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

Acute Intermittent Porphyria

Synonyms: PBGD Deficiency, Porphobilinogen Deaminase Deficiency

Eliane Sardh, MD, PhD[1] and Michela Barbaro, Sc, PhD[1]

Created: September 27, 2005; Updated: February 8, 2024.

Summary

Clinical characteristics

An acute porphyria attack is characterized by a urine porphobilinogen (PBG)-to-creatinine ratio ≥10 times the upper limit of normal (ULN) and the presence of ≥2 porphyria manifestations (involving the visceral, peripheral, autonomic, and/or central nervous systems) persisting for >24 hours in the absence of other likely explanations. Onset of acute attacks typically occurs in the second or third decade of life. Acute attacks are more common in women than men. Although attacks in most individuals are typically caused by exposure to certain endogenous or exogenous factors, often no precipitating factor can be identified. The course of acute porphyria attacks is highly variable in an individual and between individuals. Recovery from acute porphyria attacks may occur within days; however, recovery from severe attacks that are not promptly recognized and treated may take weeks or months.

The five categories of acute intermittent porphyria (AIP), caused by a heterozygous *HMBS* pathogenic variant, are based on the urine PBG-to-creatinine ratio and occurrence of acute attacks.

Active (symptomatic) AIP: An individual who has experienced at least one acute attack within the last two years.

Symptomatic high excreter: Urine PBG-to-creatinine ratio ≥4 times ULN and no acute attacks in the last two years but chronic long-standing manifestations of acute porphyria.

Asymptomatic high excreter: Urine PBG-to-creatinine ratio ≥4 times ULN and no acute attacks in the last two years and no porphyria-related manifestations.

Asymptomatic AIP: Urine PBG-to-creatinine ratio <4 times ULN and no acute attacks in the last two years but has had ≥1 acute attack in the past.

Latent (inactive) AIP: Urine PBG-to-creatinine ratio <4 times ULN and no acute porphyria-related manifestations to date.

Author Affiliation: 1 Porphyria Centre Sweden, Center for Inherited Metabolic Diseases (CMMS), Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden; Email: eliane.sardh@ki.se; Email: michela.barbaro@regionstockholm.se.

Diagnosis/testing

When the diagnosis of an AIP attack is suspected based on clinical findings, establishing the diagnosis begins with biochemical testing. If the urinary concentration of PBG is increased, molecular genetic testing is performed to confirm the diagnosis and/or to facilitate cascade screening of family members. When a multigene panel or genomic testing has identified an *HMBS* pathogenic variant, the diagnosis of an AIP attack is confirmed when the urinary concentration of PBG is increased.

Management

Treatment of manifestations: Treat intercurrent infections and other diseases promptly. For mild acute neurovisceral attacks, a high carbohydrate intake, preferably oral. When required, intravenous (IV) fluid may be used for up to 48 hours. IV fluid should contain a minimum of 5% dextrose; the recommendation in most countries is 10% glucose with added sodium (40 mmol) and potassium (20 mmol) given at a rate of 1,000 mL over 12 hours. Note that hypotonic dextrose in water solutions should be avoided because of the risk of hyponatremia. Referral to a porphyria specialist for more detailed clinical advice on treatment of AIP.

Targeted therapies: For sporadic acute neurovisceral attacks (i.e., when an individual has experienced one to ≤3 acute porphyria attacks in any 12-month period in the last two years): IV human hemin is the most effective treatment and may be lifesaving if employed early when neuronal damage is reversible. If the criteria for recurrent attacks are met, Givlaari® (givosiran) should be considered, as long-term complications of hemin such as iron overload, phlebitis, and loss of venous access can be avoided. Liver transplantation, as reported from several centers, is curative. Indications include repeated life-threatening acute porphyria attacks and poor quality of life when givosiran is not available or has shown insufficient medical efficacy. Alternative medical therapies to reduce frequency and/or severity of acute attacks when givosiran is not available include suppression of ovulation and prophylactic hemin infusion.

Supportive care: To reduce the frequency and/or severity of acute attacks, maintain adequate nutrition and seek timely treatment of systemic illness or infection. Supportive treatment involves pain relief, treatment of hypertension, prevention of nausea and vomiting, prompt treatment of seizures, and maintenance of fluid and electrolyte balance. Combined liver and kidney transplantation can be considered in individuals with AIP who have recurrent acute porphyria attacks and end-stage kidney disease.

Surveillance: For all individuals heterozygous for an *HMBS* pathogenic variant who are older than age 50 years, annual or twice a year hepatic imaging is recommended for early detection of primary liver cancer (PLC), which improves survival.

Agents/circumstances to avoid: Individuals with AIP are advised to avoid excessive alcohol consumption, as alcohol upregulates the enzyme ALAS1, the first enzyme of hepatic heme biosynthesis, and thus could be a trigger for acute attacks. In all the acute porphyrias, information on the safety of many drugs and other over-the-counter preparations is incomplete; however, evidence-based guidelines for assessment of drug porphyrogenicity have been published.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives of an individual with a known *HMBS* pathogenic variant (regardless of the presence or absence of acute porphyria-related manifestations and/or a highly elevated urine PBG-to-creatinine ratio in that individual) so that those who are heterozygous for the familial *HMBS* pathogenic variant (and thus at increased risk of developing AIP attacks and PLC) can be identified early and counseled about preventive measures and surveillance. For the same reasons it is also appropriate to try to clarify the genetic status of apparently asymptomatic family members of an individual with a biochemical diagnosis of AIP and an unknown *HMBS* pathogenic variant by assessing erythrocyte HMBS activity; however, this method is less sensitive and specific than molecular genetic testing.

Pregnancy management: Preconception counseling is recommended to advise women with AIP about the clinical manifestations of porphyria, self-care, preventative measures to avoid exacerbations (i.e., adequate and regular nutrition, rest, and carbohydrate intake for treating mild-to-moderate manifestations), and agents/ circumstances to avoid. Additionally, there is a higher risk for pregnancy-induced hypertensive disorder, gestational diabetes, and fetuses with intrauterine growth restriction. In general, risk ratios are higher among women with AIP who have high lifetime urinary PBG concentrations.

Genetic counseling

AIP is inherited in an autosomal dominant manner. The majority of individuals diagnosed with AIP inherited an *HMBS* pathogenic variant from one of their parents, who may or may not have experienced manifestations of porphyria. Rarely, individuals diagnosed with AIP have the disorder as the result of a *de novo HMBS* pathogenic variant. Each child of an individual with an *HMBS* pathogenic variant has a 50% chance of inheriting the pathogenic variant. Because clinical penetrance is low, it is not possible to predict whether offspring who inherit an *HMBS* pathogenic variant will be symptomatic or, if they are symptomatic, the age of onset, severity, or type of manifestations. However, all individuals who inherit an *HMBS* pathogenic variant should be counseled about preventive measures and surveillance. Once the familial *HMBS* pathogenic variant has been identified, prenatal and preimplantation genetic testing for AIP are possible.

GeneReview Scope

Acute Intermittent Porphyria: Clinical Designations for Individuals Heterozygous for an *HMBS* Pathogenic Variant [1]

Clinical Designation	Urine PBG [2]-to-Creatinine Ratio	Occurrence of Acute Porphyria Attacks [3]	Comment
Active (symptomatic) AIP	Not defined	≥1 in the last 2 years	- Sporadic AIP: 1-3 acute porphyria attacks in any 12-month period within the last 2 years - Recurrent AIP: ≥4 acute porphyria attacks in a maximum period of 12 months within the last 2 years
Symptomatic high excreter	≥4 times the ULN	None in the last 2 years	Individual who has chronic long-standing manifestations of acute porphyria (e.g., pain or other porphyria-related manifestations in the absence of other likely explanations)
Asymptomatic high excreter			Individual who has confirmed acute porphyria but no acute porphyria-related manifestations in the last 2 years

Acute Intermittent Porphyria: continued from previous page.

Clinical Designation	Urine PBG [2]-to-Creatinine Ratio	Occurrence of Acute Porphyria Attacks [3]	Comment
Asymptomatic AIP (acute porphyria in remission)	<4 times the ULN	None in the last 2 years	Individual who has had ≥1 acute porphyria attack at some time in the past
Latent (inactive) AIP		None to date	• Latent at-risk individual: An asymptomatic individual with a positive family history of AIP in whom an *HMBS* pathogenic variant was identified during screening of family members • Latent low-risk individual: An asymptomatic individual with no known family history of AIP in whom the identification of an *HMBS* pathogenic variant was an incidental finding [4]

Based on Stein et al [2023]

AIP = acute intermittent porphyria; PBG= porphobilinogen; ULN = upper limit of normal

1. HMBS pathogenic variant known to be associated with AIP

2. The quality of the PBG analysis should be within specifications set by Ipnet EQAS (or another EQA organization, such as RCPAQAP performance specifications) [Aarsand et al 2011].

3. An acute porphyria attack is defined as a urine PBG-to-creatinine ratio ≥10 times the upper limit of normal in the presence of two or more porphyria manifestations typically persisting for more than 24 hours in the absence of other likely explanations.

4. "Incidental finding" in this context refers to the identification of a pathogenic variant in a gene that does not account for the phenotype that prompted the diagnostic testing.

Diagnosis

Suggestive Findings

An acute porphyria attack **should be suspected** in a proband with the following clinical findings and family history **or** in an individual who experiences two or more of the following clinical findings typically persisting for more than 24 hours in the absence of other likely explanations.

Clinical findings of an acute porphyria attack

- Presence of otherwise unexplained severe, acute abdominal pain (without physical signs) in the vast majority (90%) of acute attacks [Gouya et al 2020]. The pain, which occasionally may be more severe in the back or thighs, is usually only relieved with opiate analgesia. Atypical presentations are rare.
- During attacks nausea, vomiting, constipation, tachycardia, and hypertension are common.
- Muscle weakness, seizures, mental changes, and hyponatremia are features that alone or in combination increase the probability of acute porphyria.
- The urine may be reddish brown or red; however, this should not be used as a diagnostic criterion as it is not a constant finding, especially if the sample is fresh. The color is enhanced by exposure to air and light and reflects increased urinary concentrations of porphyrins and porphobilins formed from the porphyrin precursor porphobilinogen (PBG).

Family history may suggest autosomal dominant inheritance (e.g., affected males and females in multiple generations). Because the majority of individuals heterozygous for an *HMBS* pathogenic variant do not have clinical manifestations of acute intermittent porphyria (AIP), many individuals with symptomatic AIP appear to represent a simplex case (i.e., a single occurrence in a family). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

When the diagnosis of an AIP attack is suspected based on clinical findings, begin with biochemical testing and if increased concentration of PBG is detected in urine, use molecular genetic testing to confirm the diagnosis and/or to facilitate cascade screening of family members.

When a multigene panel or genomic testing has identified an *HMBS* pathogenic variant, confirm the diagnosis of AIP with biochemical testing to determine the concentration of PBG in the urine. Note that molecular genetic testing is not sufficient to diagnose **active (symptomatic) AIP** in a proband because the relatively high prevalence of *HMBS* pathogenic variants in the general population (1:1,299) and the low penetrance of heterozygous *HMBS* pathogenic variants (0.5%-1%) can lead to misdiagnosis of AIP and inappropriate treatment of individuals with nonspecific abdominal pain [Lenglet et al 2018].

Biochemical Testing

An increased urinary PBG concentration, using a specific quantitative assay and confirmatory biochemical testing, are essential to establish an unequivocal diagnosis of an acute porphyria attack in a symptomatic individual [Lamon et al 1974, Aarsand et al 2011].

The concentration of PBG in urine is invariably increased in individuals with manifestations of AIP during an acute attack. Urine PBG-to-creatinine ratio is typically increased to more than 10 times the upper limit of normal (ULN) or significantly above the individual's baseline if baseline is more than 10 times the ULN [Stein et al 2023].

Urine PBG concentration is best analyzed in a fresh random 10 mL urine sample collected without preservative and protected from prolonged exposure to bright light [Woolf et al 2017]. Urgent testing in an as yet undiagnosed individual will typically require specific arrangements to be made with the biochemistry laboratory. Results should be available within 24 hours of sample receipt.

Note: Positive results on qualitative or semiquantitative urine PBG tests **must** be confirmed by a specific quantitative measurement of urine PBG concentration to avoid reporting of false positive test results.

Biochemical confirmation that the increased urinary PBG concentration is caused by AIP and not another acute porphyria (see Differential Diagnosis) requires evidence that:

- Total fecal porphyrin concentration or coproporphyrin isomer ratio is normal;
- Plasma porphyrin fluorescence emission scan either shows a peak around 620 nm or is normal.

Molecular Genetic Testing

Identification of a heterozygous pathogenic (or likely pathogenic) variant in *HMBS* by molecular genetic testing in a symptomatic proband (see Table 1) is suggestive of the diagnosis of AIP and requires confirmatory biochemical testing.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *HMBS* variant of uncertain significance does not establish or rule out the diagnosis.

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

Option 1

When the phenotypic and findings on biochemical testing suggest the diagnosis of AIP, molecular genetic testing approaches can include **single-gene testing** or a **multigene panel**.

- **Single-gene testing.** Following biochemical confirmation of increased urinary PBG concentration, sequence analysis of *HMBS* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

- **An inborn error of metabolism or porphyria multigene panel** that includes *HMBS* 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. To date, the majority of *HMBS* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Acute Intermittent Porphyria

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
HMBS	Sequence analysis [3]	96%-98% [4]
	Gene-targeted deletion/duplication analysis [5]	~2% [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on 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 missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data from Cerbino et al [2015] and 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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Larger deletions/duplications/insertions and whole-gene deletions have been reported. These will not be detected by single-gene sequencing but may be identified by gene-targeted deletion/duplication analysis or next-generation sequencing.

Clinical Characteristics

Clinical Description

Acute intermittent porphyria (AIP), caused by a heterozygous *HMBS* pathogenic variant, is divided into clinical designations based on clinical history (i.e., the number of acute porphyria attacks experienced previously) and urine porphobilinogen (PBG)-to-creatinine ratio (see Table 2).

Table 2. Acute Intermittent Porphyria: Clinical Designations

Clinical Designation	Individual Who is Heterozygous for an *HMBS* Pathogenic Variant Associated with AIP and Has Experienced:
Active (symptomatic) AIP	≥1 acute porphyria attack in the last 2 years. Active (symptomatic) AIP includes: • Sporadic AIP (individual has experienced 1 to ≤ 3 acute porphyria attacks); • Recurrent AIP (individual has experienced ≥4 acute porphyria attacks in a maximum period of 12 mos within the last 2 yrs).
Symptomatic high excreter	Chronic porphyria-related manifestations during the last 2 years AND a urine PBG-to-creatinine ratio ≥4 times the ULN [1]
Asymptomatic high excreter	No porphyria-related manifestations during the last 2 years AND has a urine PBG-to-creatinine ratio ≥4 times the ULN [1]
Asymptomatic AIP	≥1 acute porphyria attack in the past but has had no acute porphyria-related manifestations during the last 2 years AND urine PBG-to-creatinine ratio is <4 times the ULN [1]

Table 2. continued from previous page.

Clinical Designation	Individual Who is Heterozygous for an *HMBS* Pathogenic Variant Associated with AIP and Has Experienced:
Latent AIP	No acute porphyria-related manifestations (i.e., the individual has never experienced acute porphyria-related manifestations) AND urine PBG-to-creatinine ratio <4 times the ULN. [1] Latent AIP includes: • Latent at risk (an individual who has been found to have a pathogenic variant as part of family screening); • Latent low risk (an individual in whom the identification of an *HMBS* pathogenic was an incidental finding [2])

Based on Stein et al [2023]
AIP = acute intermittent porphyria; PBG = porphobilinogen; ULN = upper limit of normal
1. The quality of the PBG analysis should be within specifications set by Ipnet EQAS (or another EQA organization, such as RCPAQAP performance specifications) [Aarsand et al 2011].
2. "Incidental finding" in this context refers to the identification of a pathogenic variant in a gene that does not account for the phenotype that prompted the diagnostic testing.

Note that cutaneous manifestations of porphyria do not occur in AIP.

Active (Symptomatic) AIP

Manifestations of AIP, which are more common in women than men, are very rare before puberty. Onset typically occurs in the second or third decade [Wang et al 2023].

The visceral, peripheral, autonomic, and/or central nervous systems may be affected, leading to a range of findings that are usually intermittent and sometimes life-threatening. The course of acute porphyria attacks is highly variable in an individual and between individuals.

Affected individuals may recover from acute porphyria attacks within days, but recovery from severe attacks that are not promptly recognized and treated may take weeks or months. Although attacks in most individuals are typically caused by exposure to certain endogenous or exogenous factors, it is not uncommon for individuals to have acute attacks in which no precipitating factor can be identified.

Acute porphyria attacks. An acute porphyria attack is defined as an episode that includes significantly increased urinary PBG concentration and two or more of the clinical manifestations of an acute porphyria attack that typically persist for more than 24 hours in the absence of other likely explanations [Stein et al 2023].

Severe abdominal pain, which may be generalized or localized and not accompanied by muscle guarding, is the most common symptom and is often the initial sign of an acute attack. Back, buttock, or limb pain may be a feature. Gastrointestinal features including nausea, vomiting, constipation or diarrhea, and abdominal distention are common, and ileus can occur. Tachycardia and hypertension are frequent, while fever, sweating, restlessness, and tremor are seen less frequently. Urinary retention, incontinence, and dysuria may be present.

Approximately 3%-8% of individuals with AIP, mainly women, experience recurrent AIP (defined as ≥4 attacks in one year [Stein et al 2023]) for a prolonged period, often many years [Gouya et al 2020].

Acute porphyria attacks may be precipitated by endogenous or exogenous factors [Wang et al 2018]. These include the following:

• **Prescribed and recreational drugs** that are detoxified in the liver by cytochrome P450 and/or result in induction of 5-aminolevulinic acid (ALA) synthase and heme biosynthesis. Prescription drugs that can precipitate an attack include, for example, barbiturates, sulfa-containing antibiotics and antibiotics for urinary tract infections, some anti-seizure medications, progestogens, and synthetic estrogens (see Agents/ Circumstances to Avoid).

- **Endocrine factors.** Reproductive hormones play an important role in the clinical expression of AIP. In women, acute neurovisceral attacks related to the menstrual cycle, usually the luteal phase, are common [Wang et al 2018]. Pregnancy in women with AIP is usually uncomplicated, and although urinary PBG concentration may increase during pregnancy, this does not lead to a higher frequency of clinical porphyria manifestations [Vassiliou & Sardh 2022]. However, there is a higher risk for pregnancy-induced hypertensive disorder, gestational diabetes, and infants with intrauterine growth restriction. In general, risk ratios are higher among women with AIP who have high lifetime urinary PBG concentrations [Mantel et al 2023].
- **Fasting.** A recognized precipitating factor is inadequate caloric intake [Wang et al 2018] in connection with, for example, dieting or heavy exercise schedules.
- **Stress.** Psychosocial and other stresses, including intercurrent illnesses, infections, alcoholic excess, and surgery, can precipitate an attack [Storjord et al 2019].

Peripheral neuropathy is predominantly motor and is less common now than in the past, due to the availability of better treatments that reduce the risk of long duration of untreated acute porphyria attacks, the main risk factor for neurologic manifestations and long-term neurologic complications. Muscle weakness often begins proximally in the legs but may involve the arms or legs distally and can progress to include respiratory muscles, resulting in complete paralysis with respiratory failure. Bilateral axonal motor neuropathy may also involve the distal radial nerves. Motor neuropathy may also affect the cranial nerves or lead to bulbar paralysis.

Patchy sensory neuropathy may also occur.

Mild mental changes such as anxiety, insomnia, irritability, and even mild cognitive impairment occur in up to 80% of symptomatic individuals and often in the initial stages of an acute porphyria attack [Gouya et al 2020].

Severe mental symptoms attributed to acute encephalopathy characterize the severe acute porphyria attack, manifesting as aberrant behavior, hallucinations, confusion, impaired consciousness, or seizures [Pischik et al 2023, Stein et al 2023].

Brain MRI changes can be detected in 47% of individuals with severe mental changes, usually in the form of posterior reversible encephalopathy syndrome, but normal MRI examination despite acute encephalopathy also occurs [Pischik et al 2023].

Hyponatremia is present in 25%-61% of acute porphyria attacks [Pischik et al 2023] due to sodium loss, overhydration, hypothalamic involvement (i.e., syndrome of inappropriate antidiuretic hormone [SIADH]), or a combination of these conditions [Sardh & Harper 2022].

Seizures occur in 1%-20% of acute porphyria attacks, with or without hyponatremia. They are transient and only present in severe attacks with acute encephalopathy; they do not occur in remission [Pischik et al 2023].

High Excreter

Symptomatic high excreter. An individual with permanently high urinary PBG concentration is considered symptomatic (i.e., a symptomatic high excreter) when having porphyria-related manifestations, usually pain, peripheral neuropathy, and psychiatric symptoms. Management of these manifestations is based on the need for supportive drugs, all of which should be evaluated for safety in AIP.

The condition usually occurs after an acute porphyria attack and can persist for many years [Marsden & Rees 2014]. In a Swedish AIP cohort approximately 10% of adults with AIP are high excreters [Lissing et al 2022].

Asymptomatic high excreter. An asymptomatic *HMBS* heterozygote with permanently high urinary PBG concentration (urine PBG-to-creatinine ratio ≥4 times the upper limit of normal) and has had no porphyria-related manifestations during the last two years.

Asymptomatic AIP

Asymptomatic AIP (also called acute porphyria in remission) refers to a person has had one or more acute porphyria attacks in the past but has had no acute porphyria-related manifestations during the last two years and has a urine PBG-to-creatinine ratio is less than four times the upper limit of normal.

Latent AIP

Latent AIP refers to a person who is heterozygous for an *HMBS* pathogenic variant associated with AIP who has never experienced acute porphyria-related manifestations and does not have significantly elevated urinary PBG concentration.

The risk of becoming symptomatic depends on age, sex, and exposure to provoking agents, and is higher if the individual belongs to a family with other symptomatic individuals [Baumann & Kauppinen 2020].

Clinical Manifestations of AIP

In all forms of AIP, clinical manifestations must always be evaluated in relation to the urinary PBG concentration.

Chronic complications

- **Primary liver cancer (PLC).** Several studies have indicated a significant risk of PLC, mainly hepatocellular carcinoma (HCC), in individuals with AIP aged 50 years or above. Hazard ratios (HRs) vary considerably, from 36 to 108 in published studies, due to differences in the demographics of the cohorts with acute hepatic porphyria and in PLC rates in reference populations.

  A Swedish national cohort study of 1,244 individuals with acute hepatic porphyria (i.e., individuals with AIP or one of the other two types of hepatic porphyria) demonstrated a 44-fold increased risk for individuals with AIP to develop PLC compared to a matched cohort. In individuals with active disease, defined as elevated urinary PBG concentration at some point in their lifetime, the risk of developing PLC was 63 times higher [Lissing et al 2022].

  A longitudinal US study showed that 1.5% of individuals diagnosed with acute hepatic porphyria developed HCC; urine PBG concentration was not available at the time of HCC diagnosis, and three of five individuals reported having symptomatic porphyria at baseline [Saberi et al 2021].

  Although the risk of PLC appears higher in individuals with clinically and biochemically active disease, it has also been reported in individuals with asymptomatic AIP [Lissing et al 2022]. Based on these studies, it is recommended that all individuals with acute hepatic porphyria undergo surveillance for PLC, starting at age 50 years [Wang et al 2023].

- **Renal involvement.** Approximately 70% of individuals with recurrent attacks will develop progressive renal dysfunction, as shown by declining estimated glomerular filtration rate (eGFR) (<90 mL/min/1.73 m^2). This may be a result of chronic renal exposure to high concentrations of ALA and PBG [Pallet et al 2018], influenced by genetic variation in the ALA transporter PEP2 [Tchernitchko et al 2017]. Chronic kidney disease and kidney diseases overall are more common among individuals with acute porphyria and especially among those with high urinary concentration of PBG [Lissing et al 2023].

Mortality. Mortality directly related to acute porphyria attacks is now very rare in most countries as a result of improved treatment (use of human hemin; see Treatment of Manifestations) and identification and counseling of relatives with latent AIP (see Evaluation of Relatives at Risk). Long-term complications such as PLC and kidney diseases cause a higher mortality in acute porphyria and especially among females with AIP and those with high urinary PBG concentration [Lissing et al 2023]. Although liver transplantation can be a cause of

mortality in AIP, the overall survival at five years after transplantation is 82%, which is consistent with survival data for individuals transplanted for other metabolic diseases [Lissing et al 2021].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Penetrance

Penetrance of AIP in heterozygous family members of proband who has experienced manifestations of AIP. The penetrance of AIP-related manifestations is higher in heterozygous family members of an individual who either has symptomatic or asymptomatic acute porphyria or is a high excreter than in heterozygotes in the general population. However, penetrance data vary between studies, as the calculation model, inclusion criteria, and clinical categorization may differ.

- In a French cohort of 253 families including 496 individuals with active (symptomatic) AIP and 1,672 individuals with latent AIP, the estimated penetrance of AIP in heterozygous family members was 22.9% [Lenglet et al 2018].
- In a Finnish study, the average penetrance was 30% for an acute attack and 35% for acute symptoms in *HMBS* heterozygotes in a porphyria family. In women, the penetrance is higher: 41% for acute attacks and 50% for all acute symptoms related to porphyria [Baumann & Kauppinen 2020].
- In Sweden and Spain, where *HMBS* founder variants exist (see Table 5), penetrance has been estimated at 41% and 52%, respectively [Andersson et al 2000, Barreda-Sánchez et al 2019].

Although there is no proven correlation between genotype and phenotype, some *HMBS* pathogenic variants, especially null variants, have higher penetrance [Andersson et al 2000, Lenglet et al 2018].

Penetrance of AIP in heterozygous individuals in the general population. Using Exome Variant Server data, a minimal prevalence of heterozygous *HMBS* pathogenic variants in the general population was calculated to be 1:1,299 (12,990 alleles from individuals with northern European or African descent). In France the prevalence of heterozygous *HMBS* pathogenic variants in the general population was estimated at between 50,000-100,000 individuals and the penetrance at 0.5%-1%. The authors proposed that penetrance is a consequence of both environmental and genetic factors [Lenglet et al 2018]. Using only a northern European population with ~46,000 individuals, the prevalence of heterozygous *HMBS* pathogenic variants in the general northern European population was estimated to be 1:1,782 [Chen et al 2016] and the penetrance at 1%.

Nomenclature

Individuals with latent AIP are often referred to as "carriers" in the medical literature. *GeneReviews* does not use the term "carrier" for an individual who is heterozygous for a pathogenic variant associated with an autosomal dominant disorder – the term "carrier" is reserved in *GeneReviews* for those who are heterozygous for a pathogenic variant associated with an autosomal recessive disorder, and thus are not expected to ever develop manifestations of the disorder.

Active AIP, either clinically or biochemically, has also been referred to as manifest or overt AIP in the older medical literature (in which its definition varied).

Prevalence

In most countries, AIP is the most common of the acute hepatic porphyrias [Wang et al 2018].

Because the real prevalence of AIP is difficult to evaluate, in most instances it is based on estimations.

- The prevalence of "overt AIP" (defined as having at least one acute porphyria attack) in France is 1:132,000 inhabitants [Lenglet et al 2018]. This is similar to the incidence of newly diagnosed individuals in Europe (excluding Sweden), with symptomatic AIP (defined as having an acute attack) reported as 0.12:1,000,000 per year, with a calculated prevalence of 5.4:1,000,000 [Elder et al 2013].
- In Sweden the incidence and prevalence of AIP are about four times higher than in Europe due to an *HMBS* founder variant originating in northern Sweden [Floderus et al 2002] (see Table 5).
- In Spain, the prevalence in the Murcia region is 17.7 individuals in one million inhabitants due to another *HMBS* founder variant, compared to the general Spanish prevalence of 6.3 individuals in one million inhabitants [Barreda-Sánchez et al 2019] (see Table 5).

Genetically Related (Allelic) Disorders

To date, six children and six adults with biallelic germline *HMBS* pathogenic variants have been described (see Table 3).

Table 3. Phenotypes Described in Individuals with Biallelic *HMBS* Pathogenic Variants

Genotype	Phenotype
Homozygous p.Arg167Trp [1] in 1 child	Manifestations starting early in childhood incl severe ataxia, dysarthria, severe psychomotor delay, & central & peripheral neurologic manifestations. MRI studies in 1 person showed white matter abnormalities that suggested selective postnatal involvement of cerebral oligodendrocytes. [2]
Compound heterozygote p.Arg167Trp [1] & p.Arg167Gln [2] in 1 child	
Compound heterozygous p.Arg167Trp [1] & p.Arg173Gln [2] in 2 children (sibs)	
Compound heterozygous p.Thr35Met [1] & p.Arg167Gln [2] in 1 child	The child presented in infancy w/neurologic findings & abnormal CNS imaging. [3]
Homozygous p.Leu81Pro [4] in 1 child	The child was less severely affected than those described above. He had mild intellectual impairment & no signs of ataxia or dystonia. [5]
Compound heterozygous c.500G>A (p.Arg167Gln) [1] & c.674G>A (p.Arg225Gln) [2] in 4 adults (incl 3 sibs)	Affected persons presented w/slowly progressive spasticity, ataxia, peripheral neuropathy, & leukoencephalopathy on MRI. [6]
Homozygous c.251C>A (p.Ala84Asp) [4] in 2 adults (sibs)	

CNS = central nervous system
1. *HBMS* pathogenic variant identified in the heterozygous state in individuals with acute intermittent porphyria (AIP)
2. Solis et al [2004]
3. Dixon et al [2019]
4. Relatives of affected individuals who are heterozygous for these variants had decreased porphobilinogen deaminase activity but no clinical manifestations of AIP. Additionally, to date no individuals heterozygous for these *HBMS* variants have been reported to have AIP.
5. Hessels et al [2004]
6. Stutterd et al [2021]

Differential Diagnosis

Acute neurovisceral attacks. Clinically indistinguishable acute neurovisceral attacks occur in acute intermittent porphyria (AIP) and the other three acute porphyrias (see Table 4) and may complicate tyrosinemia type 1 [Puy et al 2010].

Table 4. Genetic Disorders in the Differential Diagnosis of Symptomatic Acute Intermittent Porphyria

Gene	Disorder	MOI	Clinical Features	Biochemical Characteristics [1]			
				Urine	Stool	Plasma	Erythrocytes
ALAD	ALA dehydratase deficiency porphyria (OMIM 612740)	AR	Acute attack	↑ ALA, coproporphyrin III, normal PBG concentration			↑ zinc protoporphyrin; ↓ ALA dehydratase activity
CPOX	Hereditary coproporphyria (HCP)	AD	Acute attack ± skin lesions [2]	↑ PBG concentration, ALA [3], porphyrins [4]	↑ coproporphyrin III	↑ plasma porphyrins; fluorescence emission peak ~620 nm [5]	
FAH	Tyrosinemia type 1	AR	Acute attack	↑ ALA			↓ ALA dehydratase activity
PPOX	Variegate porphyria (VP)	AD	Acute attack ± skin lesions [2]	↑ PBG concentration, ALA [3], porphyrins [4]	↑ protoporphyrin [6]	↑ plasma porphyrins; fluorescence emission peak ~626 nm [7]	

AD = autosomal dominant; ALA = 5-aminolevulinic acid; AR = autosomal recessive; MOI = mode of inheritance; PBG = porphobilinogen

1. See Table 1 for biochemical characteristics of symptomatic AIP.

2. Acute neurovisceral attacks are accompanied by porphyric skin lesions (bullae, fragile skin) in about 15% of persons with HCP and about 60% of persons with VP.

3. PBG increased more than ALA; both may decrease rapidly as symptoms resolve.

4. Uroporphyrin from in vitro polymerization of PBG and coproporphyrin; measurement is not required for diagnosis and may mislead.

5. Plasma porphyrin concentration may occasionally be normal; fluorescence emission spectroscopy does not distinguish between HCP and AIP.

6. Protoporphyrin is the main stool porphyrin, but a small increase in coproporphyrin III is also observed.

7. Plasma porphyrin concentration is always increased, and fluorescence emission spectroscopy distinguishes VP from all other porphyrias.

Lead poisoning may also mimic the symptoms (i.e., abdominal pain) of clinically manifest acute AIP and disturb heme biosynthesis; however, anemia, a feature of lead poisoning, is not a feature of AIP. Lead poisoning is characterized in urine by increased 5-aminolevulinic acid (ALA) and coproporphyrin III and normal porphobilinogen, and in erythrocytes, increased zinc protoporphyrin and decreased ALA dehydratase activity.

Guillain-Barré syndrome (GBS) is a clinically defined syndrome in which an acute-subacute bilateral development of neurologic manifestations is often accompanied by distal sensory disturbance, pain, and autonomic dysfunction. Abdominal pain, tachycardia, and gastrointestinal symptoms such as nausea and constipation occur before the onset of neurologic manifestations in individuals with AIP. In addition, urinary porphobilinogen (PBG) concentration is significantly elevated in active AIP but normal in GBS, and cerebrospinal fluid protein is usually normal in AIP but elevated in GBS.

Red discoloration of the urine. Hematuria, ingestion of beetroot, some drugs and food additives, and porphyrin excretion in other porphyrias (e.g., familial porphyria cutanea tarda, congenital erythropoietic porphyria) may produce similar red discoloration of the urine.

Note: For a general review of the genetic porphyrias, see Hereditary Coproporphyria, Differential Diagnosis.

Management

No clinical practice guidelines for acute intermittent porphyria (AIP) have been published.

Initial Evaluations

Evaluations Following Initial Diagnosis of an AIP Attack

To establish the extent of disease and needs in an individual diagnosed with AIP who is experiencing acute manifestations, the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Consider other causes of abdominal pain in addition to porphyria.
- Review all medications and discontinue any that can exacerbate acute porphyria [Stein et al 2017]. See Agents/Circumstances to Avoid.
- Initial investigations should include the following:
  - Complete blood count
  - Measurement of serum/plasma concentrations of urea, creatinine, and electrolytes
  - If there is hyponatremia, measure serum and urine osmolality, and urine sodium concentration
  - Other blood tests as indicated by the individual's condition and possible cause of the attack (e.g., C-reactive protein, blood cultures, serum creatine kinase, and plasma magnesium concentration)
  - Brain MRI when central nervous system manifestations are present
- Refer individual to a porphyria specialist for more detailed clinical advice on AIP (see Resources).
- Affected individuals should be advised to register with an organization that provides warning jewelry in case of an accident (e.g., MedicAlert® or similar).
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse is recommended to inform affected individuals and their families about the nature, mode of inheritance, and implications of AIP to facilitate medical and personal decision making.
- Assess need for family support and resources including community or online resources and home nursing referral.

Evaluations Following Identification of an *HMBS* Pathogenic Variant in an Asymptomatic Individual

To establish the extent of disease and needs in an individual found to have an *HMBS* pathogenic variant (through cascade screening or as an incidental finding) who is not known to have experienced manifestations of AIP, the following evaluations (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Perform full clinical history and examination, including neurologic evaluation.
- Review medications to assess risk versus benefit (see Agents/Circumstances to Avoid).
- Measure urinary porphobilinogen (PBG) concentration to establish a baseline for comparison with future measurements taken during clinical findings suggestive of symptomatic porphyria.
- Refer individual to a porphyria specialist for more detailed clinical advice on AIP (see Resources).
- Affected individuals should be advised to register with an organization that provides warning jewelry in case of an accident (e.g., MedicAlert® or similar).
- Consultation with a medical geneticist, certified genetic counselor, or certified advanced genetic nurse is recommended to inform affected individuals and their families about the nature, mode of inheritance, and implications of AIP to facilitate medical and personal decision making.
- Assess need for family support and resources including community or online resources and home nursing referral.

Treatment of Manifestations

Treatment of an acute porphyria attack depends on the type and severity of the attack. Targeted therapies are available.

- Treat intercurrent infections and other diseases promptly.
- For mild acute neurovisceral attacks, a high carbohydrate intake, preferably oral, is recommended. When required, intravenous (IV) fluid may be used for up to 48 hours. IV fluid should contain a minimum of 5% dextrose; the recommendation in most countries is 10% glucose with added sodium (40 mmol) and potassium (20 mmol) given at a rate of 1,000 mL over 12 hours. Note that hypotonic dextrose in water solutions should be avoided because of the risk of hyponatremia.
- If improvement is unsatisfactory or if additional and progressive neurologic features present, intravenous administration of hemin preparations is recommended (see Treatment of Sporadic Acute Neurovisceral Attacks).

Targeted Therapies

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Treatment of Sporadic Acute Neurovisceral Attacks

Intravenous human hemin is the most effective treatment for sporadic acute neurovisceral attacks (i.e., when an individual has experienced 1 to ≤3 acute porphyria attacks) (see Table 2). Intravenous administration of hemin preparations may be lifesaving if employed early, when neuronal damage is still reversible, and may help to avoid peripheral neuropathy or prevent its progression.

The recommended dose for hemin is 3-4 mg/kg by IV, given once daily for four days. Treatment may be extended, depending on the clinical course. Note: Because 100 mg of hemin contains 8 mg of iron, frequent administration of hemin may increase the risk for iron overload. Periodic monitoring of serum ferritin concentration and/or transferrin saturation is therefore appropriate in individuals treated repeatedly with hemin.

- Panhematin® is approved for treatment of acute attacks in the United States. This product is supplied as a dried powder, which must be reconstituted with sterile water immediately before IV injection and administered over ten to 15 minutes. Because the administration of Panhematin® reconstituted with sterile water is associated with transient, mild coagulopathy, concurrent anticoagulant therapy should be avoided.
- Heme arginate (Normosang®) is an arginine-stabilized form of human hemin available nearly worldwide, including in Europe, Africa, the Middle East, and South America. It is infused over at least 30 minutes. It has the same advantage as hemin in treating an acute neurovisceral attack but has fewer reported side effects [Puy et al 2010].

Note: (1) Phlebitis after IV injection can be minimized by reconstituting hematin in 20% human serum albumin solution and/or by using a large vein or a central catheter for infusion. Peripheral cannulas used to administer hematin should be replaced after each use. (2) An infusion set with an in-line filter is recommended to remove any undissolved particulate matter. (3) Rigorous flushing of venous catheters with boluses of saline totaling 200 mL is recommended.

Recurrent acute attacks are best managed with support and advice from a porphyria specialist. See information and contact details of specialist porphyria centers at the International Porphyria Network website.

If the criterion for recurrent attacks is met [Stein et al 2023], Givlaari® (givosiran) should be considered, as long-term complications of hemin such as iron overload, phlebitis, and loss of venous access can be avoided.

Prevention of Recurrent Acute Neurovisceral Attacks

Givlaari® (givosiran) is a subcutaneously delivered RNA interference therapeutic specifically targeting ALAS1 mRNA in the liver to reduce urinary excretion of 5-aminolevulinic acid (ALA) and PBG. It is approved for treatment of acute porphyria in adults and adolescents age ≥12 years in the European Union and adults in the United States. Clinical studies have shown an acceptable safety profile and clinical efficacy in reducing attack rates and use of hemin [Sardh & Harper 2022].

When available, use of this treatment has meant that older treatment alternatives such as ovulation suppression therapy and preventive hemin can be avoided. For the sporadic acute attack, hemin is still the treatment of primary choice.

Liver Transplantation

Liver transplantation is curative and reported from several centers [Lissing et al 2021]. Indications include repeated life-threatening acute porphyria attacks and poor quality of life where givosiran is not available or has shown insufficient medical efficacy.

Note that ALA toxicity is the major hypothesis proposed for the pathogenesis of the neurologic lesions causing the clinical features of acute porphyria attacks. Support for this hypothesis are (1) the success of liver transplantation as a cure for recurrent acute attacks [Lissing et al 2021]; and (2) the occurrence of acute attacks in persons who do not have AIP who have received a liver transplant from persons who experience recurrent acute attacks, implicating release of a hepatic neurotoxin, probably ALA, as their cause [Dowman et al 2011].

Alternative Medical Therapies

Alternative medical therapies to reduce the frequency and/or severity of acute porphyria attacks if givosiran is not available include ovulation suppression therapy and prophylactic hemin infusion.

- **Ovulation suppression therapy** with gonadorelin analogs has been used for women with recurrent menstrual cycle-related acute neurovisceral attacks [Schulenburg-Brand et al 2017]. Long-acting analogs that can be used to prevent ovulation should be administered during the first few days of the menstrual cycle to minimize the early stimulation effect on hormone release that can trigger an attack. Side effects can be minimized by administering estrogen, preferably by patch. Gynecologic review and bone density monitoring are recommended. This treatment should be continuously evaluated in consultation with a porphyria specialist and preferably not last longer than two years.
- **Prophylactic hemin infusion** is possible. The minimum effective infusion frequency should be employed, usually a weekly dose of hemin infused via an indwelling venous catheter. Problems include those associated with a venous access device (infection, blockage) and iron overload.

Supportive Care

Other recommendations to reduce the frequency and/or severity of acute attacks include the following:

- Assure that adequate nutrition is provided by a normal balanced diet. Avoid unsupervised diets that restrict caloric intake, particularly those that exclude carbohydrates completely.
- Seek timely treatment of systemic illness or infection.

Pain relief. Effective analgesia should be provided as soon as possible, usually in the form of parenteral opiates (morphine, diamorphine, and fentanyl are safe). Very large quantities may be required in a severe acute attack. Consider patient-controlled analgesia and support from a pain management team.

Treatment of hypertension. Sixty percent of symptomatic individuals with AIP have hypertension because of development of AIP-related chronic kidney disease [Pallet et al 2018]. Beta-blockers and renin-angiotensin-aldosterone system (RAAS)-blockers are considered safe and should be used to delay the development of end-stage kidney disease.

Prevention of nausea and vomiting. Prochloperazine, promazine, or ondansetron are considered safe.

Prompt treatment of seizures can be terminated with intravenous diazepam, clonazepam, or magnesium sulphate.

Maintenance of fluid and electrolyte balance. Intravenous fluid replacement may be required to correct dehydration or electrolyte imbalance. Dextrose in water solutions should be avoided because of the risk of hyponatremia. Chronic hyponatremia (developing over >48 hours) should be corrected slowly to minimize the risk of central pontine myelinolysis [Stein et al 2017].

Advice on safe treatment of persons with porphyria in some specific clinical situations (e.g., epilepsy, HIV, malaria, tuberculosis, hyperlipidemia, and hypertension) is available on the Porphyria South Africa website.

Combined liver and kidney transplantation, which has been successful, can be considered in individuals with AIP who have recurrent acute porphyria attacks and end-stage kidney disease [Wahlin et al 2010]. Individuals with AIP may require kidney replacement therapy [Wang et al 2018].

Surveillance for All *HMBS* Heterozygotes Over Age 50 Years

Based on current knowledge, it is not possible to distinguish whether certain groups of individuals who are heterozygous for a pathogenic *HMBS* variant have an increased risk of developing primary liver cancer (PLC). Therefore, it is recommended that all individuals who are heterozygous for a pathogenic *HMBS* variant and are over 50 years of age undergo surveillance for PLC, regardless of clinical presentation, PBG excretion level, or how they were brought to the attention of physicians, including but not limited to family screening or genetic testing (such as multigene panel, exome sequencing, or genome sequencing) performed as part of an evaluation for another condition.

Most porphyria centers recommend PLC surveillance by annual or twice a year ultrasound examination for all individuals who are heterozygous for a pathogenic *HMBS* variant starting at age 50 years. Because annual ultrasound surveillance has relatively low sensitivity for early PLC detection and, thus, might be ineffective in high-risk individuals such as those with symptomatic or asymptomatic AIP older than age 50 years who have a persistently high urinary PBG concentration, twice a year surveillance is recommended [Peoc'h et al 2019, Lissing et al 2022].

Note: Serum alpha-fetoprotein measurement is not helpful in surveillance.

Agents/Circumstances to Avoid

Individuals with AIP are advised to avoid excessive alcohol consumption. Alcohol has been shown to upregulate ALAS1, the first enzyme of hepatic heme biosynthesis [Doss et al 2000], and thus could be a trigger for acute attacks. Excessive alcohol use is defined as binge drinking (i.e., consuming four or more drinks on an occasion for a woman or five or more drinks on an occasion for a man) or heavy drinking (i.e., consuming eight or more drinks per week for a woman or fifteen or more drinks per week for a man) (see www.cdc.gov).

In all the acute porphyrias, information on the safety of many drugs and other over-the-counter preparations is incomplete; however, evidence-based guidelines for assessment of drug porphyrogenicity have been published [Hift et al 2011].

- For a searchable drug safety database, see the Drug Database.

- See the American Porphyria Foundation drug database.
- For information on prescribing medication in the context of certain conditions (e.g., HIV, epilepsy, malaria), see Porphyria South Africa.
- Safe drug lists are available at Welsh Medicines Information Centre - Porphyria Information Service.

Evaluation of Relatives at Risk

Family members of an individual with a known *HMBS* pathogenic variant (i.e., cascade screening). It is appropriate to clarify the genetic status of apparently asymptomatic at-risk relatives of an individual with a known *HMBS* pathogenic variant (regardless of the presence or absence of acute porphyria-related manifestations and/or a highly elevated urine PBG-to-creatinine ratio in that individual) so that those who are heterozygous for the familial *HMBS* pathogenic variant (and thus at increased risk of developing AIP attacks and hepatocellular carcinoma) can be identified early and counseled about preventive measures and surveillance (see Evaluations Following Identification of an *HMBS* Pathogenic Variant in an Asymptomatic Individual, Surveillance, and Agents/Circumstances to Avoid).

Providing information to individuals newly identified as being heterozygous for an *HMBS* pathogenic variant about preventive measures and surveillance is extremely important. Increased knowledge about genetic predisposition among heterozygous individuals is one of the key reasons why the frequency of acute porphyria attacks and the prevalence of long-term neurologic complications (e.g., peripheral neuropathy) has decreased in recent decades.

Family members of an individual with a biochemical diagnosis of AIP and an unknown *HMBS* pathogenic variant. Although less sensitive (84%) and specific (77%) than molecular genetic testing, erythrocyte HMBS activity may be useful when molecular testing is not available or in the rare instances when an *HMBS* pathogenic variant cannot be identified in a family [Kauppinen & von und zu Fraunberg 2002].

Note: (1) Measurement of erythrocyte HMBS activity cannot be used to detect heterozygotes if the proband has the non-erythroid variant form of acute intermittent porphyria (see Molecular Pathogenesis). (2) Identification of normal erythrocyte HMBS activity in an asymptomatic family member does not exclude latent AIP.

Urinary PBG excretion should **not** be used to screen asymptomatic family members as it is normal in all prepubertal children with latent AIP and in a majority of adults.

Predictive testing in minors. Although acute porphyria attacks are rare before puberty, children in families with AIP should be offered testing with appropriate consent from parents or guardians to provide advice/education on avoidance of precipitating factors and ensure rapid diagnosis with prompt treatment should an attack occur in adolescence.

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

Pregnancy Management

Pregnancy in women with AIP is usually uncomplicated. Although urinary PBG concentration may increase during pregnancy, this does not lead to a higher frequency of clinical manifestations of porphyria [Vassiliou & Sardh 2022].

Preconception counseling is recommended to advise women with AIP of the clinical manifestations of porphyria, self-care, and preventative measures to avoid exacerbations (i.e., adequate and regular nutrition, rest, and carbohydrate intake for treating mild-to-moderate symptoms). See also Agents/Circumstances to Avoid.

There is a higher risk for pregnancy-induced hypertensive disorder, gestational diabetes, and fetuses with intrauterine growth restriction (IUGR). In general, risk ratios are higher among women with AIP who have high lifetime urinary PBG concentrations [Mantel et al 2023].

Testing for urinary PBG concentration prior to pregnancy may establish the individual's risk levels.

Women with biochemically active acute hepatic porphyria (AHP) (i.e., urinary PBG concentration greater than four times the upper limit of normal) or a history of active AHP should be offered specialized prenatal care. Hyperemesis, a catabolic risk for precipitating acute attacks, should be treated promptly. Blood pressure should be monitored once monthly during the first and second trimesters, and weekly during the last trimester. Additional monitoring of fetal growth during pregnancy will help identify IUGR [Mantel et al 2023].

When a woman with AIP experiences abdominal pain, hypertension, and tachycardia during pregnancy, urine PBG concentration should be measured, and complications of pregnancy should be excluded in consultation with an obstetrician before the findings are attributed to an acute attack.

- If an acute porphyria attack is suspected, a urine PBG concentration should be measured before deciding on specific treatment (see Treatment of Manifestations).
- Any symptomatic treatment needed should be chosen after considering the risk of the drug triggering/aggravating an acute porphyria attack in the pregnant woman (see Treatment of Manifestations).
- An obstetrician should be consulted regarding medical treatment and possible effects on the fetus.
- Human hemin is safe to be used during pregnancy [Vassiliou et al 2020].
- No human pregnancies have been reported during or after treatment with Givlaari® (givosiran); there are no data on the presence of givosiran in human milk.
- **Note:** In an obstetric emergency, no drug should be restricted if it is likely to be of major clinical benefit or is required in a life-threatening situation.

See MotherToBaby for further information on medication use during pregnancy.

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

Acute intermittent porphyria (AIP) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- The majority of individuals diagnosed with AIP inherited an *HMBS* pathogenic variant from one of their parents, who may or may not have experienced manifestations of porphyria.

- Rarely, individuals diagnosed with AIP have the disorder as the result of a *de novo HMBS* pathogenic variant.
- Unless a parent is already known to be heterozygous for an *HMBS* pathogenic variant, molecular genetic testing for the pathogenic variant identified in the proband should be undertaken to evaluate the genetic status of the parents, clarify their need for preventive measures and surveillance, and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.
- Due to the low penetrance of clinical manifestations of AIP, a significant proportion of heterozygotes are asymptomatic and the family history of many probands will appear to be negative. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

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

- If one of the parents of the proband has an *HMBS* pathogenic variant, the risk to each sib of inheriting the pathogenic variant is 50%. Because clinical penetrance is low, it is not possible to predict whether individuals who inherit an *HMBS* pathogenic variant will be symptomatic, or, if they are symptomatic, the age of onset, severity, or type of symptoms. However, all sibs who inherit an *HMBS* pathogenic variant should be counseled about preventive measures and surveillance (see Evaluations Following Identification of an *HMBS* Pathogenic Variant in an Asymptomatic Individual, Surveillance, and Agents/Circumstances to Avoid). Increased knowledge about genetic predisposition among heterozygous individuals is one of the key reasons why the frequency of acute porphyria attacks and the prevalence of long-term neurologic complications (e.g., peripheral neuropathy) has decreased in recent decades.
- If the proband has a known *HMBS* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the risk to sibs of inheriting a pathogenic variant is estimated to be 1% because of the possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents are clinically unaffected but their genetic status is unknown, sibs of a proband should be considered to be at risk for AIP (and thus at increased risk of developing acute porphyria attacks and hepatocellular carcinoma) and should be counseled about preventive measures and surveillance. (Note: Surveillance is only offered to genetically confirmed heterozygotes.)

Offspring of a proband

- Each child of an individual with an *HMBS* pathogenic variant has a 50% chance of inheriting the *HMBS* pathogenic variant.
- Because clinical penetrance is low, it is not possible to predict whether offspring who inherit an *HMBS* pathogenic variant will be symptomatic, or, if they are symptomatic, the age of onset, severity, or type of manifestations. However, all individuals who inherit an *HMBS* pathogenic variant should be counseled about preventive measures and surveillance.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *HMBS* pathogenic variant, the parent's family members may also have the *HMBS* pathogenic variant and be at increased risk of developing acute porphyria attacks and hepatocellular carcinoma.

Related Genetic Counseling Issues

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

Family planning

- The optimal time for determination of genetic risk and discussion of the availability and indications for prenatal/preimplantation genetic testing is before pregnancy.
- Preconception counseling is recommended to advise women with AIP of the clinical manifestations of porphyria, self-care, and preventative measures to avoid exacerbations (see Pregnancy Management).
- 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.

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). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the familial *HMBS* pathogenic variant has been identified, prenatal and preimplantation genetic testing for AIP are possible. Because clinical penetrance is low, the finding of an *HMBS* pathogenic variant on prenatal testing cannot be used to predict whether an individual will become symptomatic, or, if they do become symptomatic, the age of onset, severity, or type of symptoms.

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

Resources

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

- **American Porphyria Foundation (APF)**
  Phone: 866-APF-3635
  Email: general@porphyriafoundation.org
  www.porphyriafoundation.org

- **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

- **Porphyria South Africa**

  South Africa

  Phone: +27 21-4066332

  Fax: +27 21-4066061

  Email: Peter.Meissner@uct.ac.za

  Porphyria for Patients

- **United Porphyrias Association**

  Phone: 800-868-1292

  Email: info@porphyria.org

  www.porphyria.org

- **Welsh Medicines Information Centre**

  The Welsh Medicines Information Centre (WMIC) offers a specialist advisory service on the safe use of drugs in porphyria.

  United Kingdom

  Phone: +44 029 2074 4298

  Drugs considered SAFE in the acute porphyrias

- **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. Acute Intermittent Porphyria: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
HMBS	11q23.3	Porphobilinogen deaminase	HMBS database	HMBS	HMBS

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 Acute Intermittent Porphyria (View All in OMIM)

176000	PORPHYRIA, ACUTE INTERMITTENT; AIP
609806	HYDROXYMETHYLBILANE SYNTHASE; HMBS

Molecular Pathogenesis

The gene *HMBS* encodes porphobilinogen deaminase, the third enzyme in the heme biosynthetic pathway, which functions as a monomer and is localized within the cytoplasm in all cell types, where it catalyzes the synthesis of the linear tetrapyrrole hydroxymethlbilane from four molecules of porphobilinogen [Bung et al 2019].

AIP results from *HMBS* pathogenic variants that markedly decrease porphobilinogen deaminase enzymatic activity. A large proportion of pathogenic variants are associated with a 50% reduction in porphobilinogen deaminase in all tissues because of unstable or absent protein. The remainder of disease-associated variants (mainly missense variants) affect protein stability and folding, cofactor assembly, and/or the catalytic process. Modeling studies based on the crystallographic structure have provided important insight into these mechanisms [Bustad et al 2021].

Exons 1 and 3-15 of *HMBS* encode a ubiquitous porphobilinogen deaminase isoform that is expressed in all tissues; exons 2-15 (with exon 2 being noncoding) encode an isoform that is restricted to erythroid cells via alternative splicing under the control of two promoters [Grandchamp et al 1989]. (Note that the *HMBS* exon numbers mentioned are reported as described in Grandchamp et al [1989].) Individuals with a pathogenic variant affecting exon 1 (NM_000190.4) show normal porphobilinogen deaminase enzyme activity if measured in erythrocytes [Grandchamp et al 1989]. This form of AIP in which the enzymatic defect is present in only non-erythroid cells is referred to as the non-erythroid variant.

Mechanism of disease causation. Loss of function

***HMBS*-specific laboratory technical considerations.** There are four described porphobilinogen deaminase isoforms. The reference sequence for the ubiquitous isoform 1 is NM_000190.4 (NP_000181.2) and the reference sequence for the erythroid isoform 2 is NM_001024382.2 (NP_001019553.1). The two proteins differ in their N-terminal region, with 17 amino acids missing in isoform 2.

Table 5. *HMBS* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000190.4 NP_000181.2	c.53delT	p.Met18ArgfsTer3	Founder variant in Russia (10% of probands) [Goncharova et al 2019]
	c.331G>A	p.Gly111Arg	Most common variant in Argentina; accounts for 55% of pathogenic variants [Cerbino et al 2015]. It occurs at a CpG site.
	c.346C>T	p.Arg116Trp	Founder variant in the Netherlands & recurrent variant in several populations [de Rooij et al 2009]. It occurs at a CpG site.

Table 5. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
	c.517C>T	p.Arg173Trp	Founder in Nova Scotia, Canada, & recurrent variant in several populations [Greene-Davis et al 1997]. It occurs at a CpG site.
	c.538C>T	p.Gln180Ter	Founder variant in Venezuela [Paradisi & Arias 2010]. Not at a CpG site.
	c.593G>A	p.Trp198Ter	Founder variant in northern Sweden [Floderus et al 2002]. Not at a CpG site.
	c.669_698del	p.Glu223_Leu232del	Founder variant in Spain (Murcia region) [Barreda-Sánchez et al 2019]
	c.848G>A	p.Trp283Ter	Founder variant in Switzerland; accounts for 60% of pathogenic variants [Schneider-Yin et al 2002]. Not at a CpG site.

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

Author Notes

Contact Michela Barbaro, PhD, a clinical laboratory geneticist, to inquire about review of *HMBS* variants of uncertain significance.

Author History

Michael Badminton, PhD, FRCPath; University Hospital of Wales Cardiff (2013-2023)
Michela Barbaro, Sc, PhD (2023-present)
Eliane Sardh, MD, PhD (2023-present)
Shigeru Sassa, MD, PhD; The Rockefeller University (2005-2010)
Stig Thunell, MD, PhD; Karolinska University Hospitall Huddinge (2010-2013)
Sharon Whatley, PhD, FRCPath; University Hospital of Wales Cardiff (2013-2023)

Revision History

- 8 February 2024 (bp) Comprehensive update posted live
- 5 December 2019 (bp) Comprehensive update posted live
- 7 February 2013 (me) Comprehensive update posted live
- 23 March 2010 (me) Comprehensive update posted live
- 27 September 2005 (me) Review posted live
- 3 January 2005 (ss) Original submission

References

Literature Cited

Aarsand AK, Villanger JH, Støle E, Deybach JC, Marsden J, To-Figueras J, Badminton M, Elder GH, Sandberg S. European specialist porphyria laboratories: diagnostic strategies, analytical quality, clinical interpretation,

and reporting as assessed by an external quality assurance program. Clin Chem. 2011;57:1514-23. PubMed PMID: 21937752.

Andersson C, Floderus Y, Wikberg A, Lithner F. The W198X and R173W mutations in the porphobilinogen deaminase gene in acute intermittent porphyria have higher clinical penetrance than R167W. A population-based study. Scand J Clin Lab Invest. 2000;60:643-8. PubMed PMID: 11202057.

Barreda-Sánchez M, Buendía-Martínez J, Glover-López G, Carazo-Díaz C, Ballesta-Martínez MJ, López-González V, Sánchez-Soler MJ, Rodriguez-Peña L, Serrano-Antón AT, Gil-Ferrer R, Martínez-Romero MDC, Carbonell-Meseguer P, Guillén-Navarro E. High penetrance of acute intermittent porphyria in a Spanish founder mutation population and CYP2D6 genotype as a susceptibility factor. Orphanet J Rare Dis. 2019;14:59. PubMed PMID: 30808393.

Baumann K, Kauppinen R. Penetrance and predictive value of genetic screening in acute porphyria. Mol Genet Metab. 2020;130, 87-99. PubMed PMID: 32067921.

Bung N, Roy A, Priyakumar UD, Bulusu G. Computational modeling of the catalytic mechanism of hydroxymethylbilane synthase. Phys Chem Chem Phys. 2019;21:7932-40. PubMed PMID: 30918925.

Bustad HJ, Kallio JP, Vorland M, Fiorentino V, Sandberg S, Schmitt C, Aarsand AK, Martinez A. Acute intermittent porphyria: an overview of therapy developments and future perspectives focusing on stabilisation of HMBS and proteostasis regulators. Int J Mol Sci. 2021;22:675. PubMed PMID: 33445488.

Cerbino GN, Gerez EN, Varela LS, Melito VA, Parera VE, Batlle A, Rossetti MV. Acute intermittent porphyria in Argentina: an update. Biomed Res Int. 2015;2015:946387. PubMed PMID: 26075277.

Chen B, Solis-Villa C, Hakenberg J, Qiao W, Srinivasan RR, Yasuda M, Balwani M, Doheny D, Peter I, Chen R, Desnick RJ. Acute intermittent porphyria: predicted pathogenicity of HMBS variants indicates extremely low penetrance of the autosomal dominant disease. Hum Mutat. 2016;37:1215-22. PubMed PMID: 27539938.

de Rooij FW, Kavelaars FG, Koole-Lesuis H, Wilson JH. Evidence for an ancestral founder of the common R116W mutation in the hydroxymethylbilane synthase gene in acute intermittent porphyria in The Netherlands. Cell Mol Biol (Noisy-le-grand). 2009;55:64-9. PubMed PMID: 19656453.

Dixon N, Li T, Marion B, Faust D, Dozier S, Molina A, Rudnick S, Bonkovsky HL. Pilot study of mitochondrial bioenergetics in subjects with acute porphyrias. Mol Genet Metab. 2019;128:228-35. PubMed PMID: 31153822.

Doss MO, Kühnel A, Gross U. Alcohol and porphyrin metabolism. Alcohol Alcohol. 2000;35:109-25. PubMed PMID: 10787385.

Dowman JK, Gunson BK, Bramhall S, Badminton MN, Newsome PN. Liver transplantation from donors with acute intermittent porphyria. Ann Intern Med. 2011;154:571-2. PubMed PMID: 21502660.

Elder G, Harper P, Badminton M, Sandberg S, Deybach JC. The incidence of inherited porphyrias in Europe. J Inherit Metab Dis. 2013;36:849-57. PubMed PMID: 23114748.

Floderus Y, Shoolingin-Jordan PM, Harper P. Acute intermittent porphyria in Sweden. Molecular, functional and clinical consequences of some new mutations found in the porphobilinogen deaminase gene. Clin Genet. 2002;62:288-97. PubMed PMID: 12372055.

Goncharova M, Pshenichnikova O, Luchinina Y, Pustovoit Y, Karpova I, Surin V. Molecular genetic study of acute intermittent porphyria in Russia: HMBS gene mutation spectrum and problem of penetrance. Clin Genet. 2019;96:91-7. PubMed PMID: 31044425.

Gouya L, Ventura P, Balwani M, Bissell DM, Rees DC, Stölzel U, Phillips JD, Kauppinen R, Langendonk JG, Desnick RJ, Deybach JC, Bonkovsky HL, Parker C, Naik H, Badminton M, Stein PE, Minder E, Windyga J, Bruha R, Cappellini MD, Sardh E, Harper P, Sandberg S, Aarsand AK, Andersen J, Alegre F, Ivanova A, Talbi N, Chan A, Querbes W, Ko J, Penz C, Liu S, Lin T, Simon A, Anderson KE. EXPLORE: a prospective,

multinational, natural history study of patients with acute hepatic porphyria with recurrent attacks. Hepatology. 2020;71:1546-58. PubMed PMID: 31512765.

Grandchamp B, Picat C, de Rooij F, Beaumont C, Wilson P, Deybach JC, Nordmann Y. A point mutation G----A in exon 12 of the porphobilinogen deaminase gene results in exon skipping and is responsible for acute intermittent porphyria. Nucleic Acids Res. 1989;17:6637-49. PubMed PMID: 2789372.

Greene-Davis ST, Neumann PE, Mann OE, Moss MA, Schreiber WE, Welch JP, Langley GR, Sangalang VE, Dempsey GI, Nassar BA. Detection of a R173W mutation in the porphobilinogen deaminase gene in the Nova Scotian "foreign Protestant" population with acute intermittent porphyria: a founder effect. Clin Biochem. 1997;30:607-12. PubMed PMID: 9455613.

Hessels J, Voortman G, van der Wagen A, van der Elzen C, Scheffer H, Zuijderhoudt FM. Homozygous acute intermittent porphyria in a 7-year-old boy with massive excretions of porphyrins and porphyrin precursors. J Inherit Metab Dis. 2004;27:19-27. PubMed PMID: 14970743.

Hift RJ, Thunell S, Brun A. Drugs in porphyria: from observation to a modern algorithm-based system for the prediction of porphyrogenicity. Pharmacol Ther. 2011;132:158-69. PubMed PMID: 21704073.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Kauppinen R, von und zu Fraunberg M. Molecular and biochemical studies of acute intermittent porphyria in 196 patients and their families. Clin Chem. 2002;48:1891-900. PubMed PMID: 12406973.

Lamon J, With TK and Redeker AG. The Hoesch test: Bedside screening for urinary porphobilinogen in patients with suspected porphyria. Clin Chem. 1974; 20:1438-40. PubMed PMID: 4425514.

Lenglet H, Schmitt C, Grange T, Manceau H, Karboul N, Bouchet-Crivat F, Robreau AM, Nicolas G, Lamoril J, Simonin S, Mirmiran A, Karim Z, Casalino E, Deybach JC, Puy H, Peoc'h K, Gouya L. From a dominant to an oligogenic model of inheritance with environmental modifiers in acute intermittent porphyria. Hum Mol Genet. 2018;27:1164-73. PubMed PMID: 29360981.

Lissing M, Nowak G, Adam R, Karam V, Boyd A, Gouya L, Meersseman W, Melum E, Ołdakowska-Jedynak U, Reiter FP, Colmenero J, Sanchez R, Herden U, Langendonk J, Ventura P, Isoniemi H, Boillot O, Braun F, Perrodin S, Mowlem E, Wahlin S; European Liver and Intestine Transplant Association. Liver transplantation for acute intermittent porphyria. Liver Transpl. 2021;27:491-501. PubMed PMID: 33259654.

Lissing M, Vassiliou D, Floderus Y, Harper P, Bottai M, Kotopouli M, Hagström H, Sardh E, Wahlin S. Risk of primary liver cancer in acute hepatic porphyria patients: a matched cohort study of 1244 individuals. J Intern Med. 2022;291:824-36. PubMed PMID: 35112415.

Lissing M, Vassiliou D, Floderus Y, Harper P, Yan J, Hagström H, Sardh E, Wahlin S. Risk for incident comorbidities, nonhepatic cancer and mortality in acute hepatic porphyria: a matched cohort study in 1244 individuals. J Inherit Metab Dis. 2023;46:286-99. PubMed PMID: 36546345.

Mantel Ä, Vassiliou D, Lissing M, Stephansson O, Wahlin S, Sardh E. Maternal and fetal outcomes in acute hepatic porphyria: a Swedish national cohort study. J Inherit Metab Dis. 2023;46:675-86. PubMed PMID: 37078226.

Marsden JT, Rees DC. Urinary excretion of porphyrins, porphobilinogen and δ-aminolaevulinic acid following an attack of acute intermittent porphyria. J Clin Pathol. 2014;67:60-5. PubMed PMID: 23908454.

Pallet N, Karras A, Thervet E, Gouya L, Karim Z, Puy H. Porphyria and kidney diseases. Clin Kidney J. 2018;11:191-7. PubMed PMID: 29644058.

Paradisi I, Arias S. Marked geographic aggregation of acute intermittent porphyria families carrying mutation Q180X in Venezuelan populations, with description of further mutations. J Inherit Metab Dis. 2010;33:S455-63. PubMed PMID: 20978940.

Peoc'h K, Manceau H, Karim Z, Wahlin S, Gouya L, Puy H, Deybach JC. Hepatocellular carcinoma in acute hepatic porphyrias: a Damocles sword. Mol Genet Metab. 2019;128:236-41. PubMed PMID: 30413387.

Pischik E, Baumann K, Karpenko A, Kauppinen R. Pathogenesis of acute encephalopathy in acute hepatic porphyria. J Neurol. 2023;270:2613-30. PubMed PMID: 36757574.

Puy H, Gouya L, Deybach J-C. Porphyrias. Lancet. 2010;375:924-37. PubMed PMID: 20226990.

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

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; ACMG Laboratory Quality Assurance Committee. 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.

Saberi B, Naik H, Overbey JR, Erwin AL, Anderson KE, Bissell DM, Bonkovsky HL, Phillips JD, Wang B, K Singal A, M McGuire B, Desnick RJ, Balwani M. Hepatocellular carcinoma in acute hepatic porphyrias: results from the longitudinal study of the U.S. Porphyrias Consortium. Hepatology. 2021;73:1736-46. PubMed PMID: 32681675.

Sardh E, Harper P. RNAi therapy with givosiran significantly reduces attack rates in acute intermittent porphyria. J Intern Med. 2022;291:593-610. PubMed PMID: 35067977.

Schneider-Yin X, Hergersberg M, Goldgar DE, Rüfenacht UB, Schuurmans MM, Puy H, Deybach JC, Minder EI. Ancestral founder of mutation W283X in the porphobilinogen deaminase gene among acute intermittent porphyria patients. Hum Hered. 2002;54:69-81. PubMed PMID: 12566739.

Schulenburg-Brand D, Gardiner T, Guppy S, Rees DC, Stein P, Barth J, Felicity Stewart M, Badminton M. An audit of the use of gonadorelin analogues to prevent recurrent acute symptoms in patients with acute porphyria in the United Kingdom. JIMD Rep. 2017;36:99-107. PubMed PMID: 28220410.

Solis C, Martinez-Bermejo A, Naidich TP, Kaufmann WE, Astrin KH, Bishop DF, Desnick RJ. Acute intermittent porphyria: studies of the severe homozygous dominant disease provides insights into the neurologic attacks in acute porphyrias. Arch Neurol. 2004;61:1764-70. PubMed PMID: 15534187.

Stein PE, Badminton MN, Rees DC. Update review of the acute porphyrias. Br J Haematol. 2017;176:527-38. PubMed PMID: 27982422.

Stein PE, Edel Y, Mansour R, Mustafa RA, Sandberg S; Members of the Acute Porphyria Expert Panel. Key terms and definitions in acute porphyrias: results of an international Delphi consensus led by the European porphyria network. J Inherit Metab Dis. 2023;46:662-74. PubMed PMID: 37067064.

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.

Storjord E, Dahl JA, Landsem A, Ludviksen JK, Karlsen MB, Karlsen BO, Brekke OL. Lifestyle factors including diet and biochemical biomarkers in acute intermittent porphyria: results from a case-control study in northern Norway. Mol Genet Metab. 2019;128:254-70. PubMed PMID: 30583995.

Stutterd CA, Kidd A, Florkowski C, Janus E, Fanjul M, Raizis A, Wu TY, Archer J, Leventer RJ, Amor DJ, Lukic V, Bahlo M, Gow P, Lockhart PJ, van der Knaap MS, Delatycki MB. Expanding the clinical and radiological phenotypes of leukoencephalopathy due to biallelic HMBS mutations. Am J Med Genet A. 2021;185:2941-50. PubMed PMID: 34089223.

Tchernitchko D, Tavernier Q, Lamoril J, Schmitt C, Talbi N, Lyoumi S, Robreau AM, Karim Z, Gouya L, Thervet E, Karras A, Puy H, Pallet N. A variant of peptide transporter 2 predicts the severity of porphyria-associated kidney disease. J Am Soc Nephrol. 2017;28:1924-32 PubMed PMID: 28031405.

Vassiliou D, Lempessi C, Harper P, Sardh E. Challenges in the management of acute intermittent porphyria with recurrent attacks during pregnancy: a case report. Clin Case Rep. 2020;8:2483-7. PubMed PMID: 33363763.

Vassiliou D, Sardh E. Acute hepatic porphyria and maternal health: clinical and biochemical follow-up of 44 pregnancies. J Intern Med. 2022;291:81-94. PubMed PMID: 34411356.

Wahlin S, Harper P, Sardh E, Andersson C, Andersson DE, Ericzon BG. Combined liver and kidney transplantation in acute intermittent porphyria. Transpl Int. 2010;23:e18-21. PubMed PMID: 20028496.

Wang B, Bonkovsky HL, Lim JK, Balwani M. AGA clinical practice update on diagnosis and management of acute hepatic porphyrias: expert review. Gastroenterology. 2023;164:484-91. PubMed PMID: 36642627.

Wang B, Rudnick S, Cengia B, Bonkovsky HL. Acute hepatic porphyrias: review and recent progress. Hepatol Commun. 2018;3:193-206. PubMed PMID: 30766957.

Woolf J, Marsden JT, Degg T, Whatley S, Reed P, Brazil N, Stewart MF, Badminton M. Best practice guidelines on first-line laboratory testing for porphyria. Ann Clin Biochem. 2017;54:188-98. PubMed PMID: 27555665.

License