TABLE 430-2 HUMAN HEME BIOSYNTHETIC ENZYMES AND GENES

Enzyme	Gene Symbol	Chromosomal Location	cDNA (bp)	Gene		Protein (aa)	Subcellular Location	Known Mutations[b]	Three-Dimensional Structure[c]
				Size (kb)	Exons[a]				
ALA synthase									
Housekeeping	*ALAS1*	3p21.1	2199	17	11	640	M	—	
Erythroid-specific	*ALAS2*	Xp11.2	1937	22	11	587	M	>30	—
ALA dehydratase									
Housekeeping	*ALAD*	9q32	1149	15.9	12 (1A + 2 – 12)	330	C	12	Y
Erythroid-specific	*ALAD*	9q32	1154	15.9	12 (1B + 2 – 12)	330	C	—	
HMB synthase									
Housekeeping	*HMBS*	11q23.3	1086	11	15 (1 + 3 – 15)	361	C	>315	E
Erythroid-specific	*HMBS*	11q23.3	1035	11	15 (2 – 15)	344	C	10	
URO synthase									
Housekeeping	*UROS*	10q26.2	1296	34	10 (1 + 2B – 10)	265	C	39	H
Erythroid-specific	*UROS*	10q26.2	1216	34	10 (2A + 2B – 10)	265	C	4	
URO decarboxylase	*UROD*	1p34.1	1104	3	10	367	C	108	H
COPRO oxidase	*CPOX*	3q12.1	1062	14	7	354	M	51	H
PROTO oxidase	*PPOX*	1q23.3	1431	5.5	13	477	M	129	—
Ferrochelatase	*FECH*	18q21.31	1269	45	11	423	M	125	B

[a]Number of exons and those encoding separate housekeeping and erythroid-specific forms indicated in parentheses. [b]Number of known mutations from the Human Gene Mutation Database (*www.hgmd.org*). [c]Crystallized from human (H), murine (M), *Escherichia coli* (E), *Bacillus subtilis* (B), or yeast (Y) purified enzyme; references in Protein Data Bank (*www.rcsb.org*).

Abbreviations: C, cytoplasm; M, mitochondria.

Source: From KE Anderson et al: Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias, in *The Metabolic and Molecular Bases of Inherited Diseases*, CR Scriver et al (eds). New York, McGraw-Hill, 2001, pp 2991–3062.

TABLE 430-3 DIAGNOSIS OF ACUTE AND CUTANEOUS PORPHYRIAS

Symptoms	First-Line Test: Abnormality	Possible Porphyria	Second-Line Testing if First-Line Testing Is Positive: To include: urine (U), plasma (P), and fecal (F) porphyrins; for acute porphyrias, add red blood cell (RBC) HMB synthase; for blistering skin lesions, add P and RBC porphyrins	Confirmatory Test: Enzyme Assay and/or Mutation Analysis
Neurovisceral	**Spot U:** ↑↑ALA and normal PBG	ADP	**U porphyrins:** ↑↑, mostly COPRO III **P & F porphyrins:** normal or slightly ↑ **RBC HMB synthase:** normal	Rule out other causes of elevated ALA; ↓↓RBC ALA dehydratase activity (<10%); ALA dehydratase mutation analysis
	Spot U: ↑↑PBG	AIP	**U porphyrins:** ↑↑, mostly URO and COPRO **P & F porphyrins:** normal or slightly ↑ **RBC HMB synthase:** usually ↓	HMB synthase mutation analysis
	"	HCP	**U porphyrins:** ↑↑, mostly COPRO III **P porphyrins:** normal or slightly ↑(↑ if skin lesions present) **F porphyrins:** ↑↑, mostly COPRO III	Measure RBC HMB synthase: normal activity COPRO oxidase mutation analysis
	"	VP	**U porphyrins:** ↑↑, mostly COPRO III **P porphyrins:** ↑↑(characteristic fluorescence peak at neutral pH) **F porphyrins:** ↑↑, mostly COPRO and PROTOO	Measure RBC HMB synthase: normal activity PROTO oxidase mutation analysis
Blistering skin lesions	**P:** ↑ porphyrins	PCT and HEP	**U porphyrins:** ↑↑, mostly URO and heptacarboxylate porphyrin **P porphyrins:** ↑↑ **F porphyrins:** ↑↑, including increased isocoproporphyrin **RBC porphyrins:** ↑↑ zinc PROTO in HEP[a]	RBC URO decarboxylase activity: half-normal in familial PCT (~20% of all PCT cases); substantially deficient in HEP URO decarboxylase mutation analysis: mutation(s) present in familial PCT (heterozygous) and HEP (homozygous)
	"	HCP and VP	See HCP and VP above. Also, U ALA and PBG: may be ↑	
	"	CEP	**RBC and U porphyrins:** ↑↑, mostly URO I and COPRO I **F porphyrins:** ↑↑; mostly COPRO I	↓↓ RBC URO synthase activity (<15%) URO synthase mutation analysis
Nonblistering photosensitivity	**P:** porphyrins usually ↑	EPP	**RBC porphyrins:** ↓↓, mostly free PROTO **U porphyrins:** normal **F porphyrins:** normal or ↓, mostly PROTO	*FECH* mutation analysis
	P: porphyrins usually ↑	XLP	**RBC porphyrins:** ↑↑, approximately equal free and zinc PROTO **U porphyrins:** normal **F porphyrins:** normal or ↑, mostly PROTO	*ALAS2* mutation analysis

[a]Nonspecific increases in zinc protoporphyrins are common in other porphyrias.

Abbreviations: ADP, 5-ALA dehydratase-deficient porphyria; AIP, acute intermittent porphyria; ALA, 5-aminolevulinic acid; CEP, congenital erythropoietic porphyria; COPRO I, coproporphyrin I; COPRO III, coproporphyrin III; EPP, erythropoietic protoporphyria; F, fecal; HCP, hereditary coporphyria; HEP, ; ISOCOPRO, isocoproporphyrin; P, plasma; PBG, porphobilinogen; PCT, porphyria cutanea tarda; PROTO, protoporphyrin IX; RBC, erythrocytes; U, urine; URO I, uroporphyrin I; URO III, uroporphyrin III; VP, variegate porphyria; XLP, X-linked protoporphyria.

Source: Based on KE Anderson et al: Ann Intern Med 142:439, 2005.