Porphyria is the term used to describe a group of disorders which can manifest as either skin symptoms (photosensitivity; bullous eruptions, especially on the hands), or neurological symptoms (abdominal pain, neuropathies etc.). Each type of porphyria is due to a deficiency of one of the eight intracellular enzymes, each acting in turn, needed to synthesise haeme.

Porphyrias are usually classified as either acute or cutaneous. The acute porphyrias are associated with neurological symptoms; the cutaneous porphyrias affect the skin. Two porphyrias—hereditary coproporphyria (HCP) and variegate porphyria (PV)—can be associated with either or both acute and cutaneous symptoms, depending on light exposure. South Africans are more likely to complain of cutaneous symptoms, while Finns are more likely to present with neurological symptoms.

The table below lists the porphyrias and enzyme affected, in pathway order. For Australia, the porphyrias can be arranged from the most common, PCT (incidence about 1 in 20 000), to the less common, in this order: PCT > AIP > EPP > PV > HCP, with no recorded cases of HEP, CEP, and ALADP.

Note that XLD EP has been described only in the past few years (2008). It is due to a novel gain of function mutation in the erythroid-specific aminolevulinate synthase (ALAS2) enzyme. XLD EP has normal levels of ferrochelatase and can only be distinguished from EPP by genetic testing.

The varied signs and symptoms of the cutaneous porphyrias depend on the amount and type of intermediate/s produced. The number of carboxylic acid (–COOH) side chains determines the solubility of the porphyrins: Uroporphyrin has eight, coproporphyrin four and protoporphyrin two. Uroporphyrin is water soluble; protoporphyrin is insoluble in water and is excreted in the bile, not the urine, and readily associates with lipid.

### Classification of Porphyria

<table>
<thead>
<tr>
<th>Porphyria</th>
<th>Abbrev.</th>
<th>Enzyme Affected</th>
<th>Type</th>
</tr>
</thead>
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<tr>
<td>X-linked Dominant Erythropoietic Protoporphyria</td>
<td>XLD EP</td>
<td>Delta-aminolevulinic acid (AL) synthase 2</td>
<td>Cutaneous</td>
</tr>
<tr>
<td>ALA Dehydratase Porphyria</td>
<td>ALADP</td>
<td>ALA dehydratase</td>
<td>Acute</td>
</tr>
<tr>
<td>Acute Intermittent Porphyria</td>
<td>AIP</td>
<td>Porphobilinogen (PBG) deaminase</td>
<td>Acute</td>
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<td>Congenital Erythropoietic Porphyria</td>
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<td>Uroporphyrinogen III cosynthase</td>
<td>Cutaneous</td>
</tr>
<tr>
<td>Porphyria Cutanea Tarda</td>
<td>PCT</td>
<td>Uroporphyrinogen decarboxylase UROD (~50% deficiency)</td>
<td>Cutaneous</td>
</tr>
<tr>
<td>Hepatoerythropoietic Porphyria</td>
<td>HEP</td>
<td>Uroporphyrinogen decarboxylase UROD (~90% deficiency)</td>
<td>Cutaneous and Acute</td>
</tr>
<tr>
<td>Hereditary Coproporphyria</td>
<td>HCP</td>
<td>Coproporphyrinogen decarboxylase</td>
<td>Cutaneous and Acute</td>
</tr>
<tr>
<td>Variegate Porphyria</td>
<td>PV</td>
<td>Protoporphyrinogen decarboxylase</td>
<td>Cutaneous and Acute</td>
</tr>
<tr>
<td>Erythropoietic Protoporphyria</td>
<td>EPP</td>
<td>Ferrochelatase</td>
<td>Cutaneous</td>
</tr>
</tbody>
</table>

### Causes

Most porphyrias are inherited or familial disorders and run in families. Most require only one affected gene from one parent (dominant inheritance), while others, such as EPP, require one affected gene from both parents (recessive inheritance). The risk of an affected family member developing symptoms (porphyria), or passing it on to their children, will depend on the type of porphyria. However, even when the genetic defect/reduced enzyme activity is present, there is variable penetrance; other factors are required for symptoms to develop—until symptoms develop the porphyria is said to be latent.

Some triggering factors include:

- Drugs such as barbiturates, oral contraceptives and sedatives.
- Fad dieting and fasting associated with decreased carbohydrate intake
- Alcohol consumption
- Infections
- Excess body iron
- Ovulation
- Exposure to sunlight
- Stress—physical and emotional.

About 80% of the cases of PCT, the most common porphyria in Australia, can be classified as acquired (not genetic), in that the peripheral enzyme activity is normal, but there is a substance (porphomethene) that inhibits the activity of UROD in the liver to rate-limiting levels. Production of this inhibitor is dependent on the presence of excess hepatic iron and is likely due to dysregulation of hepcidin production.
Symptoms
Symptoms of cutaneous forms of porphyria include skin fragility, blisters (commonly on the back of the hands) and itching when the skin is exposed to sunlight. EPP is commonly diagnosed in childhood, but others are tardy in development and may not present until those affected are in their fourth or fifth decade. The symptoms vary widely between patients and are somewhat related to the amount and type of porphyrin or porphyrin precursor present.

Diagnosis
For patients with active disease, the biochemical examination of blood, urine and faeces is required for diagnosis—histopathological or clinical examinations are not definitive. If initial biochemical testing is positive, further more complex testing may be required to distinguish the pattern of porphyrin present. Once the diagnosis is confirmed biochemically and the porphyrin identified, genetic testing may be indicated to identify other family members at risk of developing porphyria. Direct testing of the enzyme affected in the haeme pathway is of limited use and is no longer offered by Australian laboratories.

For patients with latent disease, where there is a positive family history of porphyria, it is important to establish the type of porphyria and whether the index case was diagnosed clinically or biochemically. The preparation of a family tree is also useful for coordinating family studies. The acute porphyrias are unlikely to manifest before puberty; PCT will not manifest until the patient is iron overloaded.

Problems in investigation of porphyria
In pseudoporphryia, patients with no biochemical evidence of the disease present with skin symptoms that resemble, both clinically and histologically, those seen in porphyria. In many cases the cause will be drug-related—for example, nalidixic acid, frusemide, tetracycline, dapsone and others.

In some cases there may be increased porphyrin excretion without porphyrnia being seen. In hepatobiliary disease, renal disease and lead poisoning, increased amounts of coproporphyrin can be found in the urine. High meat content diets, or gastrointestinal bleeding, can produce increases in faecal porphyrins, while red cell porphyrins can be mildly to moderately raised in lead poisoning and iron deficiency anaemia.

Treatment of cutaneous porphyrias
It is important that the diagnosis is confirmed in the laboratory as each type of porphyria requires a different treatment. Avoidance of the trigger factors is the first step for the cutaneous porphyrias—sun avoidance; use of sun block (sun screen is insufficient); removal of excess body iron by bloodletting; and avoidance of alcohol and some drugs. Low-dose chloroquine may also be used to decrease the amount of porphyrins in the liver.

Patients with PV or HCP may require hospitalisation during an acute attack, where treatment focuses on putting the brakes on porphyrin precursor production—glucose and haematin decrease the activity of the housekeeping version of ALAS (ALAS1 but not ALAS2).

Some patients with excessive amounts of protoporphyrins (EPP) may also benefit from high doses of beta-carotene, an anti-oxidant that is thought to mop up the free radicals produced when these porphyrins are exposed to light on the skin.

The properties of porphyrins can be utilised for treatment
The basis of photodynamic treatment of neonatal hyperbilirubinaemia is the ability of the haeme breakdown product, bilirubin, to photosensitise the production of singlet oxygen, which then brings about its own destruction. Synthetic porphyrins are also the basis for photodynamic therapy of a number of tumours, for example, bladder and skin, where the porphyrins are preferentially absorbed by the tumour and activated by a red laser to cause destruction of the tumour.

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