Review Article

PORPHYRIA CUTANEA TARDA: BRIDGING CELLULAR MECHANISMS AND LABORATORY APPROACHES – A NARRATIVE REVIEW

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ABSTRACT

Porphyria cutanea tarda (PCT) is the most prevalent subtype of porphyria, a group of rare disorders caused by defects in the heme biosynthesis pathway. This narrative review highlights the current insights into the cellular and molecular mechanisms underlying PCT, linking genetic predispositions, environmental triggers, and diagnostic challenges. The pathogenesis of PCT primarily involves the deficient activity of uroporphyrinogen decarboxylase (UROD) enzyme, leading to porphyrin accumulation and subsequent oxidative stress, particularly within hepatic and mitochondrial systems. Key contributing factors include iron overload, excessive alcohol consumption, chronic viral infections (e.g., hepatitis C virus and human immunodeficiency virus), oestrogen exposure, and genetic susceptibility, in the presence of a pathogenic variant of the *UROD* gene. Clinically, PCT is presented with photosensitive cutaneous manifestations and may be associated with underlying liver involvement, necessitating a comprehensive diagnostic evaluation. The review further outlines the critical role of laboratory diagnostics, including porphyrin profiling, and genetic testing, and emphasises the importance of multidisciplinary approaches for accurate diagnosis and management. The proposed future research direction shall focus on novel diagnostic techniques, molecular therapies, and the standardisation of clinical protocols to improve patient outcomes. This review aims to bridge the gap between cellular pathophysiology and laboratory practices, offering a comprehensive perspective for clinicians and laboratory specialists managing these rare but significant disorders.

KEYWORDS: porphyria cutanea tarda (PCT), uroporphobilinogen decarboxylase (UROD), uroporphyrin, photosensitivity, heme biosynthesis

INTRODUCTION

Porphyria represents a group of rare metabolic disorders resulting from defects in heme biosynthesis, leading to the accumulation of porphyrins and their precursors. Among the nine identified types, porphyria cutanea tarda (PCT) stands as the most common variant, first described by Waldenström in 1937 (1). PCT is characterised by skin lesions that are light-sensitive due to the buildup of porphyrins in the skin. The prevalence of PCT varies geographically, with estimates ranging from approximately 1 in 5,000 to 1 in 25,000 individuals, although robust epidemiological data remain scarce in many regions (1–5). In Malaysia, the establishment of specialised laboratory services has improved access to porphyria testing and facilitated case identification; however, published epidemiological data on PCT remain limited.

Despite the clinical recognition of PCT, the precise cellular mechanisms underlying its pathogenesis remain incompletely understood. It is established that PCT arises from diminished activity of the enzyme uroporphyrinogen decarboxylase (UROD), leading to the accumulation of porphyrins. However, the intricate relationship between genetic predisposition and environmental factors, including alcohol use, hepatitis C virus (HCV), and hormonal influences, continues to be explored (6). Laboratory diagnostics are crucial for confirming the diagnoses and monitoring diseases, although challenges regarding specificity and accessibility persist. This narrative review aims to assess the current understanding of PCT's cellular mechanisms and its laboratory diagnostic approaches.

Heme biosynthesis and disruption mechanism in PCT

Heme biosynthesis involves eight enzymatic steps that occur in both the mitochondria and the cytosol. Any disruptions within these stages can result in the accumulation of intermediate metabolites distinctive of various porphyrias. The initial and final two steps of heme production are mitochondrial, while the intermediate reaction occurs in the cytoplasm, as illustrated in Figure 1 (1).

The process begins with the enzyme aminolaevulinic acid synthase (ALAS) catalysing the formation of delta-aminolaevulinic acid (δ-ALA) and concludes with ferrochelatase incorporating iron into protoporphyrin IX. The condensation of glycine and succinyl-CoA to produce aminolaevulinic acid (ALA) marks the first committed step in heme biosynthesis. Subsequent enzymatic reactions convert δ-ALA into porphobilinogen (PBG), uroporphyrinogen III (uro'gen III), and coproporphyrinogen III (copro'gen III), ultimately generating heme through various enzymes. Heme is essential as a component of several molecules, such as, haemoglobin, myoglobin, cytochrome P450 enzymes, and other enzymes (3). Its synthesis predominantly occurs in the bone marrow (80%), and liver (15%), with additional production in other organs (1,2).

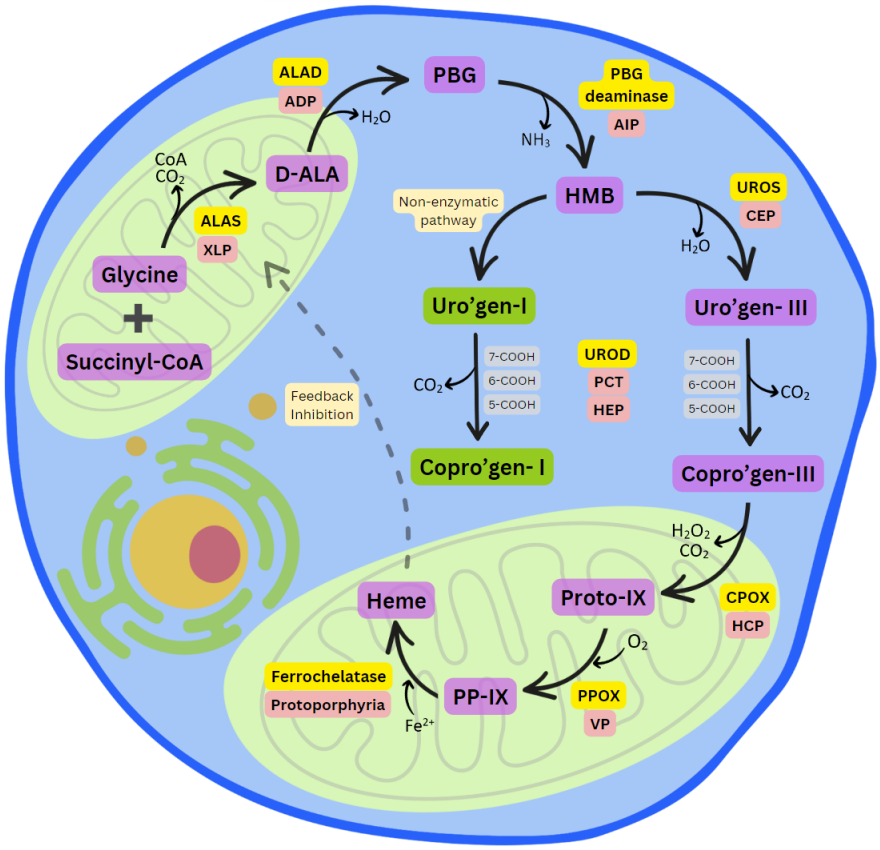


Figure 1. **Physiological Heme Biosynthesis Pathway**. The eight enzymatic steps in heme biosynthesis are highlighted in yellow; **ALAS**, aminolevulinic acid synthase; **ALAD**, aminolevulinic acid dehydratase; **PBG Deaminase**, porphobilinogen deaminase; **UROS**, uroporphyrinogen III synthase; **UROD**, uroporphyrinogen decarboxylase; **CPOX**, coproporphyrinogen oxidase; **PPOX**, protoporphyrinogen oxidase; and **Ferrochelatase**. The different porphyrias exhibited by the respective enzymatic steps highlighted in red; **XLP**, X-linked porphyria; **ADP**, aminolevulinic acid dehydratase porphyria; **AIP**, acute intermittent porphyria; **CEP**, congenital erythropoietic porphyria; **PCT**, porphyria cutanea tarda; **HEP**, hepatoerythropoietic porphyria; **HCP**, hereditary coproporphyria; **VP**, variegate porphyria; and **protoporphyria**. Substrates and enzymes within the green organelle with a double-layer membrane are located within the mitochondria. The remaining steps occur in the cytosol. Abbreviations: **D-ALA**, delta aminolevulinic acid; **PBG**, porphobilinogen; **HMB**, hydroxymethylbilane; **Uro'gen**, uroporphyrinogen; **copro'gen**, coproporphyrinogen; I or III, isomer I or isomer III; **proto-IX**, protoporphyrinogen IX; **PP-IX**, protoporphyrin IX; **7-COOH**, heptacarboxyl porphyrinogen; **6-COOH**, hexacarboxyl porphyrinogen; **5-COOH**, pentacarboxyl porphyrinogen.

In PCT, the enzymatic activity of uroporphyrinogen decarboxylase (UROD) is disrupted during the fifth step. Under normal circumstances, UROD catalyses the conversion of both isomer I and isomer III of uro'gen into their corresponding copro'gen isomers by removing four carboxylic groups from the carboxymethyl side chains of uroporphyrinogen. This enzymatic function leads to the formation of hepatcarboxyl (hepta-, or 7-COOH), hexacarboxyl (hexa-, or 6-COOH), pentacarboxylporphyrinogens (penta-, or 5-COOH), which ultimately yield copro'gen, a vital precursor in heme production (7) (see Figure 2).

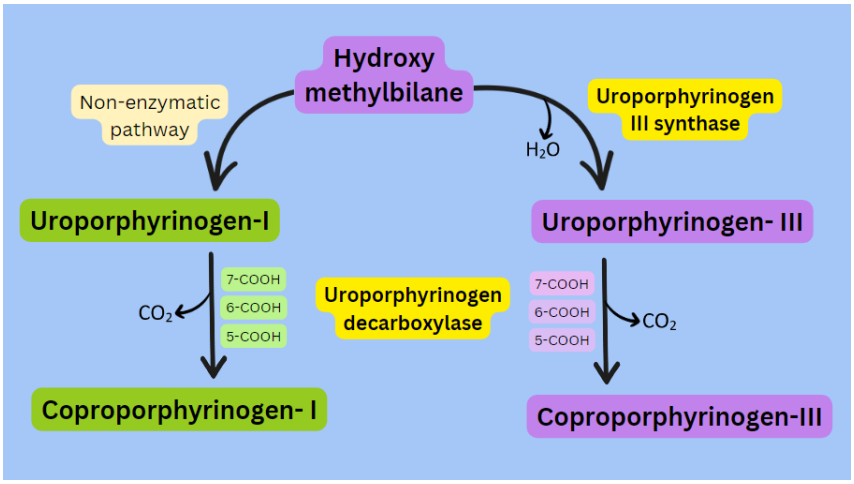


Figure 2. Uroporphyrinogen decarboxylase (UROD) catalyses multiple decarboxylation reactions, removing carboxyl groups from the substrate. This process yields intermediates including heptacarboxylporphyrinogen (7-COOH), hexacarboxylporphyrinogen (6-COOH), and pentacarboxylporphyrinogen (5-COOH). Ultimately, these reactions lead to the production of coproporphyrinogen from both isomer I and III substrates.

Disruption of this physiological mechanism impedes the conversion of uro'gen into copro'gen. Whether originating from isomer I or III, any interference in the decarboxylation process mediated by UROD causes the accumulation of uro'gen I or III along with its decarboxylate intermediates (hepta-, hexa-, and pentacarboxylporphyrinogen), which are then oxidised to uroporphyrin (and its intermediates: hepta-, hexa-, and pentacarboxylporphyrin) via CYP1A2 enzymes (5,8). In certain instances, uro'gen may undergo partial oxidation due to halogenated polycyclic aromatic hydrocarbon compounds, such as hexachlorobenzene, dioxin, and polychlorinated biphenyls, resulting in uroporphomethene formation (9,10). Although this compound can bind to UROD, it does not act as a substrate for metabolism (1). Thus, UROD inhibition may stem from intermediates produced during the partial oxidation of uro'gen III to uroporphomethene (8). The accumulation of these compounds primarily occurs in the liver and cannot be further metabolised; instead, they are released into the circulation and excreted via plasma, urine, and faeces (11).

At the cellular level, the disruption of heme biosynthesis in PCT impacts mitochondrial function. While mitochondria are essential for heme biosynthesis, the accumulation of uroporphyrin metabolites without further conversion into heme precursors leads to mitochondrial dysfunction, which affects heme production (10). Research by Yien and Perfetto in 2022, indicated that dysfunctional mitochondria produce excessive reactive oxygen species (ROS), exacerbating oxidative stress and cellular damage. Moreover, mitochondrial dysfunction compromises cellular energy metabolism, leading to ATP depletion and cellular impairment (7). Maitra et al. (2019) also observed that porphyrin-induced oxidative stress can provoke inflammatory responses in the skin and other affected tissues (12). The activation of inflammatory pathways, including the release of pro-inflammatory cytokines, such as interleukin (IL)-1 and IL-6, encourages immune cell infiltration and tissue damage (13). Chronic inflammation and tissue injury contribute to the development of cutaneous lesions, including bullae, erosions, and scarring, which are characteristic of PCT. Furthermore, genetic variants in heme biosynthetic enzymes or regulatory proteins can predispose individuals to PCT, while environmental factors may trigger its manifestation.

Molecular basis of PCT

The pathogenesis of PCT is characterised by genetic susceptibility alongside dysregulation of enzymes involved in the heme biosynthesis. Among the various types of porphyria, PCT is the least linked to genetic pathologies (14). In familial cases, a heterozygous UROD pathogenic variants (15), situated on chromosome 1p34 (9), have been identified, resulting in reduced enzyme activity and consequent accumulation of uroporphyrinogen in the hepatocytes (16). At a molecular level, the buildup of uroporphyrinogen and its subsequent oxidation to uroporphyrin leads to increased ROS production within hepatocytes, causing oxidative damage to cellular components, including lipids, proteins, and DNA (17).

Moreover, the dysregulation of enzymes involved in heme biosynthesis can disturb cellular iron homeostasis, resulting in iron overload in the liver, which contributes to oxidative stress and liver injury (7). The resulting mitochondrial oxidative stress, DNA damage, and hepatocyte dysfunction collectively illustrate the pathophysiology of PCT. Recent advancements in molecular biology techniques have shed light on the complex interactions between genetic susceptibility and environmental triggers in the development of PCT.

Contributing factors

PCT is a multifaceted disorder influenced by an array of genetic and environmental factors, with varing impacts on individuals. The primary influences on UROD function are largely associated with conditions leading to liver damage, as listed in Table 1. These damages include iron overload conditions, often linked to pathogenic variants in the *HFE* gene, excess alcohol consumption, tobacco use, oestrogen exposure, and chronic viral infections such as hepatitis C and human immunodeficiency virus (HIV) (8,9,14,18–21). Collectively, these factors trigger oxidative stress in the liver, resulting in the oxidation of uroporphyrinogen to porphyrin, which are not substrates for UROD (11).

Table 1. Factors influencing UROD function associated with conditions precipitating liver damage and their frequency.

	Alcohol	**Oestrogen**	**HCV infection**	**HIV infection**	***HFE* gene variants**	**Other factors**
Cabezas (N = 87) *(*19)	67.8%	21.8%	43.7%	12.6%	40.2%	Family history 19.5%
Singal (N = 189) (20)	76%	11%	27%	4%	33%	Smoking 61%
Jalil (N = 143) (21)	87.7%	65.9%	68.8%	12.6%	51%	Smoking 80.9%

Abbreviation: HCV, hepatitis C virus; HIV, human immunodeficiency virus

a) Iron and Haemochromatosis (*HFE*) gene variants

Iron overload is a critical factor in PCT, is often associated with haemochromatosis, where iron accumulation can reach up to 90% in affected individuals (8). Pathogenic variants in the *HFE* gene, particularly the C282Y and H63D variants, is prevalent among PCT patients and vary geographically (9). Iron contributes to UROD inhibition by generating peroxides and free radicals, which hinder heme biosynthesis and modify hepatic hepcidin production, resulting in hepatic siderosis (9,22). Furthermore, iron presence can prompt cytochrome P450 (CYP450) enzymes to convert uroporphyrinogen into uroporphomethene (9,23). Studies indicate that imbalances in iron regulation create an oxidative environment in hepatocytes, producing UROD inhibitors such as uroporphomethene, which can induce uroporphyria in animal models, and PCT in humans (15, 24, 25). Although liver siderosis is crucial in PCT, iron alone cannot instigate excessive uroporphyrin production without additional predisposing factors, emphasising the complex nature of PCT pathogenesis (26).

b) Alcohol consumption and tobacco smoke

Excessive alcohol intake and smoking are significant risk factors in PCT, affecting up to 90% of patients (8). Ethanol and its metabolites inhibit UROD enzymes, increasing oxidative stress in hepatocytes and fostering the accumulation of porphyrin intermediates (27). Similarly, cigarette smoke activates hepatic cytochromes, particularly CYP1A2, leading to UROD inhibition and heightened oxidative stress, exacerbating PCT symptoms (8).

c) Oestrogen therapy

The administration of oestrogen, whether through oral contraceptives, hormone replacement therapy, or gender-affirming hormone therapy, is associated with PCT (18). An increase in oestrogen levels stimulates hepatic ALAS enzyme, which can induce oxidative stress in hepatocytes, and disrupt heme biosynthesis (9,18,28). Research has established a correlation between oestrogen therapy and increased incidence of PCT, highlighting its relevance in the disorder's pathogenesis (29,30).

d) Viral Infections (Hepatitis C and Human Immunodeficiency Virus)

Chronic viral infections, particularly hepatitis C (HCV) and HIV, have a significant association with PCT, affecting up to 80% of patients (8). HCV-induced dysregulation of iron, coupled with oxidative stress, contributes to UROD inhibition and hepatic siderosis, promoting PCT (18). Likewise, HIV alters steroid metabolism and heme biosynthesis, potentially triggering PCT (31,32).

e) Comorbidities and Drugs

Various medical conditions, including diabetes mellitus, chronic kidney disease, lupus erythematosus, and disorders affecting the liver or haematological systems, may predispose individuals to PCT (8, 18, 20). Additionally, exposure to certain chemicals or medications, such as hexachlorobenzene and olmesartan, can provoke PCT. In patients with renal failure, PCT symptoms may worsen due to inadequate porphyrin excretion and the accumulation of uremic toxins, underscoring the need for tailored management strategies (2, 9, 33). Further investigation into the molecular mechanisms driving PCT susceptibility and progression is necessary to enhance disease management and preventive measures.

Clinical presentation of PCT

PCT typically presents with distinct signs and symptoms related to cutaneous effects and photosensitivity reactions. Dermatologists frequently encounter patients suffering from PCT due to its characteristic skin lesions, which can lead to feelings of inferiority and decreased self-esteem. Individuals with PCT often avoid sunlight, adversely affecting their quality of life. The condition primarily involves sun-exposed areas, particularly the back of the hands and face. Patients commonly report fragile skin that is susceptible to blistering, peeling, and crust formation following minor trauma or sun exposure. Photosensitivity reactions may encompass erythema, vesicles, erosion, and bullae formation, often accompanied by itching and burning sensations. Over time, scarring can develop, resulting in hyperpigmentation or hypopigmentation of the skin. Some patients may also experience increased hair growth and the formation of milia in affected areas.

Moreover, scars can lead to contractures resembling those seen in scleroderma, giving rise to the term "pseudoscleroderma" (19). Although rare, scleroderma-like changes have been documented, including typical sclerodactyly (1). Chronic thickening of the skin with sclerodermatous-like features and small whitish papules (milia) may develop due to repeated trauma and prolonged sun exposure (9).PCT typically manifests in middle-aged adults, with equal prevalence among both genders (19). Liver abnormalities, such as hepatic siderosis, steatosis, portal triaditis, and periportal fibrosis may arise, increasing the risk of cirrhosis or hepatocellular carcinoma, particularly in cases of recurrent illness or concurrent conditions like hepatitis C infection (6).

Classification of PCT

PCT is classified into three categories based on genetic status or family history (5), as summarised in Table 2.

- **Type I**, known as sporadic PCT, occurs in the absence of identifiable pathogenic variants in the UROD gene and is influenced by multiple contributing factors, resulting in hepatic UROD activity reduced to 50% normal level in hepatocytes.
- **Type II**, familial PCT (F-PCT), involves an inherited heterozygous pathogenic variant in the UROD gene and accounts for approximately 20% of cases.
- **Type III,** familial non-UROD variant PCT, a rare form, exhibits reduced hepatic UROD activity without identifiable UROD gene variants but shows familial clustering.

Each type displays unique characteristics and contributing factors, reflecting the intricate nature of PCT pathogenesis. Diagnosing PCT can be challenging due to its heterogeneous clinical presentation and overlap with other dermatological conditions, necessitating a comprehensive evaluation. This involves obtaining a detailed medical history, including family history and exposure factors, as well as conducting laboratory tests, such as urine, plasma, and faecal porphyrin analyses. Genetic testing to identify pathogenicity variants in the UROD gene and histopathological examination of skin lesions may further support the diagnosis. Collaboration between multidisciplinary specialists is essential for timely diagnosis and effective management of this complex disorder.

Table 2. Classification of PCT

PCT Type	Type I	Type II	Type III
Pattern	Sporadic or acquired	Familial or hereditary	Familial clustering
Prevalence	2/3 cases (~80%)	1/3 cases (~20%)	Very rare
UROD enzyme affected the cell	< 20% normal activity of hepatic UROD enzyme	< 20% normal activity of hepatic UROD enzyme and 50% normal activity of UROD enzyme in extrahepatic tissues	< 20% normal activity of hepatic UROD enzyme, with totally normal UROD enzyme activity in extrahepatic tissues
UROD gene variant status	Absent	Present	Absent
Family history	Absent	Present	Present
Contribution factors	Present	Present	Present

Abbreviations: UROD, uroporphobilinogen decarboxylase

Laboratory diagnostic

Laboratory diagnostics are critical in the diagnosis and management of PCT, providing essential insights into the underlying pathophysiology and guiding treatment decisions. In most clinical contexts, ruling out PCT typically constitutes the final consideration in the differential diagnosis, as diagnostic tests for PCT are often lacking in the standard hospital settings and are limited to specialised referral laboratories due to the complexity and cost associated with sample handling and analysis. Biochemical testing usually entails a comprehensive evaluation of urine, plasma, and faeces samples, along with genetic testing and histopathological examination of skin lesions (34).

a) Screening tests for PCT

Screening tests are vital for identifying individuals suspected of having PCT. Detection of suspected PCT involves fluorometric emission to identify elevated levels of total porphyrin, specifically uroporphyrin, coproporphyrin, and protoporphyrin in plasma (35).

b) Quantitative Measurement of Porphyrin Isomers

Urine and plasma porphyrin analyses are essential for diagnosing PCT, facilitating the identification of elevated porphyrin levels, particularly uroporphyrin (uro-) and heptacarboxylporphyrin (hepta-). High concentrations of these porphyrins, especially when associated with an increased urinary porphyrin to creatinine ratio, suggest a likelihood of PCT. Fractionation of porphyrins using high-pressure liquid chromatography (HPLC) is vital for diagnosing porphyria. Reverse-phase HPLC with fluorescence detection is considered the gold standard for porphyrin identification, enabling precise differentiation of isomers for accurate diagnosis (34). Secondary test using faecal samples can further corroborate a PCT diagnosis by identifying isocoproporphyrin (isocopro-), which is not detectable in urine or plasma (3,19). However, this test can be technically challenging and may not be necessary in all instances (23). Other secondary tests, such as assessing UROD activity and conducting DNA analyses, are valuable for distinguishing between sporadic and familial PCT cases (34).

c) UROD enzyme activity testing

The assessment of UROD enzyme activity provides a valuable support in the diagnostic evaluation and subclassification of PCT (36). Measurement is typically performed on erythrocytes and serves as a useful tool for distinguishing between sporadic and familial forms of the disease (37). Importantly, the differentiation between hepatic and erythrocyte UROD activity is essential for accurate classification. While hepatic UROD activity is reduced in all subtypes of PCT, reflecting the liver-specific nature of the metabolic defect, erythrocyte UROD activity remains within the normal range in sporadic (Type I) PCT but is reduced to approximately 50% of normal in familial (Type II) PCT due to heterozygous pathogenic or likely pathogenic variants in the UROD gene (36,38). This distinction provides a practical biochemical basis for subtype differentiation and helps guide the need for subsequent genetic testing. Despite its diagnostic value, UROD enzyme activity testing is not widely available and is generally limited to specialised laboratories due to technical complexity and stringent sample handling requirements. Consequently, it is most appropriately used as a complementary investigation alongside porphyrin profiling and clinical assessment, rather than as a primary diagnostic test.

d) Genetic testing for predisposing pathogenic variants

Genetic testing plays a crucial role in identifying predisposing genetic variants associated with familial forms of PCT, particularly the heterozygous pathogenic variant in the *UROD* gene (34). The condition follows an autosomal dominant inheritance pattern with reduced penetrance, indicating that not all individuals carrying the variant will develop clinical disease (4). Importantly, the presence of a pathogenic UROD variant alone is often insufficient for disease manifestation, and additional environmental or metabolic factors, such as iron overload, excess alcohol use, or chronic viral infections, are typically required to precipitate phenotypic expression (15,16,39). Genetic testing may therefore be considered in patients with early-onset disease, positive family history, and reduced erythrocyte UROD activity. Detection of these variants supports the diagnosis of familial PCT and provides important information for genetic counselling of affected individuals and their families. Although considered the gold standard for confirming genetic susceptibility, DNA analysis may be limited by cost and accessibility.

e) Histopathological examination of skin lesions

Histopathological examination of skin lesions is usually performed to exclude the diagnosis of PCT, and differentiate it from other skin conditions. Skin biopsy may reveal characteristic findings, such as subepidermal bullae, dermal fibrosis, and perivascular inflammation, supporting the clinical suspicion of PCT (9). However, it is not a mandatory step for diagnosing PCT, as characteristic elevated porphyrin levels are the primary diagnostic criteria (5).

f) Baseline investigations

Baseline tests, including liver function tests, iron studies, and serological testing for hepatitis and HIV, are essential for identifying factors contributing to PCT (19,40). Additionally, monitoring for complications such as hepatocellular carcinoma through ultrasound imaging is recommended (8,41). Given the integral role of laboratory diagnostics in accurately diagnosing and managing PCT, encompassing screening tests, porphyrin isomer analyses, genetic testing for predisposing variants, and histopathological examination of skin lesions, a multidisciplinary approach involving dermatologists, hepatologists, and clinical laboratory specialists is vital for optimal patient care and treatment decisions.

To enhance clinical applicability, a practical diagnostic algorithm is proposed that integrates biochemical testing, erythrocyte UROD activity assessment, and genetic consideration to distinguish between Type I, II and, III PCTs (Figure 3).

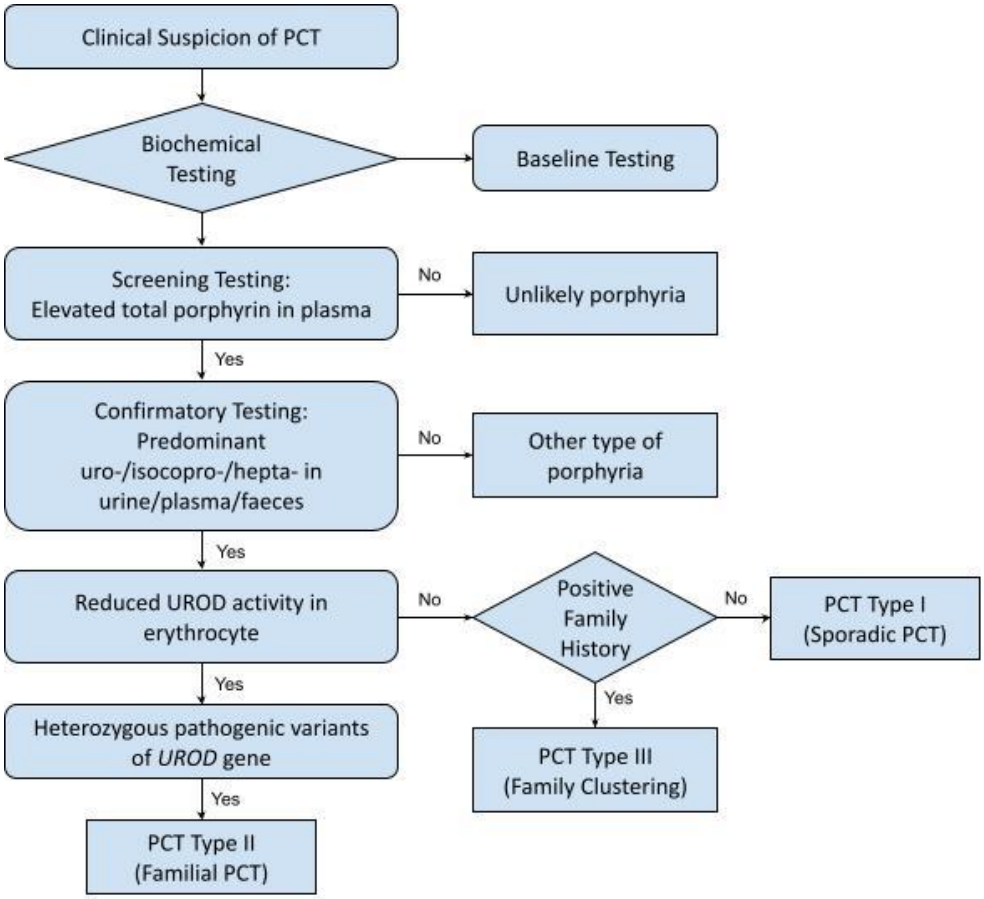


Figure 3. Proposed diagnostic algorithm for Porphyra Cutanea Tarda (PCT). The algorithm outlines a structural approach beginning with clinical suspicion, followed by biochemical confirmation through urine and plasma porphyrin analysis, baseline investigations including iron studies and viral screening, and subtype differentiation based on erythrocyte UROD activity with consideration of genetic factors where appropriate. Abbreviations: uro-, uroporphyrin; isocopro-, isocoproporphyrin; hepta-, heptacaboxylporphyrin; UROD, uroporphyrinogen decarboxylase.

Future perspectives and research directions

Recent advancements in laboratory techniques offer promising avenues for enhancing the diagnosis and management of PCT. Innovative methods for analysing porphyrin levels in urine and plasma, such as liquid chromatography-mass spectrometry (LC-MS), have demonstrated superior sensitivity and specificity compared to traditional methods (42). Moreover, the development of point-of-care testing devices for rapid porphyrin analysis may facilitate early diagnosis and monitoring of PCT in clinical settings (43). The integration of molecular diagnostic approaches, including next-generation sequencing (NGS) for identifying genetic variants associated with PCT, holds potential for personalised medical strategies and targeted therapies.

Despite significant progress, numerous areas require further investigation to enhance our understanding and management of PCT. Research aimed at clarifying the molecular mechanisms underlying PCT pathogenesis, particularly the roles of cytochrome P450 enzymes and hepatic iron metabolism, remains a priority. Prospective studies evaluating the effectiveness of emerging treatment modalities, such as iron chelators and novel pharmacological agents targeting porphyrin synthesis pathways, are necessary to optimise treatment strategies and improve patient outcomes. Furthermore, collaborative efforts to establish standardised diagnostic algorithms and clinical guidelines for managing PCT are crucial for improving clinical practice and ensuring consistency in patient care.

CONCLUSION

PCT is a nuanced, multifaceted disorder resulting from hepatic UROD deficiency, with disease expression influenced by genetic variants and environmental factors. Accurate diagnosis and subtyping (Type I - III) currently rely on specialised biochemical and genetic testing, which are not widely available in routine laboratories. Key gaps remain in understanding the precise molecular mechanisms and in evaluating emerging treatments, including iron chelation and novel pharmacological agents. There is also a pressing need for innovative, simplified diagnostic methods to improve accessibility and enable wider availability of testing. Ultimately, a concerted, multidisciplinary effort among clinicians and laboratory specialists to establish standardised diagnostic algorithms and targeted molecular therapies remains paramount for improving diagnostic consistency, therapeutic efficacy, and the overall prognosis for individuals affected by this significant disorder.

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