Cite as: Miklaszewska M, Błasiak M, Erger F, Wójcik EJ, Drożdż D, Beck BB: Nephrocalcinosis in hyperphosphataemic familial tumoural calcinosis in a 36-year-old woman. Pediatr Med Rodz 2025; 21 (1): 71–74

Monika Miklaszewska[1], Magdalena Błasiak[2,3], Florian Erger[4–6], Ewelina Jarosz Wójcik[2], Dorota Drożdż[1], Bodo B. Beck[4–6]

Received: 22.08.2024
Accepted: 17.02.2025
Published: 18.04.2025

Nephrocalcinosis in hyperphosphataemic familial tumoural calcinosis in a 36-year-old woman

Nefrokalcynoza w przebiegu rodzinnej kalcynozy guzowatej u 36-letniej kobiety

[1] Department of Paediatric Nephrology and Hypertension, Jagiellonian University Medical College, Kraków, Poland
[2] Department of Paediatric Nephrology and Hypertension, University Children's Hospital, Kraków, Poland
[3] Doctoral School of Medical and Health Sciences, Jagiellonian University Medical College, Kraków, Poland
[4] Institute of Human Genetics, University Hospital Cologne, Faculty of Medicine, University of Cologne, Cologne, Germany
[5] Centre for Molecular Medicine Cologne, University of Cologne, Cologne, Germany
[6] Centre for Rare Diseases Cologne, University Hospital Cologne, Faculty of Medicine, University of Cologne, Cologne, Germany
Correspondence: Magdalena Błasiak, Department of Paediatric Nephrology and Hypertension, University Children's Hospital, Wielicka 265, 30-663 Kraków, Poland, e-mail: magdalena.blasiak@doctoral.uj.edu.pl

[1] Klinika Nefrologii Dziecięcej i Nadciśnienia Tętniczego, Uniwersytet Jagielloński Collegium Medicum, Kraków, Polska
[2] Oddział Nefrologii Dziecięcej i Nadciśnienia Tętniczego, Uniwersytecki Szpital Dziecięcy w Krakowie, Kraków, Polska
[3] Szkoła Doktorska Nauk Medycznych i Nauk o Zdrowiu, Uniwersytet Jagielloński Collegium Medicum, Kraków, Polska
[4] Institute of Human Genetics, University Hospital Cologne, Faculty of Medicine, University of Cologne, Cologne, Germany
[5] Centre for Molecular Medicine Cologne, University of Cologne, Cologne, Germany
[6] Centre for Rare Diseases Cologne, University Hospital Cologne, Faculty of Medicine, University of Cologne, Cologne, Germany
Adres do korespondencji: Magdalena Błasiak, Oddział Nefrologii Dziecięcej i Nadciśnienia Tętniczego, Uniwersytecki Szpital Dziecięcy, Wielicka 265, 30-663 Kraków, e-mail: magdalena.blasiak@doctoral.uj.edu.pl

https://doi.org/10.15557/PiMR.2025.0009

ORCID iDs
1. Monika Miklaszewska https://orcid.org/0000-0003-0776-4946
2. Magdalena Błasiak https://orcid.org/0009-0001-9017-2572
3. Florian Erger https://orcid.org/0000-0002-2768-1702
4. Dorota Drożdż https://orcid.org/0000-0002-1281-1164
5. Bodo B. Beck https://orcid.org/0000-0003-0495-7670

Abstract

Nephrocalcinosis is characterised by the deposition of calcium oxalate or calcium phosphate in the tubulointerstitial regions of the kidney. Rarely, disturbances in phosphate homeostasis in the course of hyperphosphataemic familial tumoural calcinosis can be the cause of nephrocalcinosis. The main symptoms of this condition include ectopic calcifications, hyperostosis, and dental abnormalities. In this article, we present the clinical and genetic description of a case involving a 36-year-old woman in whom nephrocalcinosis was incidentally discovered and subsequently led to the diagnosis of hyperphosphataemic familial tumoural calcinosis. In the course of the molecular diagnostic process, whole-exome short-read sequencing detected a heterozygous in-frame deletion (c.1093_1095del; p.Gly365del) in the *GALNT3* gene, while long-read single-molecule real-time sequencing identified a complex indel (c.1382_1388delins814) in *GALNT3* exon 7. To the authors' knowledge, this is the first described case of a patient with this specific mutation.

Keywords: nephrocalcinosis, hyperphosphataemic familial tumoural calcinosis, hyperphosphataemia, fibroblast growth factor 23

Streszczenie

Nefrokalcynoza, inaczej wapnica nerek, polega na osadzaniu się złogów wapniowo-szczawianowych lub wapniowo-fosforanowych w obszarach cewkowo-śródmiąższowych nerek. Bardzo rzadką przyczyną nefrokalcynozy mogą być zaburzenia homeostazy fosforanowej w przebiegu rodzinnej kalcynozy guzowatej. Głównymi objawami tej choroby są zwapnienia w tkankach miękkich i naczyniach krwionośnych, hiperostoza oraz zaburzenia uzębienia. W artykule przedstawiono kliniczny i genetyczny opis przypadku 36-letniej kobiety, u której objawem klinicznym, który nakierował na diagnostykę rodzinnej kalcynozy guzowatej, była przypadkowo stwierdzona nefrokalcynoza. W toku diagnostyki molekularnej wykonano sekwencjonowanie krótkich fragmentów eksonów i sekwencjonowanie całego genomu metodą pojedynczej molekuły w czasie rzeczywistym, wykrywając odpowiednio heterozygotyczną delecję w ramce odczytu (c.1093_1095del; p.Gly365del) w genie *GALNT3* i złożony polimorfizm insercyjno-delecyjny (indel) (c.1382_1388delins814) w eksonie 7 *GALNT3*. Zgodnie z wiedzą autorów jest to pierwszy opisany przypadek pacjenta z tą mutacją.

Słowa kluczowe: nefrokalcynoza, rodzinna kalcynoza guzowata, hiperfosfatemia, czynnik wzrostu fibroblastów 23

© 2025 Medical Communication Sp. z o.o. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (CC BY-NC-ND). Reproduction is permitted for personal, educational, non-commercial use, provided that the original article is in whole, unmodified, and properly cited.
Authors: Miklaszewska M, Błasiak M, Erger F, Wójcik EJ, Drożdż D, Beck BB. Proofreading by ENSKA Agnieszka Kosarzycka.

INTRODUCTION

Nephrocalcinosis (NC) is associated with calcium oxalate or calcium phosphate deposits in the tubulointerstitial regions of the kidney. Currently, the term NC is used to describe radiological changes in the kidneys. In 1991, Al-Murrani et al. introduced an ultrasound classification that distinguishes three types: I – slight increase in echogenicity at the pyramid edges, II – slight increase in echogenicity involving the entire pyramids, III – significant increase in echogenicity involving the entire pyramids[1]. In the differential diagnosis of the causes of NC, acquired factors should be considered, including primary hyperparathyroidism, sarcoidosis, hypervitaminosis D_3, and congenital genetically determined disorders (distal tubular acidosis, hypophosphataemic rickets, familial hypomagnesaemia with hypercalciuria and nephrocalcinosis, Bartter's syndrome, Dent's disease, primary hyperoxaluria, and renal-enamel syndrome)[2,3].

Deficiency or resistance to the most potent phosphate-regulating hormone, called fibroblast growth factor 23 (FGF23), leads to a rare disorder which usually presents with a clinical picture opposite to that of phosphopaenic rickets – named hyperphosphataemic familial tumoural calcinosis (HFTC). The main symptoms of this condition include calcifications in soft tissues and blood vessels, hyperostosis, and dental disorders[4,5]. This article presents a case report of a woman whose initial diagnosis of accidentally discovered nephrocalcinosis ultimately led to the diagnosis of HFTC.

CLINICAL CASE DESCRIPTION

A 36-year-old Caucasian woman was consulted by a nephrologist due to NC grade I and a 5 mm hyperechoic area in the kidney cortex, incidentally identified during a routine ultrasonography (US) review. The radiologist's report described this area as an angiomyolipoma (AML). In addition, the patient's medical history revealed recurrent osteoarticular symptoms, including pain and limited mobility in large joints. Bone densitometry showed bone mineral density verging on osteopaenia.

Moreover, radiological examinations revealed periarticular calcifications in the right shoulder joint, left knee joint, and metatarsal joints. Prior to this, the patient had undergone two surgical orthopaedic surgical procedures, 17 and 2 years before her first nephrology consultation, and was at that time consulted by an orthopaedist about periarticular calcifications in her bilateral hip joints to determine eligibility for further surgery. She had also undergone surgery for carpal tunnel syndrome in her right wrist. Additionally, her ophthalmological examination revealed the presence of fine angioid streaks.

In a 24-hour urine collection, calcium excretion ranged from 3.9 mg/kg at the beginning of the disease to 6.4 mg/kg in subsequent analyses. Excretion levels of other ions, oxalates, and citrates remained within normal limits. Laboratory test results from the past decade are summarised in Tab. 1. It should be emphasised that each blood test sample exhibited hyperphosphataemia, while estimated glomerular filtration rate (eGFR) levels were confirmed to be either normal or slightly decreased. The mean eGFR, calculated according to the 2021 CKD-EPI definition using creatinine and cystatin C, indicated chronic kidney disease (CKD) stage II (84 mL/min/1.73 m^2, range: 64–102 mL/min/1.73 m^2), although the most recent eGFR level was 80 mL/min/1.73 m^2. Nonetheless, cystatin C concentrations remained within normal laboratory reference ranges throughout the observation period.

Slightly decreased eGFR levels did not account for the consistently elevated phosphate concentrations. Therefore, given the low 25-hydroxyvitamin D_3 levels, normal PTH activity, and absence of mutations in the *CYP24A1* gene, FGF23 measurement was conducted, with low levels of this phosphatonin anticipated. Nevertheless, the results exceeded more than 12 times the upper limit of the normal range. Based on these findings, HFTC was suspected, likely caused by a mutation in the FGF23 receptor.

As the next step in diagnostics, whole-exome short-read sequencing (WES) was performed, detecting a heterozygous in-frame deletion (c.1093_1095del; p.Gly365del) in the *GALNT3* gene. Short-read sequence alignment suggested an additional structural genomic variant in this gene but was unable to characterise the alteration. To resolve this, whole-genome long-read single-molecule real-time (SMRT) sequencing was conducted, which detected a second complex indel (c.1382_1388delins814) in *GALNT3* exon 7, confirming the clinical diagnosis of HFTC type 1 (Fig. 1).

Since the diagnosis of NC, the patient remained on continuous pharmacological treatment, including magnesium citrate and potassium citrate. Additionally, the water intake exceeds 2.5 litres per day. Initially, due to the diagnosis of NC, vitamin D_3 supplementation was withheld until the completion of full diagnostic evaluation, resulting in persistently suboptimal levels. Currently, the patient receives 1,000 IU of vitamin D_3 daily, with periodic monitoring of 25-hydroxyvitamin D_3 levels to maintain concentrations at the lower limit of the reference range. Due to gastrointestinal adverse effects, the patient does not tolerate calcium phosphate binders such as calcium carbonate and acetate. Owing to the lack of reimbursement of non-calcium

	Mean value	Range	Reference values
Ca serum	2.4	2.27–2.5	2.15–2.5 mmol/L
P serum	1.8	1.51–2.19	0.81–1.45 mmol/L
PTH	34.2	26.6–42.75	15–65 pg/mL
Cr serum	78.3	67–99	44–80 µmol/L
Cystatin C	0.82	0.76–0.89	0.53–0.95 mg/L
25(OH)D_3	25	17.5–28.7	31–50 ng/mL
1,25(OH)$_2D_3$	77	64.4–89.6	25–86.5 pg/mL
FGF23	1,304.5	1,085–1,524	26–110 kRU/L
Ca urine (24 h)	5.4	3.9–6.4	<4 mg/kg/day
FGF23 – fibroblast growth factor 23; **PTH** – parathormone.			

Tab. 1. Laboratory results of the patient

DOI: 10.15557/PiMR.2025.0009

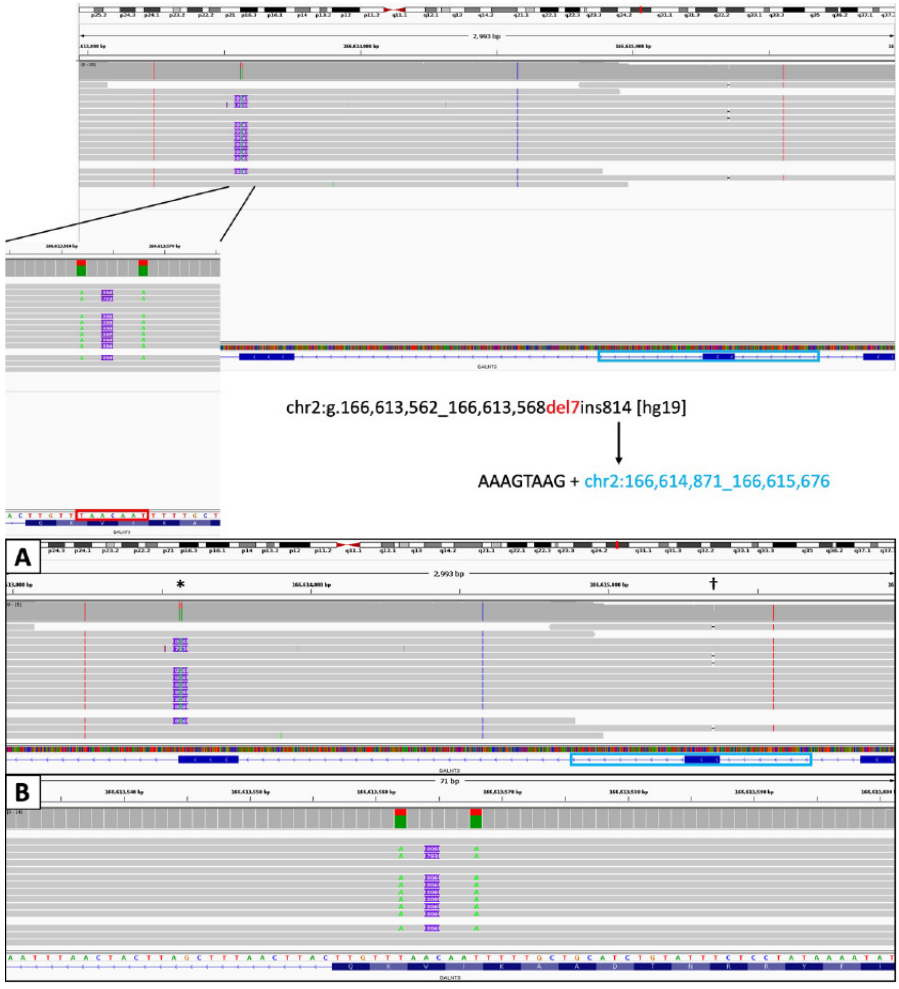

Fig. 1. Alignment representation of the GALNT3 *variants.* **A.** *Long-read alignment detects two variants: the inframe deletion c.1093_1095del (marked with †) and the complex indel c.1382_1388delins814 (marked with *). From reads spanning both variants, compound-heterozygosity is clearly demonstrated. The light blue box in the gene view corresponds to the sequence inserted at * (chr2:166,614,871_166,615,676[hg19]), which was identified using BLAST alignment search.* **B.** *Closeup of the complex indel shows two adjacent apparent single nucleotide variants. Manual sequence realignment resolves the indel as c.1382_1388delins814*

phosphate binders (which are recommended in the literature[4]) in Poland, the patient is unable to take them. She remains under ongoing supervision by a dietician and adheres to a low-phosphate diet.

DISCUSSION

HFTC is a condition characterised by elevated phosphate levels in the blood (hyperphosphataemia) and abnormal deposits of phosphate and calcium (calcinosis) in body tissues. HFTC typically develops in early childhood to early adulthood, although in some cases, including the present one, deposits first appear in infancy or later in adulthood[5,6].

HFTC results from a relative deficiency or resistance to FGF23. The clinical diagnosis is established based on the presence of tumoural calcinosis, whose symptoms may include periarticular calcinosis (around the hips, shoulders, and elbows) and in the soft tissues of the extremities, as well as in blood vessels and, in some cases, brain tissue. Other features of HFTC include corneal calcification, angioid streaks, inflammation of long bones (diaphysis), excessive bone growth (hyperostosis), and, in some individuals, dental abnormalities (enamel hypoplasia, obliteration of pulp canals and chambers, pulp stones, and bulbous roots)[4–6].

The characteristic laboratory findings include hyperphosphataemia due to inappropriately increased renal tubular reabsorption of phosphorus (TRP), elevated or inappropriately normal 1,25-dihydroxyvitamin D_3 levels, and elevated C-terminal FGF23 fragments[4,7].

HFTC is an autosomal recessive and genetically heterogeneous disorder associated with biallelic pathogenic variants in: (1) the gene encoding *FGF23*; (2) *GALNT3*, which encodes the protein (ppGalNacT3) responsible for FGF23 glycosylation; and potentially (3) *KL*, the gene encoding KLOTHO, a critical co-receptor for FGF23 signalling[8–11]. The proteins encoded by these genes are involved in general phosphate homeostasis. Identification of biallelic pathogenic variants in *FGF23*, *GALNT3*, or *KL* by molecular genetic

 DOI: 10.15557/PiMR.2025.0009

testing confirms the diagnosis, although an acquired autoimmune form of hyperphosphataemic tumoural calcinosis has also been reported[5,6].

The ppGalNacT3 protein, encoded by the *GALNT3* gene, attaches sugar molecules to FGF23 through a process called O-glycosylation, which enables FGF23 to move out of the cell and protects the protein from degradation[6]. Biallelic pathogenic variants in the *GALNT3* gene result in the production of a ppGalNacT3 protein that is presumed to be unable to O-glycosylate FGF23[8]. Consequently, the FGF23 protein undergoes rapid cleavage into biologically inactive N- and C-terminal fragments, leading to reduced circulating levels of intact (active) FGF23. This reduction is due to FGF23 being trapped inside the cell and degraded, rather than being secreted[4,6,9].

In patients with HFTC caused by a *GALNT3* mutation, serum FGF23 levels are elevated when measured with an assay that detects both the carboxy (C)-terminal fragments (cFGF23) and the intact/active molecule (iFGF23). However, when measured using an assay that detects only iFGF23, concentrations are low. This finding suggests that the biological activity of FGF23 depends on the presence of an intact molecule, which is not secreted in patients with the mutation. In these patients, the intact (active) protein is retained within the Golgi complex[12].

These disruptions to FGF23 function lead to increased phosphate absorption by the kidneys. Calcinosis occurs when excess phosphate combines with calcium to form deposits that build up in soft tissues. Although phosphate levels are increased, calcium levels typically remain within the normal range[4,7,9]. Since no causal treatment for HFTC is currently available, management focuses on lowering serum phosphate levels, mainly by limiting their absorption from the gastrointestinal tract. The efficacy of treatment with drugs that increase renal phosphate excretion, such as acetazolamide and probenecid, remains unconfirmed[4]. Additionally, symptomatic pharmacological treatment includes the use of non-steroidal anti-inflammatory drugs, as well as surgical removal of calcifications from soft tissues and joints, with variable clinical outcomes[4].

According to current literature, a mutation in the *GALNT3* gene (2p24.3) leads to low iFGF23 levels, while increasing cFGF23 concentrations[5]. Initially, this imbalance may hinder the diagnostic process of hyperphosphataemia.

The prevalence of HFTC is unknown, but it is considered a rare condition, predominantly diagnosed in individuals of Middle Eastern and African origin[7,8]. An interesting point is that NC (the first abnormality in this patient's diagnostic work-up) may play a role both in the course of hypophosphataemic rickets and HFTC. However, according to the literature, it is an extremely rare finding in the latter condition[5,13].

CONCLUSIONS

1. The identification of NC with persistently (even if only mildly) elevated phosphate concentrations, normal 25-hydroxyvitamin D_3 and PTH levels, and normal or marginally decreased eGFR levels should prompt the measurement of iFGF23 concentration and genetic testing for HFTC.
2. When conducting- laboratory diagnostics, it is important to acknowledge the limitations of the assays used when measuring serum FGF23 concentrations, as some do not detect intact/active molecules (iFGF23), which may disrupt and delay the patient's diagnostic process.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: MM, MB. Collection, recording and/or compilation of data: MM, MB, FE, BBB. Analysis and interpretation of data: MM, MB, FE, EJW, BBB. Writing of manuscript: MM, MB, EJW. Critical review of manuscript: MM, MB, DD, BBB. Final approval of manuscript: MM, MB, FE, EJW, DD, BBB.

References

1. Al-Murrani B, Cosgrove DO, Svensson WE et al.: Echogenic rings – an ultrasound sign of early nephrocalcinosis. Clin Radiol 1991; 44: 49–51.
2. Oliveira B, Kleta R, Bockenhauer D et al.: Genetic, pathophysiological, and clinical aspects of nephrocalcinosis. Am J Physiol Renal Physiol 2016; 311: F1243–F1252.
3. Mahendra A, Nirendra R, Abhijeet K et al.: Nephrocalcinosis – a gateway to the diagnosis. Indian J Nephrol 2021; 31: 562–565.
4. Ramnitz MS, Gafni RI, Collins MT: Hyperphosphatemic familial tumoral calcinosis. 2018. In: Adam MP, Feldman J, Mirzaa GM et al. (eds.): GeneReviews® [Internet]. University of Washington, Seattle 2018.
5. Boyce AM, Lee AE, Roszko KL et al.: Hyperphosphatemic tumoral calcinosis: pathogenesis, clinical presentation, and challenges in management. Front Endocrinol (Lausanne) 2020; 11: 293.
6. Carmichael KD, Bynum JA, Evans EB: Familial tumoral calcinosis: a forty-year follow-up on one family. J Bone Joint Surg Am 2009; 91: 664–671.
7. Sprecher E: Familial tumoral calcinosis: from characterization of a rare phenotype to the pathogenesis of ectopic calcification. J Invest Dermatol 2010; 130: 652–660.
8. Chefetz I, Sprecher E: Familial tumoral calcinosis and the role of O-glycosylation in the maintenance of phosphate homeostasis. Biochim Biophys Acta 2009; 1792: 847–852.
9. Farrow EG, Imel EA, White KE: Miscellaneous non-inflammatory musculoskeletal conditions. Hyperphosphatemic familial tumoral calcinosis (FGF23, GALNT3 and αKlotho). Best Pract Res Clin Rheumatol 2011; 25: 735–747.
10. Ichikawa S, Baujat G, Seyahi A et al.: Clinical variability of familial tumoral calcinosis caused by novel *GALNT3* mutations. Am J Med Genet A 2010; 152A: 896–903.
11. Yancovitch A, Hershkovitz D, Indelman M et al.: Novel mutations in *GALNT3* causing hyperphosphatemic familial tumoral calcinosis. J Bone Miner Metab 2011; 29: 621–625.
12. Benet-Pagès A, Orlik P, Strom TM et al.: An FGF23 missense mutation causes familial tumoral calcinosis with hyperphosphatemia. Hum Mol Genet 2005; 14: 385–390.
13. Haffner D, Emma F, Eastwood DM et al.: Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia. Nat Rev Nephrol 2019; 15: 435–455.

DOI: 10.15557/PiMR.2025.0009