



MODULE
01

Classification of Porphyria



Porphyria—A Group of Rare Diseases with Clinical Consequences

- Porphyria is a group of 9 metabolic disorders^{1,2}
 - Each type of porphyria involves a genetic defect in a heme biosynthesis pathway enzyme, except for PCT (porphyria cutanea tarda) which may be genetic or acquired^{1,2}
 - The types of porphyria are associated with distinct signs and symptoms^{1,3}
- Prevalence of some subtypes of porphyria may be higher than generally assumed³

Estimated Prevalence of Most Common Types of Porphyria^{1,4}

Type of Porphyria	Estimated Prevalence Based on European and US Data
Porphyria cutanea tarda (PCT)	1/10,000 (EU) ¹
Acute hepatic porphyria (AHP)	1/100,000 (US, EU*) ^{4,5}
Erythropoietic protoporphyria (EPP)	1/50,000-75,000 (EU) ¹

*Estimate Symptomatic Patients Diagnosed with AHP

1. Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet*. 2015;86:17.20.1-17.20.26. 2. Puy H et al. *Lancet*. 2010;375:924-937. 3. Bissell DM et al. *N Engl J Med*. 2017;377:862-872. 4. Elder G et al. *J Inherit Metab Dis*. 2013;36:848-857. 5. Silver, S., et al. ACG 2019.

Classification of Porphyria

Porphyria can be classified in 2 major ways^{1,2}:

1

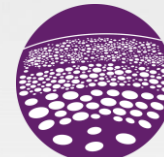
According to major physiological sites: liver or bone marrow^{1,2}



- Heme precursors originate in either the liver or bone marrow, which are the tissues most active in heme biosynthesis^{1,2}

2

According to major clinical manifestations^{1,2}



Acute Hepatic Porphyria Versus Photocutaneous Porphyria

- Major clinical manifestations are either neurovisceral symptoms (eg, severe, diffuse abdominal pain) associated with acute attacks or cutaneous lesions resulting from phototoxicity^{1,2}
- Acute hepatic porphyria may be somewhat of a misnomer since the clinical features may be prolonged and chronic and also may include cutaneous manifestations³

1. Bonkovsky HL. *Hematology Am Soc Hematol Educ Program*. 2005;24-30. 2. Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet*. 2015;86:17.20.1-17.20.26. 3. Anderson KE et al. *Ann Intern Med*. 2005;142:439-450.

Using Major Clinical Manifestations for Classification of Types of Porphryia

Neurovisceral Symptoms

AHP: Cardinal Manifestation of Acute Neurovisceral Symptoms¹

The symptoms of AHP are believed to be caused by increased concentrations of the neurotoxic intermediates ALA and PBG that accumulate due to enzyme deficiencies in the heme biosynthesis pathway, leading to nervous system injury²

ADP

AIP

HCP

VP

Photocutaneous Symptoms

Photocutaneous Porphryia: Cardinal Manifestation of Skin Lesions^{1,3}

XLDPP

CEP

HEP

PCT

EPP

The symptoms of photocutaneous porphryia are thought to be caused by increased concentrations of the photosensitizing porphyrins^{2,3}

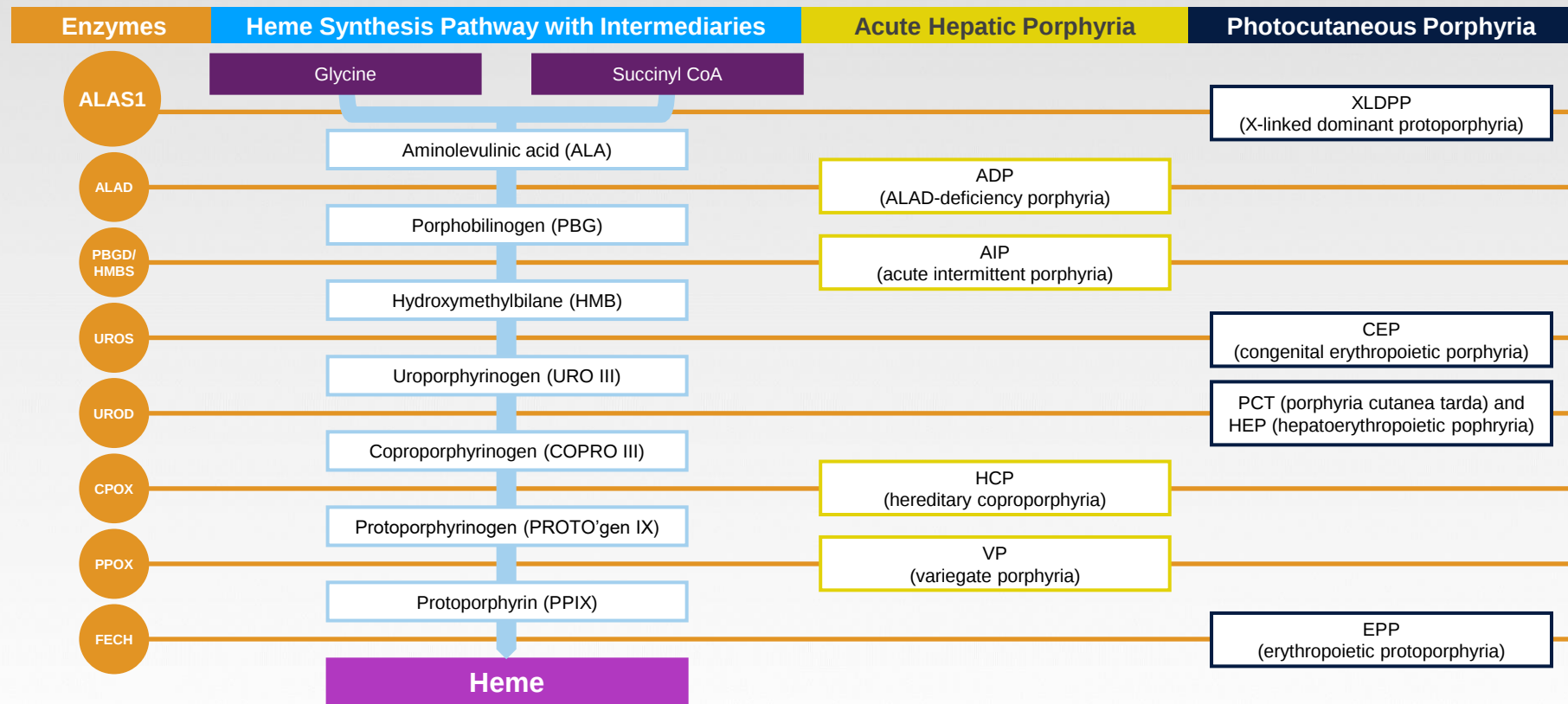
HCP and VP are associated with both acute neurovisceral symptoms and skin lesions¹

ADP=aminolevulinic acid dehydratase-deficiency porphryia; AIP=acute intermittent porphryia; ALA=aminolevulinic acid; CEP=congenital erythropoietic porphryia; EPP=erythropoietic protoporphyria; HCP=hereditary coproporphyria; PBG=porphobilinogen; PCT=porphryia cutanea tarda; VP=variegate porphryia; XLDPP=X-linked dominant protoporphyria; HEP=Hepatoerythropoietic porphryia.

1. Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26. 2. Bissell DM et al. *N Engl J Med*. 2017;377:862-872. 3. Wang B et al. *Hepatol Commun*. 2019; 3;3:193-206.

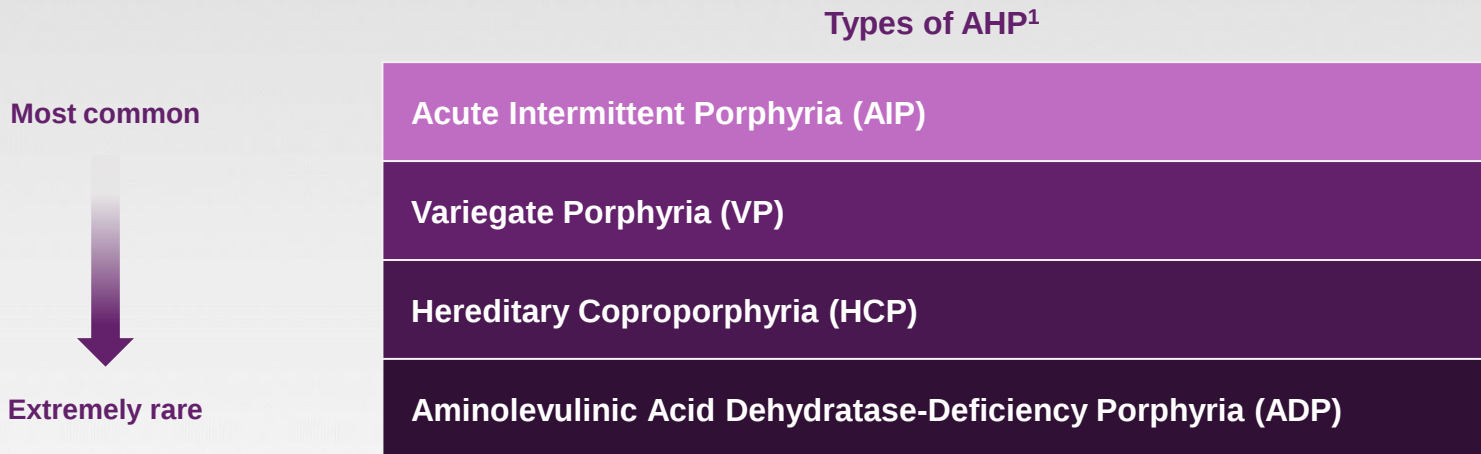
Heme Biosynthesis Pathway, Defective Enzymes, and Related Porphyria¹

The Rate-Limiting Step for the Pathway is the Formation of ALA, Catalyzed by ALAS1²



1. Bissell DM et al. *N Engl J Med*. 2017;377:862-872. 2. Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26.

The Relative Prevalence of the Four Different Types of Acute Hepatic Porphryia (AHP)



- AIP accounts for about 80% of AHP cases⁴
- The prevalence of AIP may be underreported due to estimates based on patients with symptomatic disease rather than estimates based on a genetic mutation leading to enzyme deficiency⁵
 - There is even less information about the other types of AHP
- 1 in 100,000 people in the US are diagnosed with symptomatic AHP

1. Anderson KE et al. *Ann Intern Med.* 2005;142:439-450. 4. Simon A et al. *Patient.* 2018;11(5):527-537. 5. Bissell DM, Wang B. *J Clin Transl Hepatol.* 2015;3:17-26.

AHP is a Genetic Disease with a Combination of Hormonal and Environmental Triggers

- Acute attacks in genetically predisposed patients are frequently preceded by environmental or hormonal triggers¹⁻⁴
 - When manifested, the disease can be debilitating and even life threatening as symptoms can progress to respiratory failure or paralysis, which could be fatal or lead to a temporary or permanent disability⁵
- Signs and symptoms predominantly affect women with AHP of reproductive age but can occur in men as well³
 - It is rare to experience AHP symptoms before puberty⁶
 - Attacks are less likely after menopause²

- Some hormonal and environmental triggers of AHP triggers^{1,2,4}:
 - Woman's menstrual cycle
 - The use of some medications in the following drug classes:
 - Anesthetics, Antimicrobials, Oral contraceptives, Hormones, Anticonvulsants, Migraine drugs, Antihistamines, Sedatives, Antihyperglycemics
 - Extreme dieting
 - Smoking
 - Excessive alcohol consumption
 - Stress caused by:
 - Infections, Physical exhaustion, Surgery, Psychological stress

1. Anderson KE et al. *Ann Intern Med.* 2005;142:439-450. 2. Bissell DM et al. *N Engl J Med.* 2017;377:862-872. 3. Bissell DM, Wang B. *J Clin Transl Hepatol.* 2015;3:17-26. 4. Bylesjö I et al. *Scand J Clin Lab Invest.* 2009;69:612-618. 5. Ventura P et al. *Eur J Intern Med.* 2014;25:497-505. 6. Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet.* 2015;86:17.20.1-17.20.26.

Summary

Definition and classification of porphyria

- Porphyria is a group of 9 metabolic disorders caused by defects in enzymes involved in the heme biosynthesis pathway¹
- Categorized as AHP or photocutaneous porphyria based on clinical manifestations²
 - The signs and symptoms of AHP are believed to be due to increased levels of the neurotoxic intermediates ALA and PBG, which can lead to nervous system injury²
 - The signs and symptoms of photocutaneous porphyria are thought to be caused by increased levels of photosensitizing porphyrins²

AHP associated with debilitating and life-threatening signs and symptoms

- The cardinal presentation of AHP is severe, diffuse abdominal pain and other signs and symptoms (eg, nausea/vomiting, limb pain/weakness) that can progress to neurologic damage and even death³
- The term *acute* hepatic porphyria may not capture the frequent prolonged and chronic clinical features of this disease³

Is the prevalence of AHP higher than thought?

- The combined prevalence of AHP types has been estimated to be approximately 1 case/100,000³
- However, the prevalence of AHP may be higher than current estimates because these estimates are usually limited to those with symptomatic disease⁴
- AHP is also associated with potential misdiagnosis due to overlapping symptomology with more common conditions³
- Diagnosis of AHP can be delayed up to 15 years⁷

1. Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet*. 2015;86:17.20.1-17.20.26. 2. Bissell DM et al. *N Engl J Med*. 2017;377:862-872. 3. Anderson KE et al. *Ann Intern Med*. 2005;142:439-450. 4. Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26. 7. Bonkovsky HL, et al. *Am J Med*. 2014;127(12):1233-1241.