



MODULE 01

Classification of Porphyria

Porphyria—A Rare Disease of Clinical Consequence

- Porphyria is a group of at least 8 metabolic disorders^{1,2}
 - Each subtype of porphyria involves a genetic defect in a heme biosynthesis pathway enzyme^{1,2}
 - The subtypes of porphyria are associated with distinct signs and symptoms in patient populations that can differ by gender and age^{1,3}
- Prevalence of some subtypes of porphyria may be higher than generally assumed³

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

Subtype of Porphyria	Estimated Prevalence Based on European and US Data
Porphyria cutanea tarda (PCT)	1/10,000 (EU) ¹
Acute intermittent porphyria (AIP)	0.118-1/20,000 (EU) ^{1,4} 5/100,000 (US) ¹
Erythropoietic protoporphyria (EPP)	1/50,000-75,000 (EU) ¹

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.

Classification of Porphyria

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

1

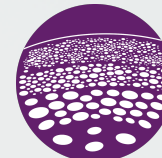
According to major physiological sites: liver or bone marrow^{1,2}



- 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 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 chronic³

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 8 Porphyrria Subtypes

Acute Hepatic Porphria: Cardinal Manifestation of Acute Neurovisceral Symptoms¹

The symptoms of AHP are 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 Porphria: Cardinal Manifestation of Skin Lesions¹

XLDPP

CEP

PCT

EPP

The symptoms of photocutaneous porphria are caused by increased concentrations of the photosensitizing porphyrins²

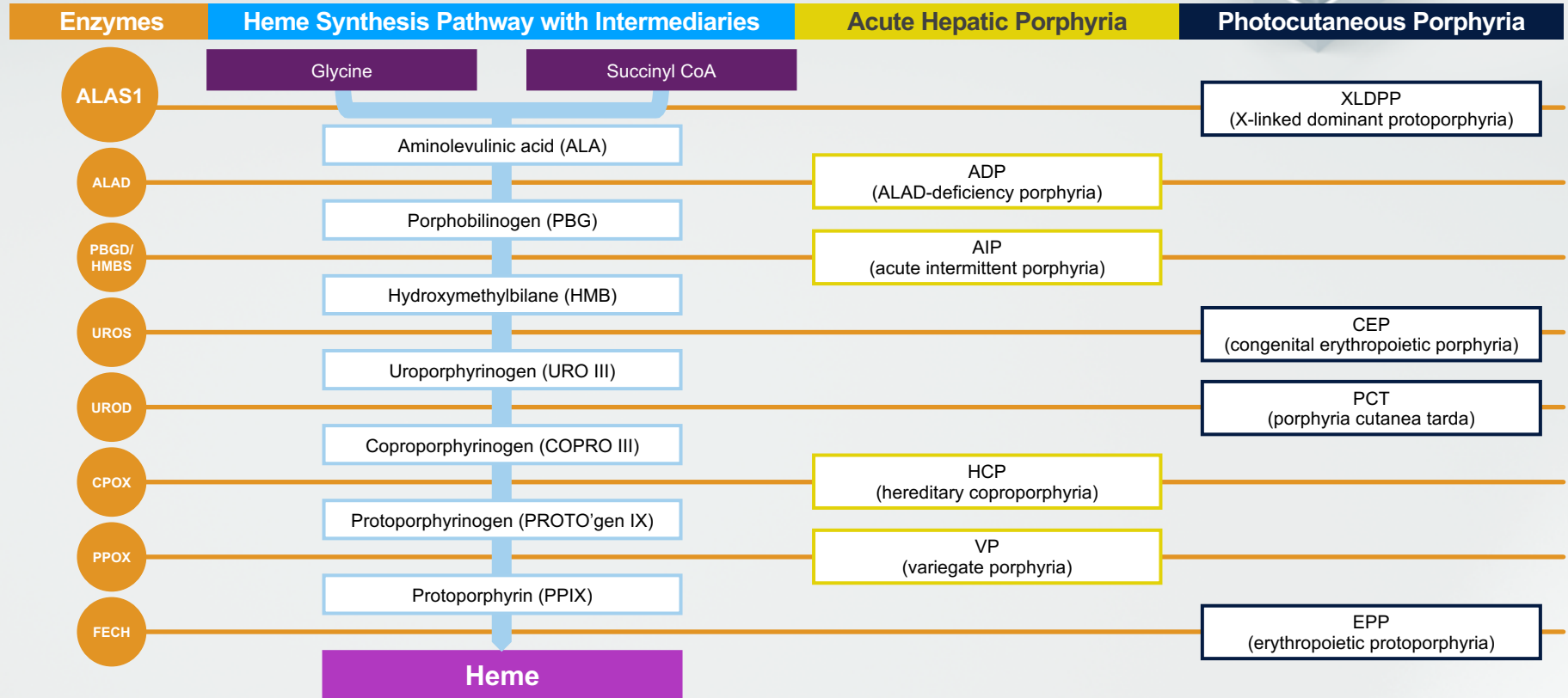
HCP and VP are associated with both acute neurovisceral symptoms and skin lesions¹

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

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.

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 Prevalence of the Four Different Subtypes of AHP

Subtype of AHP ¹	Prevalence
AIP (Acute Intermittent Porphyrism)	0.118-1/20,000 (EU*) ^{2,3} 5/100,000 (US*) ³
HCP (Hereditary Coproporphyrism)	2/1,000,000 (Denmark*) ³
VP (Variegate Porphyrism)	3.2/1,000,000 (EU*) ²
ADP (Aminolevulinic Acid Dehydratase-Deficiency Porphyrism)	6 cases of ADP reported worldwide at time of publication ³

- AIP accounts for about 80% of AHP cases⁴
- The prevalence of AIP may be underreported due to estimates based on patients with symptomatic disease only rather than an enzyme mutation⁵
 - There is even less information about the other subtypes of AHP

*Prevalence data from these particular countries were cited due to ongoing research and relatively high prevalence.

1. Anderson KE et al. *Ann Intern Med.* 2005;142:439-450. 2. Elder G et al. *J Inherit Metab Dis.* 2013;36:848-857. 3. Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet.* 2015;86:17.20.1-17.20.26. 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 Precipitating Factors

- Acute attacks in genetically predisposed patients are frequently preceded by environmental or hormonal precipitating factors¹⁻⁴
 - When manifested, the disease can be debilitating and even life threatening⁵
- Signs and symptoms are predominant in women 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
- There is higher prevalence in Caucasians, especially northern Europeans, but AHP can occur in all races and ethnic groups^{4,7}

- Hormonal and environmental precipitating factors of AHP attacks^{1,2,4}:
 - Woman's menstrual cycle
 - Many drugs metabolized by CYP450 enzymes (eg, barbiturates, synthetic progestins, sulfonamide antibiotics)
 - Crash dieting
 - Cigarette smoking
 - Excessive alcohol use
 - Infections and 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. 7. Besur S et al. *Metabolites.* 2014;4:977-1006.

Summary

Definition and classification of porphyria

- Porphyria is a group of at least 8 metabolic disorders caused by alterations 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 due to increased levels of the neurotoxic intermediates ALA and PBG, leading to nervous system injury²
 - The signs and symptoms of photocutaneous porphyria are 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 does 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 subtypes has been estimated to be approximately 5 cases/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 delayed diagnosis and misdiagnosis³

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.