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 assumed[3]

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]

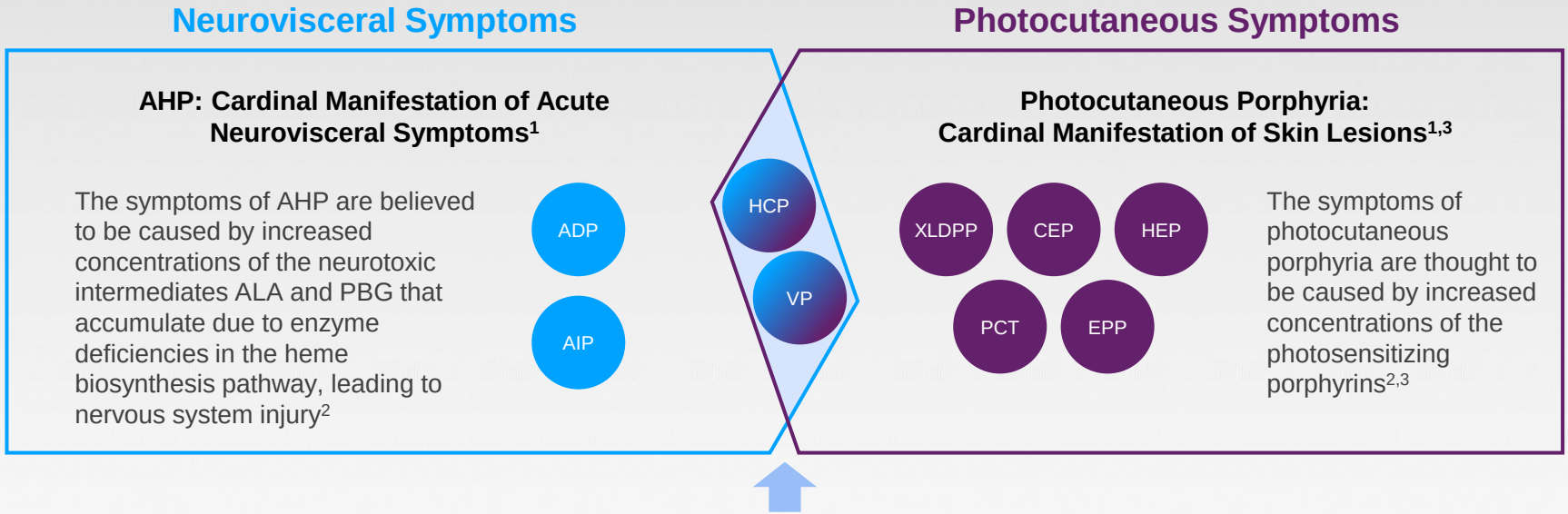
2 According to major clinical manifestations[1,2]

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 manifestations[3]

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 Porphyria



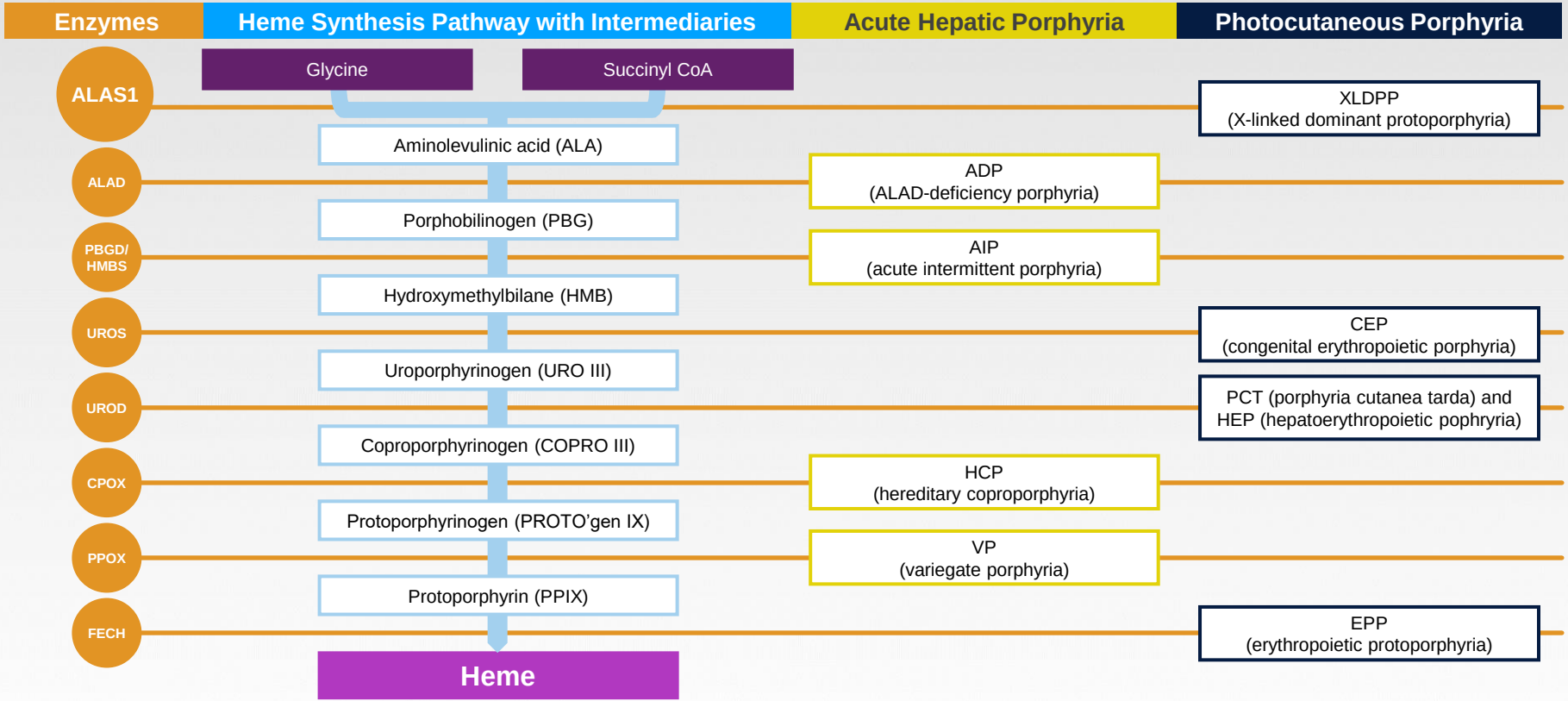
HCP and VP are associated with both acute neurovisceral symptoms and skin lesions[1]

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

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.

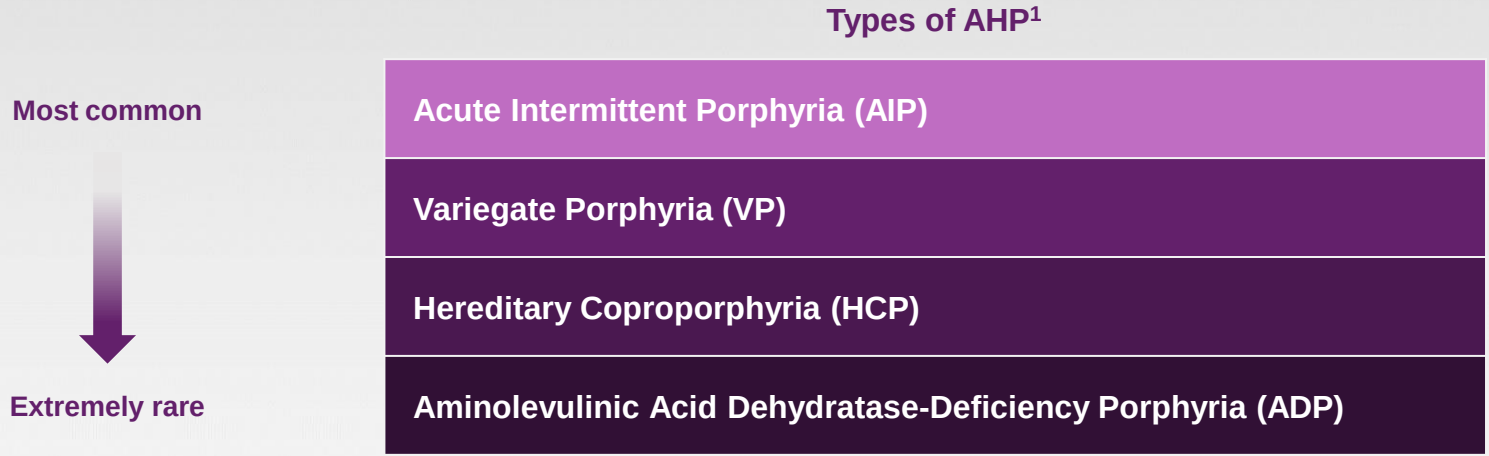
Heme Biosynthesis Pathway, Defective Enzymes, and Related Porphyria[1]

The Rate-Limiting Step for the Pathway is the Formation of ALA, Catalyzed by ALAS1[2]



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 Porphyria (AHP)



- AIP accounts for about 80% of AHP cases[4]
- 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 deficiency[5]
  - 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 triggers[1-4]
  - 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 disability[5]
- Signs and symptoms predominantly affect women with AHP of reproductive age but can occur in men as well[3]
  - It is rare to experience AHP symptoms before puberty[6]
  - Attacks are less likely after menopause[2]

- 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 pathway[1]
- Categorized as AHP or photocutaneous porphyria based on clinical manifestations[2]
  - 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 injury[2]
  - The signs and symptoms of photocutaneous porphyria are thought to be caused by increased levels of photosensitizing porphyrins[2]

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 death[3]
- The term *acute* hepatic porphyria may not capture the frequent prolonged and chronic clinical features of this disease[3]

Is the prevalence of AHP higher than thought?

- The combined prevalence of AHP types has been estimated to be approximately 1 case/100,000[3]
- However, the prevalence of AHP may be higher than current estimates because these estimates are usually limited to those with symptomatic disease[4]
- AHP is also associated with potential misdiagnosis due to overlapping symptomology with more common conditions[3]
- Diagnosis of AHP can be delayed up to 15 years[7]

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.