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Original article

PORPHYRIA CUTANEA TARDA IN CHILDREN: EPIDEMIOLOGICAL STUDY OF A RARE DISEASE IN ARGENTINA

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Abstract

Introduction: Porphyria cutanea tarda (PCT), the most common porphyria, is caused by a decreased activity of uroporphyrinogen decarboxylase (UROD). PCT is generally sporadic, but in about 25% of cases, the disease is transmitted as an autosomal dominant trait (familial PCT). Few cases of PCT with onset in childhood have been reported to date. The aim was to perform a retrospective analysis of these rare cases, including all patients diagnosed with PCT from 1977 to present, with disease onset occurring before the age of 18.

Materials and methods: We analyzed 28 patients, 15 males and 13 females, ranging from 3 to 16 years old.

Results: Characteristic biochemical alterations, such as elevated urinary levels of porphyrins with typical excretion pattern, high plasma porphyrin index, reduced erythrocyte UROD activity, and typical cutaneous lesions of PCT were observed in all patients. Molecular analysis revealed the genetic heterogeneity inherent to PCT, with certain variants being prominent within the Argentinian cohort. Potential precipitating factors of the disease were also described.

Discussion: This study provides a comprehensive analysis of childhood-onset PCT in the Argentinian population, shedding light on both genetic and environmental factors contributing to the disease. We emphasize the crucial need for early diagnosis, particularly in pediatric cases, and remark on the importance of genetic studies among family members to prevent the delayed recognition of PCT in high-risk individuals. Additionally, the study discusses the role of environmental factors in disease onset and the importance of carefully monitoring drug use in PCT patients.

Key words: porphyria cutanea tarda, genetic-heterogeneity, uroporphyrinogen-decarboxylase, childhood, precipitating-factors

Resumen

Porfiria cutánea tardía en niños: estudio epidemiológico de una enfermedad rara en Argentina

Introducción: La porfiria cutánea tardía (PCT), la forma más común de porfiria, es causada por la disminución de la actividad de la uroporfirinógeno descarboxilasa (UROD). Aunque generalmente es esporádica, en el 25% de los casos se transmite en forma autosómica dominante (PCT familiar). Se han documentado pocos casos de PCT con inicio en la infancia. El objetivo de este estudio fue realizar un análisis retrospectivo de estos casos raros incluyendo todos los pacientes diagnosticados con PCT desde 1977 a la fecha, con desencadenamiento antes de los 18 años.

Materiales y métodos: Se analizaron 28 pacientes (15 varones, 13 mujeres), con manifestación entre 3 y 16 años.

Resultados: Se observaron alteraciones bioquímicas características, como niveles elevados de porfirinas

urinarias con un patrón de excreción característico, alto índice de porfirinas plasmáticas, actividad reducida de UROD eritrocitaria y lesiones cutáneas típicas en todos los pacientes. El análisis molecular reveló la heterogeneidad genética de la PCT, con ciertas variantes predominantes dentro de la cohorte argentina. También se describieron factores precipitantes de la enfermedad.

Discusión: Este estudio proporciona un análisis completo de la PCT de inicio infantil en la población argentina, destacando tanto los factores genéticos como ambientales que contribuyen a su manifestación. Subrayamos la necesidad de un diagnóstico temprano, especialmente en los casos pediátricos, y la importancia de los estudios genéticos entre familiares para prevenir el desencadenamiento de la PCT en individuos de alto riesgo.

Palabras clave: porfiria cutánea tardía, heterogeneidad-genética, uroporfirinógeno-decarboxilasa, infancia, factores-precipitantes

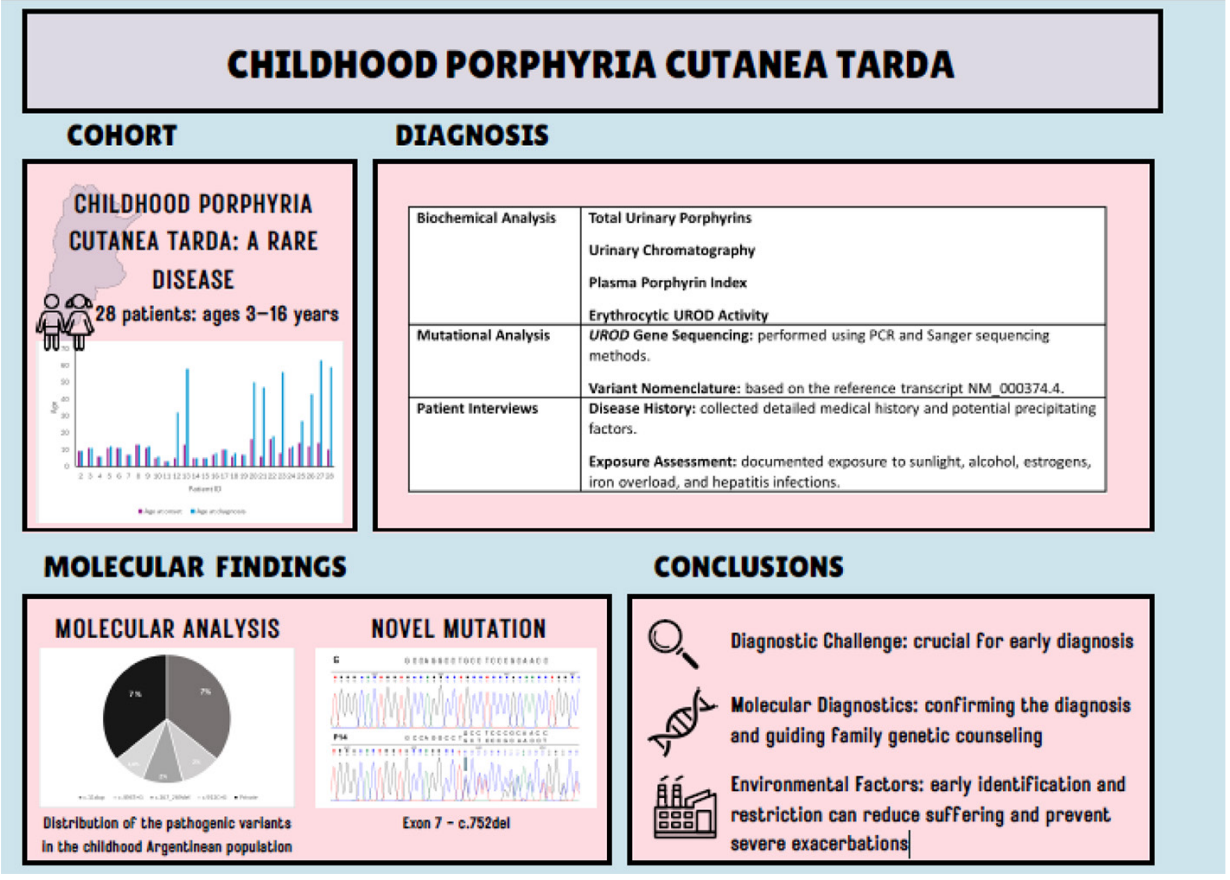
KEY POINTS
Current knowledge

- Childhood-onset porphyria cutanea tarda (PCT) is rare but shows characteristic clinical features
- Environmental exposures may accelerate disease onset in paediatric PCT cases.

Contribution of the article to current knowledge

- A novel *UROD* frameshift mutation expands the genetic diversity of PCT.
- Early diagnosis and family genetic counselling can reduce the burden of delayed detection.

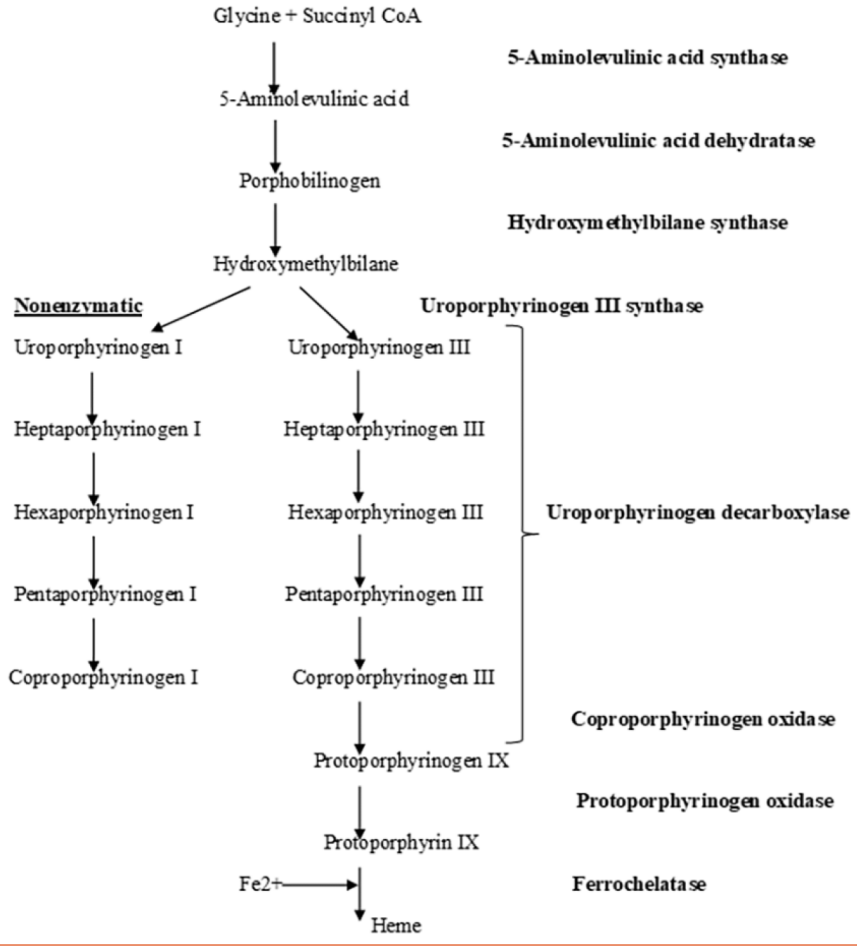
Graphical abstract



Porphyria cutanea tarda (PCT; OMIM: 176100) is the most common type of porphyria resulting from decreased activity of uroporphyrinogen decarboxylase (UROD; E.C.4.1.1.37), the fifth enzyme of the heme biosynthetic pathway (Fig. 1)[1-3]. Uroporphyrinogen decarboxylase (UROD) deficiency leads to the accumulation of highly carboxylated porphyrinogens in the liver, mainly uroporphyrinogen and heptaporphyrinogen, which are oxidized to the corresponding porphyrins that circulate in plasma and are excreted in urine[4]. The disease usually manifests in adulthood, is more common in men and is characterized by skin photosensitivity with blistering on sun-exposed areas, skin fragility, hyperpigmentation, and hypertrichosis[5]. The onset of PCT is frequently associated with exposure to known precipitating agents, including polyhalogenated aromatic hydrocarbons, alcohol abuse, estrogen administration, iron overload, and infections with hepatitis C and B virus (HCV and HBV) and HIV[5-9]. The overproduction of porphyrins causes the clinical manifestations of the disease. These factors contribute to liver dysfunction, a common sign in PCT patients.

There are two main forms of PCT: type I (sporadic) and type II (familial)[10]. Type II PCT is transmitted as a dominant trait with low penetrance and the enzyme activity is reduced to approximately 50% of normal in all tissues due to heterozygosity for mutations in the *UROD* gene[10, 11]. Type I PCT accounts for about 75% of cases where no *UROD* gene mutations have been found and subnormal UROD activity is restricted to the liver[10-12]. For this reason, both types of PCT can be differentiated by measuring erythrocyte UROD activity[13].

Figure 1 | Heme biosynthetic pathway



Few cases of PCT with onset in childhood have been reported to date[14-17]. In the present work, we include all PCT patients whose clinical manifestations occurred in childhood and were diagnosed at our Center to perform a comprehensive analysis of these rare cases.

Material and methods

Patients

This study includes all patients diagnosed with PCT at our center from 1977 to the present with disease onset occurring before the age of 18. The study was conducted following the guidelines stated in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects) and informed consent was obtained from all patients.

This study was approved by the Institutional Research Ethics Committee of the Research Center on Porphyrins and Porphyrias (CIPYP), Argentina) (UBA-CONICET).

Diagnosis of porphyria cutanea tarda

Urinary porphyrins, their excretion pattern, plasma porphyrin index (PPI), and erythrocytic UROD activity were determined by the methodologies already published[18]. PCT diagnosis was confirmed based on characteristic cutaneous lesions, elevated amounts of porphyrins in plasma (porphyrin peak at 618-619 nm) as well as an increase in the urinary excretion of porphyrins, predominantly uroporphyrin and heptaporphyrin. Where feasible, mutational analysis of the *UROD* gene was performed as previously described[19-21]. Due to the extensive duration of the study, different methods were used for gene amplification and sequencing. The sequencing was initially performed manually starting in 1996, and from 2000 onwards, automated sequencing was carried out at Macrogen (Korea). All detailed information on the methods used can be found in the cited bibliography[19-21]. Variant nomenclature and exonic numbering were performed using reference transcript NM_000374.4. Patients and their families were interviewed regarding potential disease-precipitating factors. In brief, the algorithm used for the diagnosis is shown in Figure 2.

Results

Patients

In this study, we analyzed 28 patients diagnosed with PCT from 1977 to the present, with disease onset before age 18. The cohort comprised 15 males and 13 females. Of these, 20 patients had no familial relation, while four had relatives who also exhibited early-onset PCT. The onset age ranged from 3 to 16 years, with a median age of 10 years, while the median age at diagnosis was 11 years (range 3-63 years). In nearly 70% of patients, the diagnosis was at onset or within two years after. In 8 patients, the diagnosis was in adulthood (32 to 63 years).

Biochemical analysis

All patients exhibited elevated levels of urinary porphyrins, predominantly uroporphyrin and heptacarboxyl-porphyrin and elevated amount of porphyrins in plasma with a fluorescent emission peak at 618-619 nm (Table 1). The plasma porphyrin index (PPI) values varied significantly among patients, ranging from 1.38 to 9.71, with a median of 3.72. Erythrocytic UROD activity was reduced in all those patients in whom it was determined (Table 1).

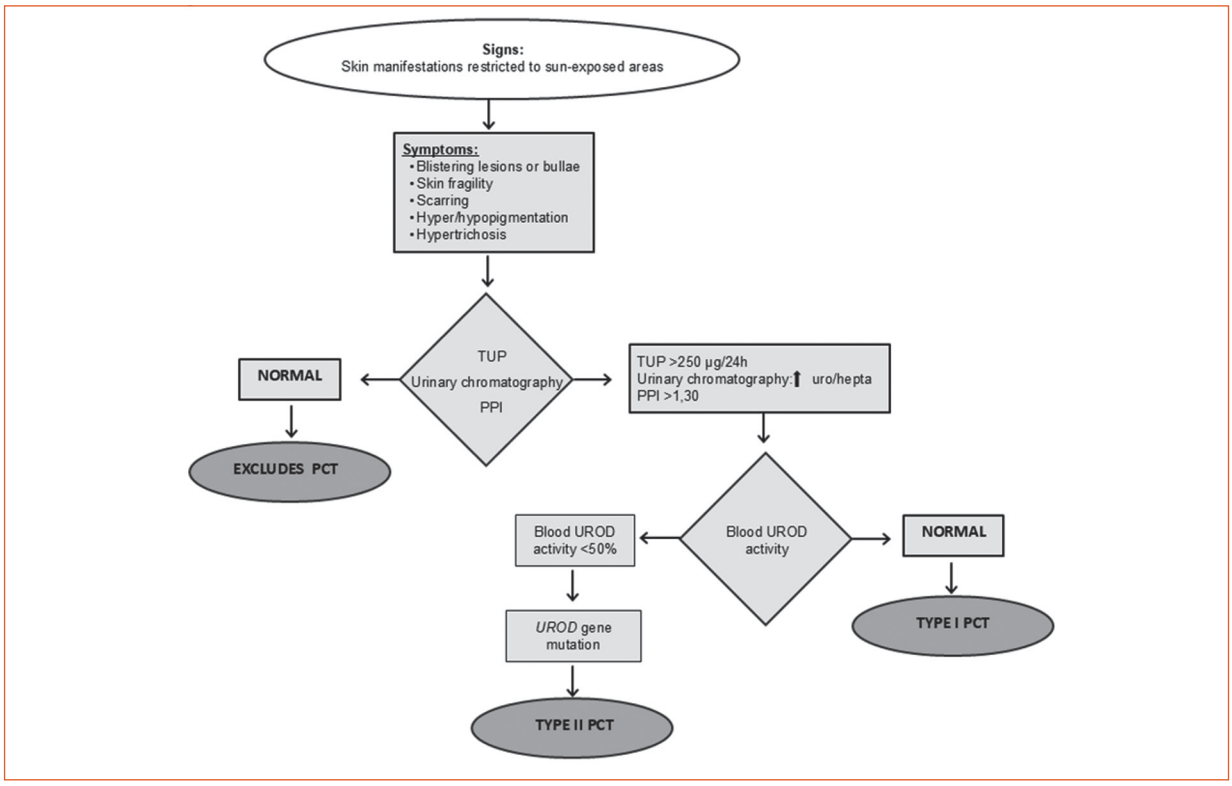
Molecular analysis

Mutational analysis of the *UROD* gene was performed in 24 patients. The results are summarized in Table 2[19-25]. Several mutations were identified for the first time in our center including: two frameshift mutations one in exon 1 (c.11dupA) and the other is a cytosine deletion in exon 7 (c.752delC), two missense mutations: c.494T>G, p.Met165Arg (exon 6) and c.912C>G, p.Asn304Lys (exon 9), an in-frame deletion in exon 4 (c.267_269del, p.Val90del) and three splicing defects (c.213+1G>T, c.942G>A, c.943-1G>C). Despite the genetic heterogeneity inherent to PCT, certain variants exhibited prominence within the cohort. The c.11dupA mutation was the most common in 7 non-related patients (35%). This is also the commonest *UROD* mutation in Argentina and is very old or occurred more than once[19]. Other prevailing pathogenic variants were c.494T>G p.Met165Arg (10%), c.267_269del p.Val90del (10%) and c.912C>G p.Asn304Lys (10%). Additionally, a subset of variants remained private to specific individuals (35%).

Clinical manifestations

All patients exhibited the typical cutaneous lesions of PCT, including blistering on sun-ex-

Figure 2 | Diagnosis algorithm for porphyria cutanea tarda



TUP: total urinary porphyrins; PPI: plasmatic porphyrin index; Hepta: heptaporphyrin; Uro: uroporphyrin; UROD activity: erythrocyte uroporphyrinogen decarboxylase activity

Reference values: TUP: 20-250 µg/24h, PPI: ≤1.30 (λ = 619 nm), Urinary chromatography: Coproporphyrin: 100%. UROD activity: percentage of the mean value from 50 healthy individuals: 4.2±0.6 nmol coproporphyrinogen III/h/mlRBC

posed areas, skin fragility, hyperpigmentation, and hypertrichosis.

Potential precipitating factors

Interviews with patients and their families revealed several potential disease-precipitating factors (Table 3). These included ingestion of iron and vitamins, hepatitis virus infections and hemodialysis. In many cases, more than one precipitating factor could be identified.

Discussion

This study provides a comprehensive analysis of childhood-onset PCT in the Argentinian population, shedding light on genetic and environmental factors contributing to the disease. Late diagnosis, which was observed in seven patients aged 32 to 63, often led to prolonged suffering and exacerbation of clinical symptoms. This underlines the crucial need for early diagnosis, particularly in pediatric cases, and emphasizes the importance of genetic studies in family members to prevent the delayed recognition of PCT in high-risk individuals. Pediatric dermatologists should maintain a high index of suspicion for porphyria when encountering skin manifestations in children, especially in locations where PCT is less frequently recognized[5,26].

Our study shows the genetic basis of childhood PCT in the Argentinian population. A main finding is that the frequency of the most common *UROD* mutations in children is the same as in adults[27]. This means that these genetic variants are important regardless of age or environment.

The finding of a new frameshift mutation c.752del, a cytosine (C) deletion in exon 7

Table 1 | Biochemical values in porphyria cutanea tarda patients

Patient	Sex	Biochemical parameters							
		TUP (µg/24 h)	PPI λ = 619 nm	UROD activity (%)	Urinary chromatography				
					C%	P%	H%	HP%	U%
1*	M	ND	3.66	57.9			ND		
2	F	7528	5.87	52.0	6	3	1	30	60
3	M	1627	9.71	ND	5	0	5	50	40
4	F	1424	2.82	48.0	15	5	0	35	45
5	M	2672	3.00	46.0	10	4	2	36	48
6	M	1257	4.20	37.0	15	3	2	35	45
7	F	3174	5.80	44.0	15	3	2	35	45
8	F	934	1.45	48.0	5	5	5	35	50
9	M	2277	4.26	54.2	8	4	4	42	42
10	M	2412	3.00	45.0	7	2	5	28	58
11	F	1347	1.63	42.0	14	5	0	38	43
12	F	2295	1.38	46.0	11	4	5	27	53
13	M	1526	1.93	57.6	10	5	5	30	50
14	M	1813	2.10	30.0	5	3	0	38	52
15	F	3591	4.32	54.2	8	7	6	30	40
16	F	1298	2.80	ND	20	8	2	30	40
17	M	2018	2.20	45.0	7	6	5	35	47
18	F	863	5.71	ND	11	9	2	33	45
19	F	1113	2.30	51.0	12	5	3	35	45
20	M	10837	8.20	44.8	3	3	3	30	61
21	F	8910	7.48	45.0	4	4	5	37	40
22	F	5352	3.80	47.4	14	8	8	30	40
23	M	14338	9.00	46.0	5	5	5	35	50
24	M	1937	4.88	42.0	10	5	5	30	40
25	F	1030	2.25	39.1	11	11	2	29	47
26	M	6168	3.00	54.7	7	5	2	29	57
27	M	4944	3.78	62.6	5	5	5	35	50
28	M	4430	4.78	52.5	15	5	10	30	40

TUP: total urinary porphyrins; PPI: plasmatic porphyrin index; UROD activity: erythrocyte uroporphyrinogen decarboxylase activity; C: coproporphyrin; P: pentaporphyrin; H: hexaporphyrin, HP: heptaporphyrin; U: uroporphyrin; ND: not determined.
Reference values: TUP=20-250 µg/24h, PPI: ≤1.30, Urinary chromatography: only coproporphyrin (C=100%). UROD activity: percentage of the mean value from 50 healthy individuals (RV=4.2±0.6 nmol coproporphyrinogen III/h/mlRBC).
*In Patient 1, urinary parameters were unavailable due to hemodialysis. In this case, total porphyrins were determined in feces (TFP) (TFP=461 µg/g dry weight, RV= 20-130 µg/g dry weight)

shows that we need to keep expanding the list of pathogenic variants (Fig. 3). This mutation which likely leads to nonsense-mediated decay[28], adds to the genetic diversity of PCT and shows the importance of molecular diagnosis to find new mutations that can contribute to early disease onset. Notably, genetic mutations seem to play a more important role in childhood PCT than in adult PCT where environmental factors are more common. This means that hereditary factors are key in pediatric presentations, so a genetic approach is important for diagnosis and management.

The finding of specific *UROD* mutations provides a solid ground for targeted genetic counseling. Families of affected children, especially those with prevalent mutations like c.11dupA can benefit from predictive genetic testing to

Table 2 | *UROD* gene variants in porphyria cutanea tarda patients

Patient	Sex	Molecular studies				Reference
		Genetic variant	Protein effect	Gen location	Type of mutation	
1	M			ND		
2	F	c.11dup	p.(Asn4Lysfs*14)	Exon 1	Frameshift	19
3	M	c.494T>G	p.Met165Arg	Exon 6	Missense	19
4	F	c.11dup	p.(Asn4Lysfs*14)	Exon 1	Frameshift	19
5	M	c.213+1G>T	p.?	Intron 3	Splicing defect	22
6	M	c.11dup	p.(Asn4Lysfs*14)	Exon 1	Frameshift	19
7	F	c.11dup	p.(Asn4Lysfs*14)	Exon 1	Frameshift	19
8	F	c.11dup	p.(Asn4Lysfs*14)	Exon 1	Frameshift	19
9	M	c.239C>G	p.Ala80Gly	Exon 4	Missense	23
10	M	c.267_269del	p.Val90del	Exon 4	In frame deletion	21
11	F	c.494T>G	p.Met165Arg	Exon 6	Missense	19
12	F	c.494T>G	p.Met165Arg	Exon 6	Missense	19
13	M	c.912C>G	p.Asn304Lys	Exon 9	Missense	19
14	M	c.752del	p.(Ala251fsX258)	Exon 7	Frameshift	This study
15	F	c.11dup	p.(Asn4Lysfs*14)	Exon 1	Frameshift	19
16	F	c.11dup	p.(Asn4Lysfs*14)	Exon 1	Frameshift	19
17	M			ND		
18	F	c.942+1G>A	p.?	Intron 9	Splicing defect	24
19	F	c.912C>G	p.Asn304Lys	Exon 9	Missense	19
20	M	c.942G>A	p.?	Exon 9	Splicing defect	19
21	F	c.942G>A	p.?	Exon 9	Splicing defect	19
22	F			ND		
23	M	c.11dup	p.(Asn4Lysfs*14)	Exon 1	Frameshift	19
24	M			ND		
25	F	c.659A>C	p.His220Pro	Exon 7	Missense	25
26	M	c.267_269del	p.Val90del	Exon 4	In frame deletion	21
27	M	c.943-1G>C	p.?	Intron 9	Splicing defect	20
28	M	c.943-1G>C	p.?	Intron 9	Splicing defect	20

ND: not determined

identify at-risk relatives. This enables early detection and intervention and reduces the burden of late diagnosis.

While the findings are specific to our population, they open the door to studying similar patterns in other populations. Regional studies are necessary to understand the population specific dynamics of childhood PCT. Our ongoing research will explore whether other genetic factors or modifiers are involved in the clinical variability of childhood PCT. This will help to have personalized management and to better understand the genetic basis of PCT.

The skin manifestations of PCT, including blistering and fragility, are a direct consequence of the phototoxic nature of accumulated porphyrins in the dermis when exposed to sunlight. The pathogenic wavelength for the excitation of these porphyrins is around 408 nm (within an exciting waveband of 400–420 nm). The great majority of patients in this study lived in rural areas, where exposure to sunlight is usually more prolonged and intense, due to agricultural work or outdoor lifestyles. This continuous interaction between high levels of cutaneous porphyrins and visible light produces the generation of reactive oxygen species, leading to severe tis-

Table 3 | Age of onset, diagnosis and possible precipitating factors in porphyria cutanea tarda patients

Patient	Sex	Age of onset	Age at diagnosis	Potential precipitating factors
1	M	15	16	Hemodialysis - Kidney transplant Spironolactone - Iron supplement
2	F	9	9	Hemodialysis - Kidney transplant Iron and vitamins supplement
3	M	11	11	NI
4	F	6	6	Fipronil - Metamizole sodium
5	M	11	12	NI
6	M	11	11	NI
7	F	7	7	NI
8	F	13	13	NI
9	M	11	12	Pesticides
10	M	5	6	NI
11	F	3	3	Trimethoprim Iron supplement
12	F	5	32	NI
13	M	13	58	NI
14	M	5	5	HBV
15	F	5	5	NI
16	F	7	8	NI
17	M	10	10	Hexachlorobenzene
18	F	6	8	Chlorpheniramine
19	F	7	7	NI
20	M	16	50	NI
21	F	6	47	NI
22	F	16	18	NI
23	M	8	56	NI
24	M	11	12	NI
25	F	14	27	NI
26	M	12	43	NI
27	M	14	63	Enalapril maleate
28	M	10	59	Hexachlorobenzene

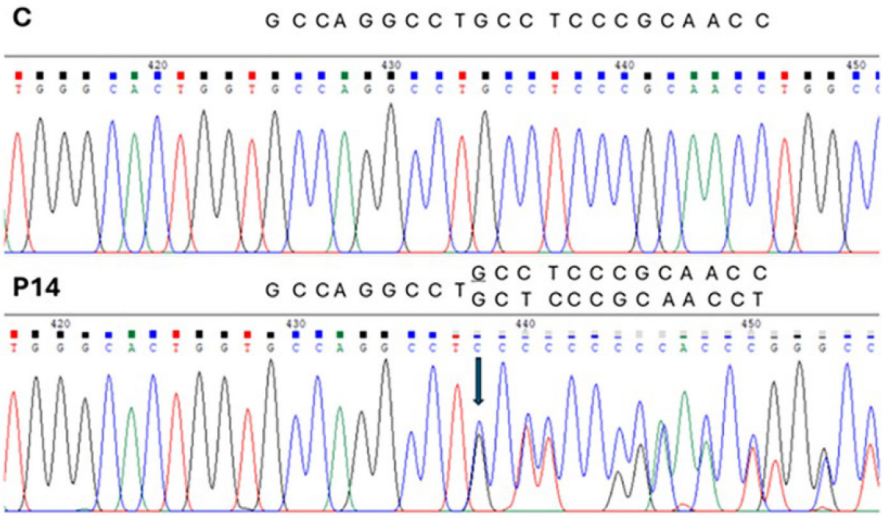
NI: not identified; HBV: hepatitis B virus

Patients from the same family are indicated in bold: Family 1 (patients 6, 7), Family 2 (patients 11, 12), Family 3 (patients 20, 21), and Family 4 (patients 27, 28)

sue damage. Moreover, these individuals had an underlying genetic predisposition, which, when combined with a triggering factor and prolonged sun exposure, could account for an earlier disease manifestation. Furthermore, their rural environment likely involved chronic exposure to various environmental toxins, including certain pesticides and herbicides such as hexachlorobenzene, which is well-known to act as a triggering factor for PCT. In addition, some patients were subjected to treatment with iron supplements, thus iron overload may have contributed to the clinical and biochemical symptoms[5,8,15].

In addition, several of the drugs mentioned in Table 1, including spironolactone (diuretic), metamizole sodium (Dipyrone, analgesic), and trimethoprim (antibiotic), have been associated with liver function alteration, which could exacerbate

Figure 3 | Novel exonic mutation in the UROD gene, c.752del



Electropherograms showing the relevant parts of the genomic sequence in a (C) control individual and the (P14) affected patient. The arrow indicates the beginning of the deletion, and the deleted nucleotide is underlined. Patient is numbered according to Table 2

porphyria symptoms[29,30]. Chlorpheniramine (antihistamine) and fipronil (insecticide) while not directly linked to porphyria, may complicate the clinical picture in patients predisposed to PCT due to their environmental or metabolic effects[31]. The precipitating agent could not be determined in many cases, however its presence cannot be excluded.

Several therapeutic alternatives exist for the management of PCT, including the use of chloroquine, repeated phlebotomies, S-Adenosyl-L-Methionine (SAM), and combined treatments. The positive effect of phlebotomy is attributed to the removal of excess free iron, which is a key contributor to the disease. Chloroquine, on the other hand, is highly effective in sequestering porphyrins from the liver, and facilitating their excretion through urine. SAM increases glutathione (GSH) levels, which in turn mobilizes free iron, enhancing its uptake and transport to the bile by forming adduct between the thiol and the metal in the liver. In our study, as all patients were children phlebotomy was not an option. They received treatments with various therapeutic approaches, but the most commonly used and effective therapy was a combination of oral SAM (12-15 mg/kg/day for 3 weeks), oral chloroquine (200 mg/week), and a hepatoprotective diet[32]. All of these children showed full clinical and biochemical recovery, at least during the follow-up period. Improvement was typically observed within 60 days of starting treatment. Once normal porphyrin levels were reached in urine, a remission of cutaneous symptoms was observed, along with the normalization of the porphyrin excretion pattern[14,15,32]. In pediatric patients undergoing hemodialysis, treatment presents significant challenges. As they are often anuric or oligoanuric, chloroquine cannot be applied. In these cases, SAM administration is the only therapeutic alternative[14].

This study provides considerable insight into the genetic and environmental origins of pediatric onset of PCT in an Argentinian population. Its strength is that it was feasible to analyse a large pediatric cohort, something rare considering that PCT has an adult onset. The large series provides an in-depth assessment of the clinical presentation of the disease along with genetic variation and precipitating factors. Genetic study, due to the nature of this study, was not feasible in four patients due to a lack of follow-up.

These findings emphasize the importance of carefully monitoring drug use in PCT patients. Identifying and limiting the use of these precipitating factors early on can help mitigate prolonged suffering and prevent severe disease exacerbations[33].

The establishment of a national registry for PCT patients could also facilitate better understanding and management of the disease in Argentina.

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Conflict of interest: None to declare

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