Novel *UROD* mutation for porphyria cutanea tarda, type 2: a case report

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Background: Porphyria cutanea tarda (PCT) is usually caused by acquired defects in uroporphyrinogen decarboxylase (UROD) activity in the liver. This more common form of PCT is called type 1 PCT. Major known risk factors for PCT include iron overload, such as occurs due to mutations in HFE, associated with classical hereditary hemochromatosis, chronic hepatitis C infection, heavy alcohol use, tobacco use, and estrogen therapy. In addition, in about 25% of patients with PCT, namely, those with PCT type 2, an inherited partial defect in UROD activity is found. In such persons, this partial defect, which is found in all cells, including hepatocytes, red blood cells, and others, contributes to the development of biochemically and clinically active disease.

Case Description: Herein we describe salient features of a man in his eighth decade of life with onset of clinical PCT. Among risk factors were heavy alcohol and tobacco use. Genetic testing revealed a novel mutation in one of his alleles of the *UROD* gene, namely, c.224 G>C; p. Arg 75 Pro, and enzymatic testing revealed that red blood cell UROD activity was decreased by 50%. This mutation in the *UROD* gene is predicted to have a major effect on protein structure and function, confirmed by the 50% decrease in activity of the enzyme.

Conclusions: The previously undescribed mutation in *UROD*, found in this man, namely, c.224 G>C; p. Arg 75 Pro is pathogenic.

Keywords: Cutaneous porphyria; heme; iron; uroporphyrinogen decarboxylase (UROD); case report

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Introduction

Porphyria cutanea tarda (PCT) is usually caused by acquired defects in uroporphyrinogen decarboxylase (UROD) activity in the liver (1). This disorder is called PCT type 1. About 25% of cases occur in patients who have a partial decrease in UROD activity that is genetically determined, a disorder called PCT type 2. We describe a case of a man with a novel *UROD* mutation causing PCT type 2. We present this case

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in accordance with the CARE reporting checklist (available at https://acr.amegroups.com/article/view/10.21037/acr-23-66/rc).

Case presentation

A 77-year-old male patient was evaluated for painful, bullous blistering over the dorsal surfaces of both hands and forearms and, to a lesser extent, his head, who initially had presented to an outside clinic 6 months earlier (*Figure 1A*). The rash initially had appeared intermittently but became more severe and persistent over time. His medical history was notable for systemic arterial hypertension, a stroke, from which he had largely recovered, and localized melanoma of the skin, treated and cured with local excision. He reported a longstanding history of heavy alcohol and tobacco use. He reported no known family history of porphyria.

He was retired from his occupation as the owner of a manufacturing facility, with history of exposure to various chemicals, including industrial cooling agents, lubricants, weed killers, various oils, and chemicals used to shine metals. Medications taken daily at the time of his initial visit included the following: aspirin, cholecalciferol, vitamin B12, omega-3 fatty acids, fish oil, simvastatin, and tamsulosin.

Physical examination revealed tense bullae with milia and hyperpigmented macules on dorsal hands and forearms bilaterally (*Figure 1A*). Biopsies of one of the blisters on his right hand revealed a subepidermal blister containing rare neutrophils with fibrin. There was also evidence of festooning of the vessels into the blister cavity. Direct immunofluorescence was negative for IgA, IgG, IgM, and complement (C3). This biopsy was interpreted by a dermatopathologist as consistent with PCT.

Highlight box

Key findings

- A 77-year-old male patient was diagnosed with porphyria cutanea tarda (PCT) type 2.
- The patient was found to have a novel mutation in the uroporphyrinogen decarboxylase (*UROD*) gene that markedly affects the activity and predicted structure of the protein.

What is known and what is new?

- It was known that PCT is caused by defects in UROD activity in the liver and that lifestyle modifications, hydroxychloroquine, and iron reduction therapy can reduce disease activity.
- It was known that about 25% of patients with PCT, when tested, are found to have inherited partial defects in activity of UROD in all tissues; this type of PCT is called PCT type 2 or familial PCT.
- This report describes a new mutation in the *UROD* gene (c.224 G>C; p. Arg 75 Pro) with markedly decreased red blood cell UROD activity, indicating that the mutation virtually abolishes activity of the UROD enzyme.

What is the implication and what should change now?

- We conclude that the newly described, previously not-reported mutation in *UROD* is indeed pathogenic
- Our report emphasizes the importance of factors that increase development of clinically active PCT, including alcohol, iron, hepatitis C, smoking, and in about 25% of patients, inherited or *de novo* mutations in *UROD*.

Methods and results

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Laboratory assays, obtained at initial visit at Wake Forest Baptist Medical Center, revealed serum aspartate aminotransferase 63 U/L (ref 5–40 U/L), alanine aminotransferase 64 U/L (ref 5–50 U/L), alkaline phosphatase 54 U/L (ref 25–104 U/L), and total bilirubin 0.8 mg/dL (ref 0.2–1.2 mg/dL). Iron profile was normal [serum ferritin =128 ng/mL (ref 20–300 ng/mL), transferrin saturation =48% (ref 20–50%)], and antibodies against HIV and hepatitis A, B, and C were negative. Genetic testing for classical hereditary hemochromatosis (*HFE*) revealed heterozygosity only for the minor mutation: $C282Y^{-/-}$; $H63D^{+/-}$. Total plasma porphyrins were elevated to 13.4 mcg/dL (ref ≤1.0 mcg/dL). Fractionated urine, stool, and plasma porphyrins were obtained (*Table 1*). Urinary uro- and hepta-carboxyl porphyrins were markedly elevated, consistent with PCT (2). Genetic testing revealed a novel mutation of the *UROD* gene (c.224 G>C; p. Arg 75 Pro) with red blood cell UROD activity decreased by 50%. This mutation is not present in the Human Mutation Gene Database or in GNOMAD.

Clinical course

The patient was advised to start hydroxychloroquine at a low dose, namely, 100 mg 3 times weekly, and to avoid

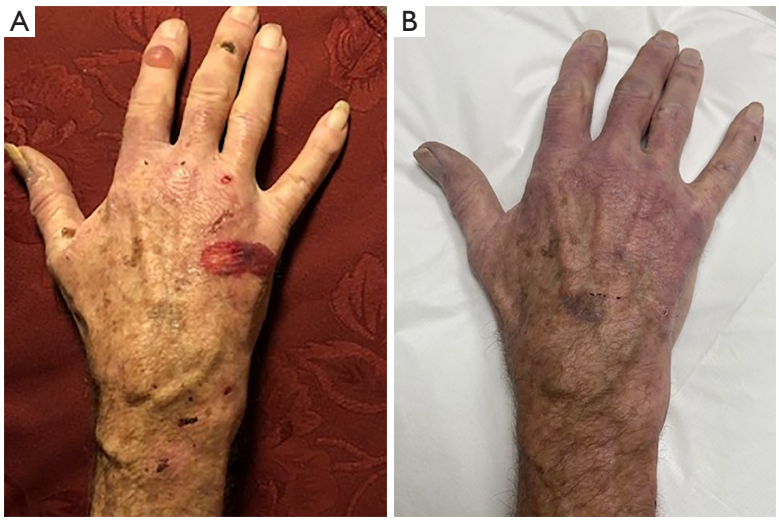

Figure 1 Time course of the skin lesions of PCT in the subject studied. (A) Dorsal aspect of the right hand at presentation; (B) dorsal aspect of the right hand at 7-month follow-up. PCT, porphyria cutanea tarda.

Table 1 Results of selected laboratory studies

Analyte	Presentation	3 months after treatment initiation	7 months after treatment initiation	Reference ranges
Urine creatinine (mmol/L)	6.90	6.98	9.91	
Urine ALA (mcmol ALA/mmol Cr)	1.16	1.13	1.21	≤15
Urine PBG (mcmol PBG/mmol Cr)	0.07	0.06	0.05	≤1.3
Plasma ALA (nmol/mL)	0.2	Not assessed	Not assessed	≤0.5
Plasma PBG (nmol/mL)	0.1	Not assessed	Not assessed	≤0.5
Uroporphyrinogen decarboxylase, whole blood (RU)	0.45 (L)	Not assessed	Not assessed	≥1.0
Uroporphyrin, urine (nmol/mmol Cr)	1080 (H)	931 (H)	149 (H)	≤30
Heptacarboxyl-porphyrin, urine (nmol/mmol Cr)	568 (H)	201 (H)	12.7 (H)	≤7
Hexacarboxyl-porphyrin, urine (nmol/mmol Cr)	18.8 (H)	6.85 (H)	1.1 (H)	≤2
Pentacarboxyl-porphyrin, urine (nmol/mmol Cr)	51.5 (H)	74.8 (H)	2.5	≤5
Coproporphyrin, urine (nmol/mmol Cr)	81.6	84.7	11.7	≤110
Total plasma porphyrins (mcg/dL)	13.8 (H)	7.3 (H)	2.9 (H)	≤1.0
Uroporphyrin, plasma (mcg/dL)	6.7 (H)	5.3 (H)	2.2 (H)	≤1.0
Heptacarboxyl-porphyrin, plasma (mcg/dL)	4.6 (H)	1.2 (H)	0.4	≤1.0
Hexacarboxyl-porphyrin, plasma (mcg/dL)	1.6 (H)	0.3	<0.1	≤1.0
Pentacarboxyl-porphyrin, plasma (mcg/dL)	0.7	0.3	<0.1	≤1.0
Coproporphyrin, plasma (mcg/dL)	<0.1	<0.1	<0.1	≤1.0
Protoporphyrin, plasma (mcg/dL)	<0.1	0.2	0.2	≤1.0

Laboratory studies of blood, urine and stool were collected at Wake Forest Baptist Health in Winston Salem, NC. Samples were wrapped in foil, for protection from light exposure, frozen, and shipped to the Mayo Clinic Laboratory in Rochester, MN. Lab testing was performed based on standard methods of the Mayo Clinic Laboratory. Stool porphyrins at presentation showed elevated hepta-, isohexa-, isopenta-, and isocopro-porphyrins. L, low; H, high; ALA, 5-aminolevulinic acid; Cr, creatinine; PBG, porphobilinogen; RU, relative unit.

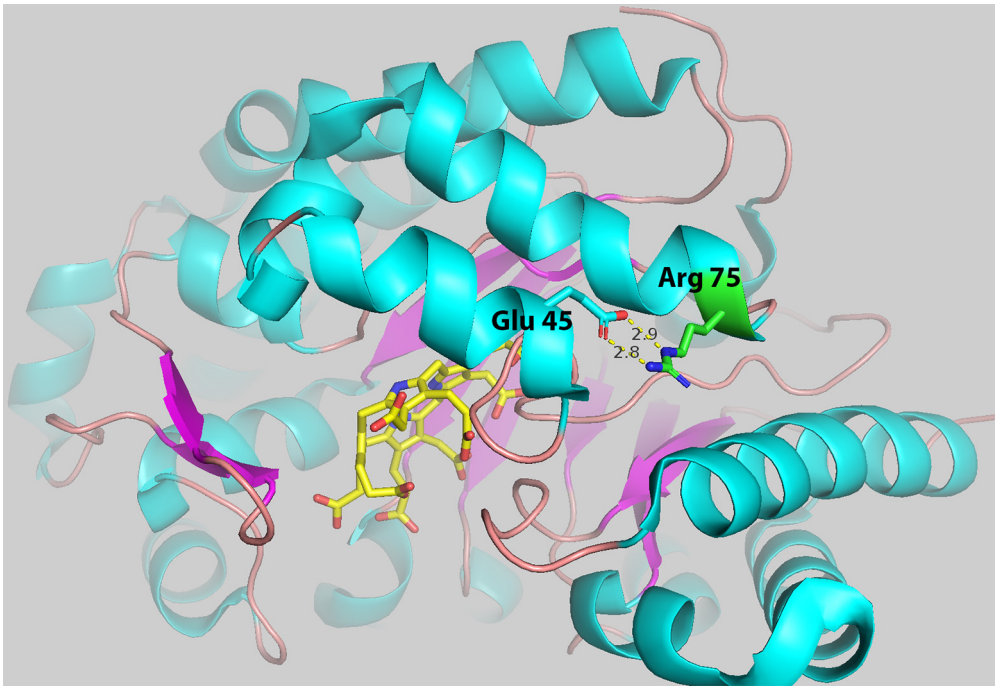

Figure 2 Structure of UROD showing the substrate (yellow) in the active site at the C-terminal end of the beta-sheets (magenta) that form the core of the TIM-barrel structure. Arg 75, shown in green, is the penultimate residue in one of the eight corresponding alpha-helices surrounding the central core. Arg 75 forms two hydrogen bonds with Glu 45 of the preceding helix in the structure. This hydrogen-bonding network supports the tertiary fold of the protein in this otherwise solvent-exposed region. The patient's *UROD* mutation (Arg 75 Pro) disrupts the helix with premature termination, eliminates the hydrogen-bonding network, and disrupts the secondary and tertiary structure of the protein (6). Thus, loss of catalytic activity, as also shown by the 50% decrease in UROD activity in red blood cells, is not surprising. TIM, triose phosphate isomerase; UROD, uroporphyrinogen decarboxylase; Arg 75, arginine 75; Glu 45, glutamic acid 45.

alcohol, tobacco, and sun exposure. He was advised to wear opaque gloves and a wide-brimmed hat. Due to severity and slow improvement (perhaps also related to the patient's not stopping use of tobacco), iron reduction therapy was added at month 7 after treatment initiation.

The patient returned to Wake Forest Baptist Medical Center at 3 and 7 months after the index visit. He indicated that he had stopped all alcohol use but continued to smoke cigarettes. The rash on his hands had improved (*Figure 1B*). He reported adherence with therapy and denied any associated adverse events. Repeat assessment of urine and serum porphyrins showed improvement (*Table 1*).

Discussion

Inheriting a *UROD* mutation on a single allele is not sufficient to cause clinical manifestations of PCT. Other factors that increase oxidative stress are also required (3-5). Chief among these in this case are alcohol use and smoking. Other known triggers of PCT, including hepatitis C infection, iron overload, and oral estrogen use, were considered and determined not to be factors in this case (3). This patient harbors a mutation in the *UROD* gene not previously described in PCT type 2. This mutation has a major effect on UROD activity, consistent with its predicted effect on protein structure and function (6) (*Figure 2*). Nonetheless, even with this mutation, the patient did not clinically manifest PCT type 2 until age 77 years, emphasizing the importance of other environmental and acquired factors in disease pathogenesis.

Conclusions

A novel, not heretofore described, mutation in the gene that encodes *UROD*, specifically, c. 224 G>C, p. Arg 75 Pro, is pathogenic. It decreases activity of the enzyme by about 50%, as assessed by measurement of UROD activity in red blood cells.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://acr.amegroups.com/article/view/10.21037/acr-23-66/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://acr.amegroups.com/article/view/10.21037/acr-23-66/coif). All authors report this work was supported by a cooperative agreement with the National Institute of Diabetes and Digestive and Kidney Diseases of the U.S. National Institutes of Health (grant numbers 2 U 54 DK 083909 and DK 020503), by the Wake Forest University Clinical and Translational Science Institute (grant number UL1TR001420), and by Protect the Future Funds from the American Porphyria Foundation. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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