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Molecular mechanisms of dominant expression in porphyria

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Summary: Partial deficiency of enzymes in the haem synthetic pathway gives rise to a group of seven inherited metabolic disorders, the porphyrias. Each deficiency is associated with a characteristic increase in haem precursors that correlates with the symptoms associated with individual porphyrias and allows accurate diagnosis. Two types of clinical presentation occur separately or in combination; acute life-threatening neurovisceral attacks and/or cutaneous symptoms. Five of the porphyrias are low-penetrance autosomal dominant conditions in which clinical expression results from additional factors that act by increasing demand for haem or by causing an additional decrease in enzyme activity or by a combination of these effects. These include both genetic and environmental factors. In familial porphyria cutanea tarda (PCTF), environmental factors that include alcohol, exogenous oestrogens and hepatotropic viruses result in inhibition of hepatic enzyme activity via a mechanism that involves excess iron accumulation. In erythropoietic protoporphyria (EPP), co-inheritance of a functional polymorphism *in trans* to a null ferrochelatase allele accounts for most clinically overt cases. In the autosomal dominant acute hepatic porphyrias (acute intermittent porphyria, variegate porphyria, hereditary coproporphyria), acute neurovisceral attacks occur in a minority of those who inherit one of these disorders. Although various exogenous (e.g. drugs, alcohol) and endogenous factors (e.g. hormones) have been identified as provoking acute attacks, these do not provide a full explanation for the low penetrance of these disorders. It seems probable that genetic background influences susceptibility to acute attacks, but the genes that are involved have not yet been identified.

The human porphyrias are metabolic disorders resulting from partial deficiency of the enzymes of the haem synthetic pathway (Figure 1). Haem is essential for life and, although it is synthesized in all nucleated cells, the majority is made in the liver and bone marrow. Of the eight enzymes in the pathway, a distinct porphyria has been ascribed

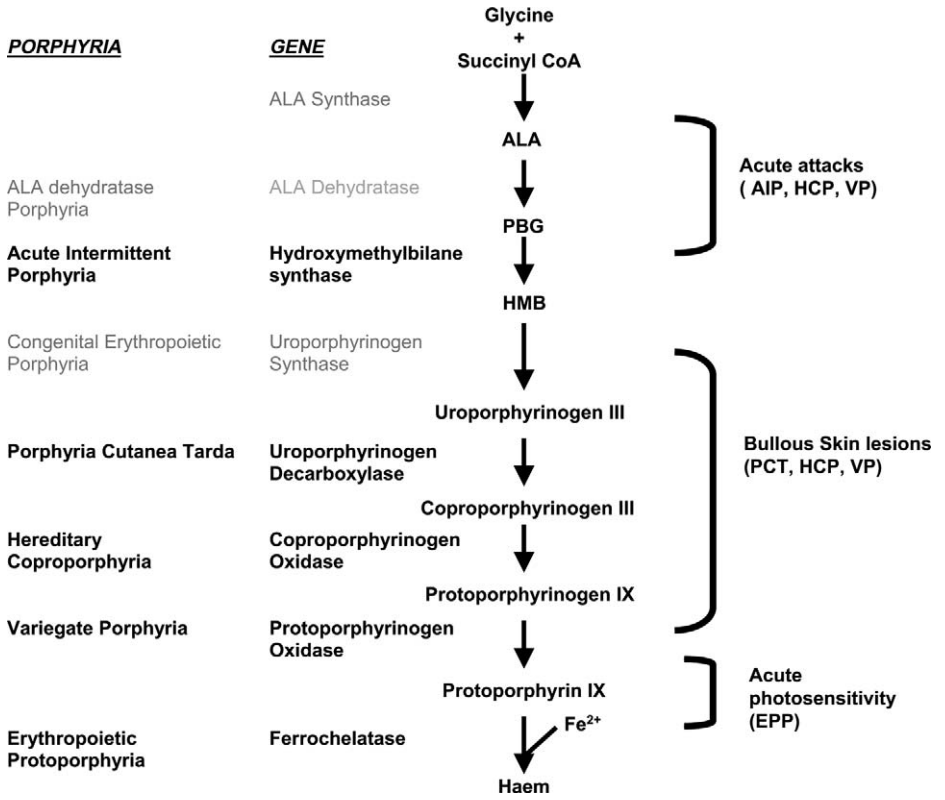

Figure 1 The haem biosynthetic pathway in humans consists of eight enzymes, of which the first and the last three are situated within the mitochondria. Increased 5-aminolevulinate (ALA) and porphobilinogen (PBG) is found in the autosomal dominant acute porphyrias as a consequence of primary (AIP) or secondary (VP, HCP) deficiency of PBG-deaminase (also known as hydroxymethylbilane (HMB) synthase). The porphyrinogens are rapidly oxidized to the porphyrin equivalent, which can be measured in urine, faeces or blood. PBG exceeds ALA excretion in AIP, HCP and VP, but not in ALA dehydratase deficiency porphyria, where PBG is normal or slightly increased. Bullous skin lesions are associated with increases in the water-soluble porphyrins (uroporphyrin and coproporphyrin), whereas acute photosensitivity occurs following accumulation of the more hydrophobic protoporphyrin. The autosomal dominant porphyrias appear in bold

to partial deficiency of seven enzymes (Table 1), the exception being the first enzyme in the pathway 5-aminolevulinic acid (ALA) synthase (ALAS). Mutations in the erythroid-specific *ALAS* gene (ALAS2) are associated with X-linked sideroblastic anaemia, whereas no metabolic disorder has been ascribed yet to deficiency of ALAS1 (Anderson et al 2001). In each disorder the deficiency gives rise to a characteristic increase in precursors that at least in part gives rise to the particular symptoms associated with individual porphyrias, and also allows accurate diagnosis following

Table 1 Molecular genetics of the porphyrias

Porphyria	*Enzyme*	*Gene*	*Chromosome*	*Inheritance*
ALA dehydratase deficiency porphyria (ADP)	ALA dehydratase	*ALAD*	9q34	AR
Acute intermittent porphyria (AIP)	Hydroxymethylbilane synthase	*HMBS*	11q24.1–24.2	AD
Congenital erythropoietic porphyria (CEP)	Uroporphyrinogen III synthase	*UROS*	10q25.2–26.3	AR
Porphyria cutanea tarda (PCT)	Uroporphyrinogen decarboxylase	*UROD*	1p34	Sporadic (80%) AD (20%)
Hereditary coproporphyria (HCP)	Coproporphyrinogen oxidase	*CPO*	3q12	AD
Variegate porphyria (VP)	Protoporphyrinogen oxidase	*PPOX*	1q21–23	AD
Erythropoietic protoporphyria (EPP)	Ferrochelatase	*FECH*	18q21.3	AD

AD, autosomal dominant; AR, autosomal recessive

haem precusor measurement in plasma, urine, faeces and erythrocytes (Table 2) (Deacon and Elder 2001). Two types of clinical presentation occur separately or in combination: acute neurovisceral attacks, which are associated with an increase in ALA and porphobilinogen; and cutaneous symptoms that result from photosensitization by porphyrins (Figure 1).

Five of the porphyrias are autosomal dominant (AD) disorders; the remaining two disorders, congenital erythropoietic porphyria (CEP) and ALA dehydratase deficiency porphyria (ADP), are very rare autosomal recessive conditions. Of the AD porphyrias, three are acute hepatic porphyrias that may present with acute attacks only (acute intermittent porphyria (AIP)) or acute attacks and/or bullous skin lesions (variegate porphyria (VP) and hereditary coproporphyria (HCP)). The other two AD porphyrias present with cutaneous symptoms only: familial (type 2) porphyria cutanea tarda (PCTF), which accounts for approximately 20% of PCT cases (Elder et al 1989); and erythropoietic protoporphyria (EPP). EPP characteristically presents during early childhood (Cox 2003) and PCT in children, though rare, is usually autosomal dominant in type. Other AD porphyrias are very rare in children; there are only a small number of reports of acute hepatic porphyria becoming clinically manifest before puberty (Anderson et al 2001).

Low clinical penetrance is an important feature of all the autosomal dominant porphyrias. The genes for each disorder are sufficiently common in the general population for rare homozygous, or compound heterozygous, variants of each type of AD porphyria to have been described. These variants usually present earlier in life, often during childhood, and may show a more severe clinical phenotype (Elder 1997), including additional clinical features such as chronic neurological disease and skeletal abnormalities that result from the substantially lower residual enzyme activity and possible effects on development of haem insufficiency and/or haem precursor toxicity (Elder 1997; Solis et al 2004).

Table 2 Clinical presentation and characteristic biochemical findings in samples taken when patient is symptomatic

Porphyria	*Clinical*	*Increased haem precursors*[b]
ADP	Acute	U: ALA RBC: Protoporphyrin (zinc)
AIP	Acute	U: *ALA*, *PBG* P: Peak at 615–620 nm
CEP	Cutaneous (bullous)	U: Uroporphyrin I, coproporphyrin I F: Coproporphyrin I RBC: Protoporphyrin (zinc and free), uroporphyrin I P: Peak at 615–620 nm
PCT	Cutaneous (bullous)	U: Uroporphyrin, 7-carboxyporphyrin F: Isocoproporphyrin, 7-carboxy- and 5-carboxyporphyrin, P: Peak at 615–620 nm
HCP	Acute ± cutaneous (bullous)	U: ALA PBG, coproporphyrin III F: *Coproporphyrin III (isomer III:I ratio > 1.4)* P: Peak at 615–620 nm
VP	Acute ± cutaneous (bullous)	U: PBG, ALA, coproporphyrin III F: *Protoporphyrin>coproporphyrin III* P: Peak at 624–627 nm
EPP	Cutaneous (acute photosensitivity)	U: Normal RBC: Protoporphyrin (free) P: Peak at 626–634 nm

[a] Haem precursors in italics are those that may also be found in presymptomatic or latent acute hepatic porphyria patients. Isocoproporphyrins are generated from the increased 5-carboxyl porphyrin through metabolism involving the gut microflora

[b] U, urine; F, faeces; RBC, erythrocyte; P, plasma; Peak, peak fluorescence emission; ALA, 5-aminolevulinic acid; PBG, porphobilinogen

A large number of disease-specific mutations have been identified in the genes that encode the enzymes that are deficient in the AD porphyrias (Krawczak and Cooper 1997; http://www.hgmd.org). Most are restricted to one or a few families, but a few have become widely distributed within discrete populations by founder effects, notably those causing VP in South Africa (Meissner et al 1996) and AIP in Sweden (Lee and Anvret 1991). Inheritance of one copy of these mutations decreases enzyme activity by about 50%; no mutation has yet been described in the AD porphyrias that decreases activity below this level by exerting a dominant-negative effect. Output from the haem synthetic pathway appears to be sufficient for normal cellular metabolism in individuals with 50% residual enzyme activity. Clinical presentation appears to require additional factors that affect the haem pathway by increasing demand for haem, by causing an additional decrease in enzyme activity, or by a combination of both these effects. The additional decrease in enzyme activity may result from direct inhibition of the cellular enzyme, which may be organ specific, or from a genetic factor that affects the efficiency of transcription and/or translation from the *trans* allele.

These effects may be influenced by genes at loci other than those directly involved in haem biosynthesis.

The following sections deal with the clinical presentations of AD porphyria, acute porphyrias, familial PCT and EPP, and our current understanding of factors that affect penetrance in this group of mostly adult-onset low-penetrance inherited metabolic disorders.

THE ACUTE PORPHYRIAS

Clinical presentation

Acute neurovisceral attacks, which are always associated with overproduction of the porphyrin precursors porphobilinogen (PBG) and ALA, occur in a minority of patients who inherit the gene defect for an autosomal dominant acute porphyria, and clinical features result from neuronal damage in the central, peripheral and autonomic nervous systems (Meyer et al 1998). Attacks are exceptionally rare before puberty, have a peak occurrence in the third decade and are also less likely to occur after the menopause (Elder at al 1997). Females are more likely to be affected than males. In virtually all cases the acute attack presents with severe pain, usually abdominal, and is associated with nausea, vomiting and constipation. Complications include convulsions, hypertension, tachycardia and progressive motor neuropathy that can mimic Guillain–Barré syndrome and require ventilatory support. Hyponatraemia is a common finding and may be partly responsible for the convulsions. Psychiatric manifestations may occur during the attack but invariably resolve when the patient is in remission and do not result in ongoing psychiatric illness (Millward et al 2001). Chronic complications include an increased risk of developing liver cancer (Andant et al 2000) and renal disease leading to hypertension and kidney failure (Andersson et al 2000a).

Management in the acute phase involves identifying and removing obvious precipitating factors, and symptomatic treatment with analgesics, antiemetics and anxiolytics. Intravenous fluid therapy is usually required, taking care to avoid worsening the profound hyponatraemia often associated with the acute attack. Specific therapy involves the administration of intravenous haem, which aims to inhibit hepatic ALAS1 and thereby suppress the production of precursors. A minority of patients, usually female, suffer repetitive acute attacks with serious, life-threatening consequences and require individualized treatment regimes such as suppression of ovulation (Anderson et al 1990), regular administration of haem (Elder and Hift 2001), or even liver transplantation (Soonawalla et al 2004).

Family screening and counselling are important aspects of management and aim to identify and inform patients with presymptomatic disease on how to limit the risk of acute attacks by simple lifestyle modifications such as avoiding alcohol and unsafe prescribed drugs (Badminton and Elder 2002; www.porphyria-europe.com). Identification of patients with presymptomatic or latent acute porphyria requires specialist laboratory expertise backed up by genetic analysis, particularly in children (de Rooij et al 2003).

Molecular genetics and pathogenesis

The measured enzyme activities are consistently half-normal in all patients who inherit one of the AD acute porphyrias, indicating the presence of a normal allele *trans* to the mutation that severely decreases or abolishes activity. Most individuals who inherit a mutation for an acute hepatic porphyria never have an acute attack. Penetrance in AIP appears to be higher within families, with estimates varying from about 10% to 50% (Anderson et al 2001; Andersson et al 2000a; Elder et al 1997; Schuurmans et al 2001), than is suggested by population studies (Nordmann et al 1997). In most European countries, acute attacks of porphyria occur in about 1–2 per 100 000 of the general population. If, within these families, only 10% of those who inherit AIP ever develop symptoms, the derived prevalence of individuals with AIP mutations is about 1 in 7 500 of the general population. However, studies of blood donors show a much higher prevalence of about 1 in 1500 (Nordmann et al 1997), suggesting that clinical penetrance is very low. As yet, there is little information on genetic or other factors that determine penetrance, although it has been suggested that some mutations may be associated with a higher penetrance than others (Andersson et al 2000a). Clinical presentation appears to be triggered by factors that increase hepatic haem synthesis either by direct induction, for example prescribed drugs or endocrine factors, particularly progesterone, or by increasing haem breakdown (e.g. fasting). It is also possible that some drugs or other factors may act by inhibiting PBG-deaminase directly. Environmental factors such as endocrine changes or contact with drugs, possibly in combination, contribute to the development of symptoms but are by no means the sole explanation. Even within families, tolerance to certain drugs may vary, indicating that the general genetic background is likely to play a major role (Kauppinen and Mustajoki 1992). What appears certain, however, is that genetic factors associated with the *trans* allele do not appear to have any significant impact on penetrance, at least in AIP and VP (Gouya et al 2004). However, although involvement of several other genetic loci has been proposed, to date there is no conclusive evidence about which factors may be influencing penetrance and causing the wide variability in clinical presentation.

PORPHYRIA CUTANEA TARDA: GENETIC AND NONGENETIC FACTORS

Clinical presentation

Porphyria cutanea tarda (PCT) is the commonest of the porphyrias and in the majority of patients is not associated with a molecular defect in the uroporphyrin decarboxylase (UROD) gene (Elder 2003). Clinical presentation is identical in familial and sporadic PCT, albeit at an earlier mean age in PCTF. The bullous skin lesions, which occur in sun-exposed areas, result from accumulation of the more water-soluble porphyrins and are common to several other porphyrias, including CEP, HCP and VP. Skin changes result from photoactivation of porphyrins with the production of reactive oxygen species that damage the cells of the dermis. This results in skin

fragility, spontaneously occurring blisters (bullae) that rupture resulting in scarring, milia, areas of over- or underpigmentation and hypertrichosis. The diagnosis is established on biochemical grounds and familial PCT may be distinguished from sporadic PCT by measuring erythrocyte UROD activity or by molecular analysis of the *UROD* gene (Christiansen et al 2000). Management involves avoidance of sunlight and withdrawal of precipitating agents as well as more specific treatment: either depletion of iron stores by venesection or low-dose oral chloroquine (Sarkany 2001). PCT patients have an increased risk of clinical relapse and hepatocellular carcinoma (Linet et al 1999), particularly those with long-standing untreated disease, and should be kept under surveillance (Sarkany 2001).

Molecular genetics and pathogenesis

Half-normal enzyme activity is also inherited in an autosomal dominant pattern in familial (type 2) PCT. However, in contrast to the autosomal dominant acute porphyrias, in which enzyme activities are the same whether or not symptoms are present, hepatic enzyme activities in familial PCT are decreased to below half-normal in individuals with symptoms (Moran et al 1998). The additional decrease in hepatic UROD activity results from reversible inactivation by an iron-dependent process that has yet to be fully elucidated but appears to be initiated by a number of possible associated conditions and risk factors. These include both environmental factors such as alcohol, hepatotropic viruses, iron intake and oral oestrogens, and genetic factors that may influence susceptibility to these causes (Elder 2003).

One of the strongest genetic associations described to date is with mutations in the haemochromatosis (*HFE*) gene. In PCT patients of northern European origin, 20–25% are homozygous for the C282Y *HFE* mutation (Bulaj et al 2000; Roberts et al 1997) and in familial PCT co-inheritance of *UROD* and *HFE* mutations results in earlier onset of symptoms (Brady et al 2000). However, as hepatic iron content is similar in PCT patients with and without *HFE* mutations (Tannapfel et al 2001), other factors relating to iron metabolism are clearly also involved. Other candidate predisposing genes include *ALAS1* and the cytochrome P450 (*CYP*) genes; experiments in mouse models of experimental uroporphyria are starting to elucidate additional susceptibility loci (Robinson et al 2002).

ERYTHROPOIETIC PROTOPORPHYRIA: GENETIC DEFECTS *IN TRANS*

The accumulation of free protoporphyrin in skin, a consequence of the deficiency of ferrochelatase activity (Figure 1), leads to a distinct clinical presentation that is characteristic of only one porphyria, EPP. Presentation is usually in early childhood and photosensitivity is lifelong (Todd 1994). Within minutes of exposure to sunlight, patients suffer burning, stinging pain with subsequent erythema and oedema in exposed areas of skin. The characteristic history should alert the clinician to this disorder, as there is usually very little to find on examination when the patient is seen by a clinician. Very occasionally there may be purpuric lesions following acute exposure. Long-term changes include skin thickening, especially over the knuckles, and small elliptical scars, particularly on the face. A minority of patients develop

liver dysfunction, of whom a small proportion go on to develop life-threatening liver failure (Meerman 2000). Diagnosis requires analysis of whole blood for erythrocyte protoporphyrin levels and the condition may be missed if inappropriate samples are analysed (i.e. urine and stool).

The mainstay of treatment involves measures to limit sunlight exposure, including specially formulated topical sunscreens, clothing and window filters. Narrowband UV therapy may also improve tolerance to sunlight and a proportion of patients respond to oral β-carotene therapy (Cox 2003). In patients with protoporphyric liver dysfunction, measures to reduce production and enhance excretion of protoporphyrin may slow or halt progression. However, where these measures fail, liver transplantation becomes the only life-saving option (Cox 2003).

Molecular genetics and pathogenesis

Recent evidence has shown that in most EPP families clinical expression requires inheritance of a low-expression allele, carried by approximately 10% of the population in France, *trans* to a severe mutation in the *FECH* gene (Gouya et al 2002); the frequency of the low-expression allele is similar in the United Kingdom (Whatley et al 2004). Gouya and colleagues 2002 have shown that the substitution of a T nucleotide for a C at position IVS3−48 modulates the use of an alternative intronic splice acceptor site generating an aberrant mRNA that is rapidly degraded by the nonsense-mediated mRNA decay mechanism. Together with a severe *FECH* mutation, which is inherited in an autosomal dominant pattern in EPP families, the low-expression allele decreases FECH activity to below about 35% of normal, the threshold at which sufficient protoporphyrin accumulates to produce photosensitivity. EPP might therefore be considered to be an autosomal recessive condition as the disease requires a genetic contribution from both alleles. However, in contrast to a classical recessive disorder, homozygosity for one of these alleles (IVS3−48C) does not cause disease, and it is perhaps more accurate to regard it as an autosomal dominant disorder in which penetrance is modulated by expression of wild-type FECH (Gouya et al 2002). A minority of patients with EPP have autosomal recessive disease with *FECH* mutations on both alleles. The clinical significance of this mode of inheritance has not been fully established, although it may increase the risk of severe liver disease as it has been suggested that this risk is inversely proportional to the level of residual enzyme activity (Chen et al 2002; Whatley et al 2004). Mutational analysis to determine the low-expression-allele status in the partner of an EPP patient facilitates preconception counselling by allowing calculation of the risk of having a child with overt disease.

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