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Hepatoerythropoietic Porphyria

Synonym: *UROD*-Related Hepatoerythropoietic Porphyria

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Summary

Clinical characteristics

Hepatoerythropoietic porphyria (HEP) is characterized by blistering skin lesions, hypertrichosis, and scarring over the affected skin areas. Disease manifestations occur during infancy or childhood and with similar frequency in females and males. Mild anemia/hemolysis are not uncommon.

Diagnosis/testing

The diagnosis of HEP is established in a proband with elevated porphyrins in the urine (predominantly uroporphyrin and heptacarboxylporphyrin), significantly increased erythrocyte zinc protoporphyrin, and/or biallelic pathogenic (or likely pathogenic) variants in *UROD* identified by molecular genetic testing.

Management

Treatment of manifestations: No treatment regimens can restore uroporphyrinogen decarboxylase (UROD enzyme levels in individuals with HEP. The mainstays of therapy are avoidance of sunlight (including the long-wave ultraviolet light sunlight that passes through window glass) by use of protective clothing and topical application of opaque sunscreens. On sun-exposed areas of the skin, bullous lesions develop that require prompt management of resultant skin infections when appropriate. Phlebotomy and chloroquine, which are usually effective in treating the allelic disorder familial porphyria cutanea tarda, are generally ineffective in individuals with HEP.

Agents/circumstances to avoid: Exposure to sunlight in persons of all ages. Older individuals should avoid known susceptibility factors: alcohol, oral estrogen, iron overload, smoking, and drugs that induce the cytochrome P450s.

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* See Chapter Notes, Acknowledgments.

Evaluation of relatives at risk: If the family-specific *UROD* pathogenic variants are known, it is reasonable to clarify the genetic status of at-risk relatives so that those with biallelic *UROD* pathogenic variants can be counseled regarding sun protection and avoidance of known susceptibility factors.

Genetic counseling

HEP is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *UROD* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic *UROD* pathogenic variants and having HEP, a 50% chance of inheriting one pathogenic variant and having familial porphyria cutanea tarda, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the *UROD* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

Hepatoerythropoietic porphyria (HEP) **should be suspected** in infants or children with the following clinical findings, suggestive laboratory findings, and family history.

Clinical features (typically developing in infancy to early childhood)

- Blistering skin lesions/vesicles/bullae
- Hypertrichosis
- Scarring
- Passage of red urine

Note: The features of HEP generally resemble those of congenital erythropoietic porphyria.

Biochemical findings

- **First-line testing** (performed in reference laboratories). Urine or plasma total porphyrins are elevated.
- **Second-line testing** (performed in laboratories at centers with experience in diagnostic modalities for the porphyrias) (Table 1)
  - Urine and plasma porphyrins show an increase predominantly of uroporphyrin and heptacarboxylporphyrin.
  - Consider erythrocyte zinc protoporphyrin levels, which are significantly increased in HEP, to differentiate HEP from congenital erythropoietic porphyria.
- **Third-line testing.** Molecular genetic testing (See Establishing the Diagnosis.)

Table 1. Biochemical Characteristics of Hepatoerythropoietic Porphyria [1]

Specimen	Biochemical Finding
Plasma	↑ uroporphyrin, heptacarboxylporphyrin (~620 nm) [2]
Urine	↑ uroporphyrin, heptacarboxylporphyrin
Erythrocytes	↑ zinc protoporphyrin

1. For information on the role of the hepatic enzyme uroporphyrinogen decarboxylase (UROD), see Clinical Characteristics, Pathophysiology.
2. Fluorescence emission peak of diluted plasma at neutral pH, following excitation at 400-410 nm

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

Establishing the Diagnosis

The diagnosis of HEP **is established** in a proband with significantly elevated porphyrins in the urine (predominantly uroporphyrin and heptacarboxylporphyrin) in addition to significantly increased erythrocyte zinc protoporphyrin and/or biallelic pathogenic (or likely pathogenic) variants 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 biallelic *UROD* variants of uncertain significance (or of one known *UROD* pathogenic variant and one *UROD* variant of uncertain significance) does not establish or rule out a 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 is an option to consider in individuals with suggestive biochemical findings (see Table 1). 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 only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

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 Hepatoerythropoietic Porphyria

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
UROD	Sequence analysis [3]	14/16 [4]
	Gene-targeted deletion/duplication analysis [5]	2/16 [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. 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.
6. Large deletions involving *UROD* have been described in HEP, including deletion of the entire gene in one individual [de Verneuil et al 1992] and a large deletion in another [Méndez et al 2012].

Clinical Characteristics

Clinical Description

Hepatoerythropoietic porphyria (HEP) is characterized by extreme photosensitivity, skin lesions with fluid-filled blisters that break and heal slowly, hypertrichosis, and scarring over the affected skin areas. Signs and symptoms of HEP start during infancy or childhood, with similar frequency in females and males, and generally resemble those of congenital erythropoietic porphyria.

Repeated sun exposure can lead to scleroderma-like changes that result in photomutilation [Elder 1997].

With high levels of circulating porphyrins there may be a red-brown discoloration of teeth (erythrodontia) as a result of the deposition of porphyrins in the enamel layer of the developing tooth.

No increased risk for hepatocellular carcinoma has been identified in persons with HEP.

Note: The clinical features of HEP and familial porphyria cutanea tarda (F-PCT) (see Genetically Related Disorders) are indistinguishable. However, in striking contrast to HEP, F-PCT rarely if ever manifests in infancy or childhood. Rather, as is the case for PCT type 1 (nonfamilial, acquired), F-PCT is a disease of middle-aged persons, usually with several risk factors for development of overt disease (see Differential Diagnosis).

Pathophysiology

Reduced activity of the hepatic enzyme uroporphyrinogen decarboxylase (UROD) to 15%-20% of normal in all tissues leads to the accumulation of substrate, uroporphyrinogen, and the intermediate products of the reaction in all cells. Cells with a high demand for heme production include erythrocytes and hepatocytes; thus, accumulation is more pronounced in these cell types (predominantly in the liver).

The substrates and intermediates accumulate in cells in the form of oxidized porphyrins (mostly uroporphyrin and heptacarboxylporphyrin) that are then transported into the plasma, where they are deposited in the skin and other tissues. In the skin, these porphyrins interact with blue light (the Soret band, ~410 nm) to produce skin damage.

Excess plasma porphyrins (i.e., uroporphyrin and heptacarboxylporphyrin) are excreted via the urine. Intermediates further along in the pathway (i.e., protoporphyrin and zinc protoporphyrin) are eliminated in the bile. For more information about the proposed pathophysiology of HEP, click here.

Susceptibility factors. The rarity of HEP makes identification of additional risk factors difficult to assess. However, the existence of instances of late-onset disease suggest that susceptibility factors may play a role in some individuals [Triviboonvanich et al 2019]. Based on what is known of UROD enzyme activity regulation in F-PCT or PCT type 1, it is reasonable to avoid the identified susceptibility factors in those diseases (see Familial Porphyria Cutanea Tarda, Susceptibility Factors).

Genotype-Phenotype Correlations

No *UROD* genotype-phenotype correlations are known.

In HEP, at least one *UROD* pathogenic variant must preserve some degree of catalytic activity, as the presence of biallelic null variants is lethal [Phillips et al 2007].

Nomenclature

HEP may also be referred to as "*UROD*-related hepatoerythropoietic porphyria" based on the naming approach proposed by Biesecker et al [2021] to delineate mendelian genetic disorders.

Table 3. Porphyria Classification Systems [1]

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
Familial porphyria cutanea tarda (F-PCT)	Cutaneous	Hepatic
Variegate porphyria (VP)	Cutaneous & neurologic	Hepatic
X-linked protoporphyria (XLP)	Cutaneous	Erythropoietic

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

Prevalence

Fewer than 100 individuals with HEP have been reported in the literature. The frequency of HEP can only be inferred based on that of familial porphyria cutanea tarda (F-PCT), which occurs in one in 20,000 individuals. Note: Over a ten-year period from 2007 to 2017, a referral center / porphyria-specific diagnostic laboratory provided molecular diagnostic testing on four unrelated individuals with HEP, identifying one novel variant [Weiss et al 2019].

Two founder variants have been identified in Norway [Aarsand et al 2009]. See Table 5.

Genetically Related (Allelic) Disorders

Familial porphyria cutanea tarda (F-PCT). Individuals with a heterozygous pathogenic variant in *UROD* have F-PCT. The skin lesions of F-PCT resemble those of hepatoerythropoietic porphyria; however, they may be less severe and generally develop later in life (see Differential Diagnosis).

Differential Diagnosis

Other types of hereditary porphyria in the differential diagnosis of hepatoerythropoietic porphyria (HEP) are summarized in Table 4.

Table 4. Other Types of Porphyria in the Differential Diagnosis of Hepatoerythropoietic Porphyria

Gene	Disorder	MOI	Skin Lesions	Distinguishing Features / Comment
CPOX	Hereditary coproporphyria (HCP)	AD	Blistering skin lesions closely resembling lesions of CEP	• HCP, an acute hepatic porphyria, is generally accompanied by neurovisceral features, esp bouts of severe abdominal pain, which are not observed in HEP. Development of blistering skin disease is uncommon in HCP, whereas it is present & severe in HEP. Mild manifestations of HEP can be mistaken for HCP. • ↑ in zinc protoporphyrin is seen in HEP & not in HCP. In CEP fecal porphyrin levels of coproporphyrin III are significantly ↑.
PPOX	Variegate porphyria (VP)	AD	Blistering skin lesions are nearly identical to those in HEP. Cutaneous manifestations in HEP are chronic & blistering (like in VP) but are usually more severe than those of VP, because circulating porphyrin levels in HEP are usually much higher than in VP.	• VP is a cutaneous & acute porphyria & can present w/cutaneous manifestations &/or acute attacks of neurovisceral manifestations similar to AIP. • Plasma porphyrin fluorescence scanning of diluted plasma at neutral pH w/peak wavelength ~626 nm is seen w/VP. This is very useful in differential diagnosis. In PCT & HEP, peak emission wavelength is ~619-622 nm.
UROD	Familial porphyria cutanea tarda (F-PCT)	AD	Skin lesions resemble those of HEP but are less severe & typically begin later, in the 5th or 6th decade of life.	Because laboratory findings in F-PCT & HEP can be clinically indistinguishable at time of diagnosis, molecular genetic testing is necessary to discriminate between these disorders. Measurement of UROD enzyme activity is not an accurate method to distinguish between F-PCT & HEP.
UROS *GATA1*	Congenital erythropoietic porphyria (CEP)	AR XL [1]	The skin lesions of CEP, like those seen in HEP, appear early in life (i.e., in infancy or childhood) & are severe & mutilating.	In both CEP (a cutaneous, erythropoietic porphyria) & HEP, ↑ severity is attributed to plasma concentration of porphyrin. Although CEP can be mistaken for HEP, urine porphyrin analysis (which shows marked ↑ in uroporphyrin & coproporphyrin type I in CEP) helps exclude other cutaneous porphyrias. Fecal analysis may be necessary, particularly for persons w/late onset.

AD = autosomal dominant; AIP = acute intermittent porphyria; AR = autosomal recessive; HEP = hepatoerythropoietic porphyria; MOI = mode of inheritance; PCT = porphyria cutanea tarda; UROD = uroporphyrinogen decarboxylase; XL = X-linked

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

Other Disorders in the Differential Diagnosis of HEP

Sporadic porphyria cutanea tarda (i.e., porphyria cutanea tarda type 1 that is not associated with a *UROD* pathogenic variant) is clinically indistinguishable from HEP and familial PCT and is highly influenced by

susceptibility factors associated with PCT (see Familial Porphyria Cutanea Tarda, Susceptibility Factors). In these cases, the excess porphyrins are produced only in the liver.

Pseudoporphyria. Although the skin histopathologic findings of pseudoporphyria are similar to those of HEP, pseudoporphyria is not associated with porphyrin biochemical abnormalities. Medications, chronic renal insufficiency, and excessive sun exposure / UV radiation have been reported to cause pseudoporphyria [Beer et al 2014].

Management

No clinical practice guidelines for hepatoerythropoietic porphyria (HEP) have been published.

Evaluations Following Initial Diagnosis

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

- Evaluation of skin findings including blistering/vesicles over sun-exposed areas of skin with resultant scarring and hypertrichosis
- Laboratory evaluation for hemolytic anemia
- 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 HEP in order to facilitate medical and personal decision making

Treatment of Manifestations

There are no effective treatment regimens to restore UROD enzyme activity levels in individuals with HEP.

Treatment recommendations at this time are similar to those for familial porphyria cutanea tarda (F-PCT).

- Prompt treatment of any infection superimposed on skin lesions
- Low-dose chloroquine and oral charcoal (to bind stool porphyrins), which have been used in specific circumstances with variable success
- Strict avoidance of sunlight, including the long-wave ultraviolet light sunlight that passes through window glass, because of the high risk for severe skin damage and possible mutilation
- Identification and avoidance of susceptibility factors (where applicable) (See Agents/Circumstances to Avoid.)
- Avoidance of drugs and agents that induce the hepatic cytochrome P450s
- Routine vaccination against hepatitis A and B

Surveillance

There are currently no recommendations or guidelines for surveillance in individuals with HEP.

Monitoring urinary porphyrin levels annually or at some other interval, perhaps determined by clinical findings, may be reasonable.

Agents/Circumstances to Avoid

Persons of all ages should avoid exposure to sunlight.

Older individuals should avoid the known precipitating factors (e.g., alcohol, oral estrogen, smoking, and drugs that induce the cytochrome P450s).

Note: The rarity of HEP makes identification of additional risk factors difficult to assess. However, the existence of instances of late-onset disease suggest that susceptibility factors may play a role in some individuals [Triviboonvanich et al 2019]. Based on what is known of UROD enzyme activity regulation in F-PCT, it is reasonable to avoid the identified susceptibility factors in that disease. See Familial Porphyria Cutanea Tarda, Susceptibility Factors.

Evaluation of Relatives at Risk

It is reasonable to clarify the genetic status of at-risk relatives in order to identify as early as possible those with a heterozygous (or biallelic) *UROD* pathogenic variant(s) who should be counseled regarding sun protection and known susceptibility factors (see Pathophysiology and Familial Porphyria Cutanea Tarda, Susceptibility Factors).

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

Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

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

Hepatoerythropoietic porphyria (HEP) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *UROD* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *UROD* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- The heterozygous parents of a proband with HEP have familial porphyria cutanea tarda (F-PCT) but are generally asymptomatic. If susceptibility factors are present, heterozygotes are at increased risk of developing signs and symptoms of F-PCT (see Familial Porphyria Cutanea Tarda, Susceptibility Factors).

(Note: Heterozygous parents may not have sufficient susceptibility factors to be symptomatic at the time of their child's diagnosis.)

Sibs of a proband

- If both parents are known to be heterozygous for a *UROD* pathogenic variant, each sib of an affected individual has at conception a 25% chance of inheriting biallelic *UROD* pathogenic variants and having HEP, a 50% chance of inheriting one pathogenic variant and having F-PCT, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygous sibs have F-PCT but are generally asymptomatic. If susceptibility factors are present, heterozygous sibs are at increased risk of developing signs and symptoms of F-PCT (see Familial Porphyria Cutanea Tarda, Susceptibility Factors).

Offspring of a proband. The offspring of an individual with HEP are obligate heterozygotes for a pathogenic variant in *UROD*. (Heterozygotes have F-PCT but are generally asymptomatic; see F-PCT.)

Other family members. Each sib of the proband's parents is at a 50% risk of being heterozygous for a pathogenic variant in *UROD*. (Heterozygotes have F-PCT but are generally asymptomatic; see F-PCT.)

Heterozygote Detection

Targeted genetic testing for at-risk relatives requires prior identification of the *UROD* pathogenic variants in the 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 have HEP.
- *UROD* genetic testing for the reproductive partners of individuals with HEP or F-PCT should be considered, particularly if both partners are of the same ethnic background. Two founder variants have been identified in Norway (see Table 5).

Prenatal Testing and Preimplantation Genetic Testing

Once the *UROD* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for HEP 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.

- **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. Hepatoerythropoietic Porphyria: 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 Hepatoerythropoietic Porphyria (View All in OMIM)

176100	PORPHYRIA CUTANEA TARDA
613521	UROPORPHYRINOGEN DECARBOXYLASE; UROD

Molecular Pathogenesis

UROD encodes the enzyme uroporphyrinogen decarboxylase (UROD). UROD enzyme activity is approximately 15%-20% of normal in all cells. Loss of enzyme activity results in accumulation of highly carboxylated porphyrins (mostly uroporphyrin and heptacarboxylporphyrin) that accumulate in the liver and are then transported out of hepatocytes into the plasma and eventually into the urine. These excess plasma porphyrins are deposited in the skin and other tissues.

In hepatoerythropoietic porphyria (HEP) the developing red blood cell accumulates porphyrin intermediates, including uroporphyrin as well as protoporphyrin and specifically zinc protoporphyrin. These intermediates are at the terminal end of the pathway and are much more hydrophobic and must be eliminated through the liver into the bile (see Erythropoietic Protoporphyria and X-Linked Protoporphyria).

Mechanism of disease causation. Loss of function; severe deficiency in UROD activity results in clinical manifestations.

Table 5. Notable *UROD* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000374.5 NP_000365.3	c.578G>C	p.Arg193Pro	These two founder variants account for 74% of pathogenic variants in Norway [Aarsand et al 2009].
NM_000374.5	c.636+1G>C	--	

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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References

Literature Cited

Aarsand AK, Boman H, Sandberg S. Familial and sporadic porphyria cutanea tarda: characterization and diagnostic strategies. Clin Chem. 2009;55:795–803. PubMed PMID: 19233912.

Beer K, Applebaum D, Nousari C. Pseudoporphyria: discussion of etiologic agents. J Drugs Dermatol. 2014;13:990–2. PubMed PMID: 25116980.

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.

de Verneuil H, Bourgeois F, de Rooij F, Siersema PD, Wilson JH, Grandchamp B, Nordmann Y. Characterization of a new mutation (R292G) and a deletion at the human uroporphyrinogen decarboxylase locus in two patients with hepatoerythropoietic porphyria. Hum Genet. 1992;89:548–52. PubMed PMID: 1634232.

Elder GH. Hepatic porphyrias in children. J Inherit Metab Dis. 1997;20:237–46. PubMed PMID: 9211196.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Méndez M, Rossetti MV, Gómez-Abecia S, Morán-Jiménez MJ, Parera V, Batlle A, Enríquez de Salamanca R. Molecular analysis of the UROD gene in 17 Argentinean patients with familial porphyria cutanea tarda: characterization of four novel mutations. Mol Genet Metab. 2012;105:629–33. PubMed PMID: 22382040.

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.

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.

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.

Triviboonvanich S, Junnu S, Srisawat C, Silpa-archa N. Late-onset hepatoerythropoietic porphyria presenting with facial deformities and erythrodontia. Thai J Dermatol. 2019;35:73–80.

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. Molec Genet Metab. 2019;128:363–6. PubMed PMID: 30514647.

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