levels of functional ferrochelatase [Whatley et al 2010].

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, Valle D, Childs B, Vogelstein B, eds. *The Metabolic and Molecular Basis of Inherited Disease*. 8 ed. New York, NY: McGraw-Hill; 2001:2991-3062.

Aplin C, Whatley SD, Thompson P, Hoy T, Fisher P, Singer C, Lovell CR, Elder GH. Late-onset erythropoietic porphyria caused by a chromosome 18q deletion in erythroid cells. J Invest Dermatol. 2001;117:1647–9. PubMed PMID: 11886534.

Balwani M, Doheny D, Bishop DF, Nazarenko I, Yasuda M, Dailey HA, Anderson KE, Bissell DM, Bloomer J, Bonkovsky HL, Phillips JD, Liu L, Desnick RJ; Porphyrias Consortium of the National Institutes of Health Rare Diseases Clinical Research Network. Loss-of-function ferrochelatase and gain-of-function erythroid-specific 5-aminolevulinate synthase mutations causing erythropoietic protoporphyria and x-linked protoporphyria in North American patients reveal novel mutations and a high prevalence of X-linked protoporphyria. Mol Med. 2013;19:26–35. PubMed PMID: 23364466.

Balwani M, Naik H, Anderson KE, Bissell DM, Bloomer J, Bonkovsky HL, Phillips JD, Overbey JR, Wang B, Singal AK, Liu LU, Desnick RJ. Clinical, biochemical, and genetic characterization of North American patients with erythropoietic protoporphyria and X-linked protoporphyria. JAMA Dermatol. 2017;153:789–96. PubMed PMID: 28614581.

Blagojevic D, Schenk T, Haas O, Zierhofer B, Konnaris C, Trautinger F. Acquired erythropoietic protoporphyria. Ann Hematol. 2010;89:743–4. PubMed PMID: 19902211.

Bloomer JR. The liver in protoporphyria. Hepatology. 1988;8:402–7. PubMed PMID: 3281889.

Biolcati G, Marchesini E, Sorge F, Barbieri L, Schneider-Yin X, Minder EI. Long-term observational study of afamelanotide in 115 patients with erythropoietic protoporphyria. Br J Dermatol. 2015;172:1601–12. PubMed PMID: 25494545.

Brancaleoni V, Balwani M, Granata F, Graziadei G, Missineo P, Fiorentino V, Fustinoni S, Cappellini MD, Naik H, Desnick RJ, Di Pierro E. X-chromosomal inactivation directly influences the phenotypic manifestation of X-linked protoporphyria. Clin Genet. 2016;89:20–6. PubMed PMID: 25615817.

Do KD, Banner BF, Katz E, Szymanski IO, Bonkovsky HL. Benefits of chronic plasmapheresis and intravenous heme-albumin in erythropoietic protoporphyria after orthotopic liver transplantation. Transplantation. 2002;73:469–72. PubMed PMID: 11884947.

Gouya L, Puy H, Lamoril J, Da Silva V, Grandchamp B, Nordmann Y, Deybach JC. Inheritance in erythropoietic protoporphyria: a common wild-type ferrochelatase allelic variant with low expression accounts for clinical manifestation. Blood. 1999;93:2105–10. PubMed PMID: 10068685.

Gouya L, Puy H, Robreau AM, Bourgeois M, Lamoril J, Da Silva V, Grandchamp B, Deybach JC. The penetrance of dominant erythropoietic protoporphyria is modulated by expression of wildtype FECH. Nat Genet. 2002;30:27–8. PubMed PMID: 11753383.

Harms JH, Lautenschlager S, Minder CE, Minder EI. Mitigating photosensitivity of erythropoietic protoporphyria patients by an agonistic analog of alpha-melanocyte stimulating hormone. Photochem Photobiol. 2009;85:1434–9. PubMed PMID: 19656325.

Heerfordt IM, Wulf HC. Patients with erythropoietic protoporphyria have reduced erythrocyte protoporphyrin IX from early in pregnancy. Br J Dermatol. 2016 Dec 10. PubMed PMID: 27943252.

Holme SA, Anstey AV, Badminton MN, Elder GH. Serum 25-hydroxyvitamin D in erythropoietic protoporphyria. Br J Dermatol. 2008;159:211. PubMed PMID: 18476956.

Holme SA, Anstey AV, Finlay AY, Elder GH, Badminton MN. Erythropoietic protoporphyria in the U.K.: clinical features and effect on quality of life. Br J Dermatol. 2006;155:574–81. PubMed PMID: 16911284.

Holme SA, Thomas CL, Whatley SD, Bentley DP, Anstey AV, Badminton MN. Symptomatic response of erythropoietic protoporphyria to iron supplementation. J Am Acad Dermatol. 2007;56:1070–2. PubMed PMID: 17504727.

Holme SA, Whatley SD, Roberts AG, Anstey AV, Elder GH, Ead RD, Stewart MF, Farr PM, Lewis HM, Davies N, White MI, Ackroyd RS, Badminton MN. Seasonal palmar keratoderma in erythropoietic protoporphyria indicates autosomal recessive inheritance. J Invest Dermatol. 2009;129:599–605. PubMed PMID: 18787536.

Langendonk JG, Balwani M, Anderson KE, Bonkovsky HL, Anstey AV, Bissell DM, Bloomer J, Edwards C, Neumann NJ, Parker C, Phillips JD, Lim HW, Hamzavi I, Deybach JC, Kauppinen R, Rhodes LE, Frank J, Murphy GM, Karstens FP, Sijbrands EJ, de Rooij FW, Lebwohl M, Naik H, Goding CR, Wilson JH, Desnick RJ. Afamelanotide for erythropoietic protoporphyria. N Engl J Med. 2015;373:48–59. PubMed PMID: 26132941.

Lyoumi S, Abitbol M, Andrieu V, Henin D, Robert E, Schmitt C, Gouya L, de Verneuil H, Deybach JC, Montagutelli X, Beaumont C, Puy H. Increased plasma transferrin, altered body iron distribution, and microcytic hypochromic anemia in ferrochelatase-deficient mice. Blood. 2007;109:811–8. PubMed PMID: 17003376.

McCullough AJ, Barron D, Mullen KD, Petrelli M, Park MC, Mukhtar H, Bickers DR. Fecal protoporphyrin excretion in erythropoietic protoporphyria: effect of cholestyramine and bile acid feeding. Gastroenterology. 1988;94:177–81. PubMed PMID: 3335288.

McGuire BM, Bonkovsky HL, Carithers RL Jr, Chung RT, Goldstein LI, Lake JR, Lok AS, Potter CJ, Rand E, Voigt MD, Davis PR, Bloomer JR. Liver transplantation for erythropoietic protoporphyria liver disease. Liver Transpl. 2005;11:1590–6. PubMed PMID: 16315313.

Méndez M, Poblete-Gutiérrez P, Morán-Jiménez MJ, Rodriguez ME, Garrido-Astray MC, Fontanellas A, Frank J, de Salamanca RE. A homozygous mutation in the ferrochelatase gene underlies erythropoietic protoporphyria associated with palmar keratoderma. Br J Dermatol. 2009;160:1330–4. PubMed PMID: 19298273.

Minder EI. Afamelanotide, an agonistic analog of α-melanocyte-stimulating hormone, in dermal phototoxicity of erythropoietic protoporphyria. Expert Opin Investig Drugs. 2010;19:1591–602. PubMed PMID: 21073357.

Minder EI, Gouya L, Schneider-Yin X, Deybach JC. A genotype-phenotype correlation between null-allele mutations in the ferrochelatase gene and liver complication in patients with erythropoietic protoporphyria. Cell Mol Biol (Noisy-le-grand). 2002;48:91–6. PubMed PMID: 11929053.

Minder EI, Schneider-Yin X, Mamet R, Horev L, Neuenschwander S, Baumer A, Austerlitz F, Puy H, Schoenfeld N. A homoallelic FECH mutation in a patient with both erythropoietic protoporphyria and palmar keratoderma. J Eur Acad Dermatol Venereol. 2010;24:1349–53. PubMed PMID: 20337824.

Minder EI, Schneider-Yin X, Steurer J, Bachmann LM. A systematic review of treatment options for dermal photosensitivity in erythropoietic protoporphyria. Cell Mol Biol (Noisy-le-grand). 2009;55:84–97. PubMed PMID: 19268006.

Poh-Fitzpatrick MB. Human protoporphyria: reduced cutaneous photosensitivity and lower erythrocyte porphyrin levels during pregnancy. J Am Acad Dermatol. 1997;36:40–3. PubMed PMID: 8996259.

Rand EB, Bunin N, Cochran W, Ruchelli E, Olthoff KM, Bloomer JR. Sequential liver and bone marrow transplantation for treatment of erythropoietic protoporphyria. Pediatrics. 2006;118:e1896–9. PubMed PMID: 17074841.

Sarkany RP, Ross G, Willis F. Acquired erythropoietic protoporphyria as a result of myelodysplasia causing loss of chromosome 18. Br J Dermatol. 2006;155:464–6. PubMed PMID: 16882191.

Schneider-Yin X, Gouya L, Meier-Weinand A, Deybach JC, Minder EI. New insights into the pathogenesis of erythropoietic protoporphyria and their impact on patient care. Eur J Pediatr. 2000;159:719–25. PubMed PMID: 11039124.

Spelt JM, de Rooij FW, Wilson JH, Zandbergen AA. Vitamin D deficiency in patients with erythropoietic protoporphyria. J Inherit Metab Dis. 2010;33:S1–4. PubMed PMID: 24137761.

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.

Wahlin S, Floderus Y, Stål P, Harper P. Erythropoietic protoporphyria in Sweden: demographic, clinical, biochemical and genetic characteristics. J Intern Med. 2011a;269:278–88. PubMed PMID: 20412370.

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.

Wahlin S, Stal P, Adam R, Karam V, Porte R, Seehofer D, Gunson BK, Hillingsø J, Klempnauer JL, Schmidt J, Alexander G, O'Grady J, Clavien PA, Salizzoni M, Paul A, Rolles K, Ericzon BG, Harper P; European Liver and Intestine Transplant Association. Liver transplantation for erythropoietic protoporphyria in Europe. Liver Transpl. 2011b;17:1021–6. PubMed PMID: 21604355.

Whatley SD, Ducamp S, Gouya L, Grandchamp B, Beaumont C, Badminton MN, Elder GH, Holme SA, Anstey AV, Parker M, Corrigall AV, Meissner PN, Hift RJ, Marsden JT, Ma Y, Mieli-Vergani G, Deybach JC, Puy H. C-terminal deletions in the ALAS2 gene lead to gain of function and cause X-linked dominant protoporphyria without anemia or iron overload. Am J Hum Genet. 2008;83:408–14. PubMed PMID: 18760763.

Whatley SD, Mason NG, Holme SA, Anstey AV, Elder GH, Badminton MN. Gene dosage analysis identifies large deletions of the FECH gene in 10% of families with erythropoietic protoporphyria. J Invest Dermatol. 2007;127:2790–4. PubMed PMID: 17597821.

Whatley SD, Mason NG, Holme SA, Anstey AV, Elder GH, Badminton MN. Molecular epidemiology of erythropoietic protoporphyria in the united kingdom. Br J Dermatol. 2010;162:642–6. PubMed PMID: 20105171.

Chapter Notes

Acknowledgments

The EPP contribution to *GeneReviews* was supported in part by the Porphyrias Consortium of the NIH-supported Rare Diseases Clinical Research Network (NIH grant: 5 U54 DK083909), including:

- Dr Karl Anderson, University of Texas Medical Branch, Galveston, TX

- Dr Montgomery Bissell, University of California, San Francisco, CA
- Dr Herbert Bonkovsky, Carolinas Medical Center, Charlotte, NC
- Dr John Phillips, University of Utah School of Medicine, Salt Lake City, UT

Revision History

- 7 September 2017 (ha) Comprehensive update posted live
- 16 October 2014 (me) Comprehensive updated posted live
- 27 September 2012 (me) Review posted live
- 10 April 2012 (rd) Original submission

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (http://www.genereviews.org/) and copyright (© 1993-2024 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the GeneReviews® Copyright Notice and Usage Disclaimer. No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the GeneReviews® Copyright Notice and Usage Disclaimer.

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.