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CLINICAL INSIGHTS

# A case of diffuse kidney hyperechogenicity in early childhood associated with biallelic *PKHD1* variants

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## Abstract

**Background** Nephrocalcinosis (NC) is characterized by an excessive accumulation of calcium deposits in the kidneys. In children, it is often incidentally discovered with an uncertain prognosis.

**Case-diagnosis/treatment** A 3-month-old girl suspected to have a milk protein allergy underwent an ultrasound that revealed increased echogenicity in the kidney pyramids suggestive of medullary NC. At the age of 18 months, imaging findings revealed not only hyperechogenicity in the medulla but also in the cortex. Over the course of a long follow-up, her kidneys maintained size within the upper limits but showed an increase by age 7. Genetic analysis identified *PKHD1* variants, which required structural predictive tools to guide clinical diagnosis. Until the age of 7, her kidney function has remained intact; however, her prognosis is uncertain.

**Conclusions** NC in newborns is a rare condition, but its incidence is rising. Recurrent urinary infections or kidney stones may lead to kidney failure. A proactive approach in sporadic NC enables an early diagnosis to orientate clinical supervision and facilitates counseling to support family planning decisions.

**Keywords** Nephrocalcinosis · Mimicking phenotype · Medullary sponge kidney · *PKHD1* · Genetic counseling

## Case report

A full-term baby girl, born to non-consanguineous parents after an uneventful pregnancy, was suspected of having cow's milk protein allergy due to colic and diarrhea with mucus. At 3 months of age, her abdominal ultrasound (US) revealed normally sized and shaped kidneys. However, there was an increased echogenicity within the kidney pyramids, raising suspicions of nephrocalcinosis (NC), with no signs of urinary tract dilation. At 9 months of age, she experienced a urinary tract infection caused by *Klebsiella pneumoniae*, which prompted periodic US examinations.

At the age of 18 months, images not only revealed hyperechogenic foci in the kidney pyramids but also showed diffuse echogenicity in the cortex. These findings persisted until the last US examination conducted at the age of 7 years. Throughout this period, no hepatic anomalies were identified, and the bladder maintained a normal appearance with thin walls and anechoic content.

Regarding the size of the kidneys, monitoring took place from 18 months to 7 years of age. Throughout this period, annual examinations indicated that her kidneys remained within the normal range but at the upper limit. Notably, during her last visit at 7 years old, kidney enlargement was observed, evidenced by sizes of 10 cm for the right kidney and 9.9 cm for the left kidney, surpassing the 95th percentile threshold (9.35 cm) according to pediatric radiology normal measurements.

Laboratory testing at the age of 6 revealed biochemical blood parameters within the normal range, except for marginally altered phosphate and bicarbonate levels (refer to Supplementary Table 1). The urine analysis indicated that

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citrate, oxalate, and uric acid were within normal ranges, while calcium approached the upper limit in relation to creatinine levels for her age (Supplementary Table 2). At the age of 7, a urine analysis was conducted, revealing a calcium-to-creatinine ratio of 0.17, discarding hypercalciuria.

At the age of 6, the kidneys exhibited normal perfusion, size, shape, and positioning; however, increased echogenicity persisted in the cortex, and small hyperechogenic foci remained in the pyramids (Fig. 1). Due to the persistent phenotype, the nephrologist recommended a panel involving 401 genes associated with nephropathies. Surprisingly, the analysis revealed two missense variants in *PKHD1*: c.1829A > G (p.Y610C) and c.10444C > T (p.R3482C) inherited from the father and the mother, respectively. Both parents (ages 34 and 35) underwent echographic examinations and laboratory tests, which were all normal. The preliminary analysis classified Y610C as a variant of uncertain significance (VUS) and R3482C as pathogenic. The mCSM program (https://biosig.lab.uq.edu.au/mcsm/) predicted Y610C and R3482C variants as destabilizing with DDG equal to − 2.078

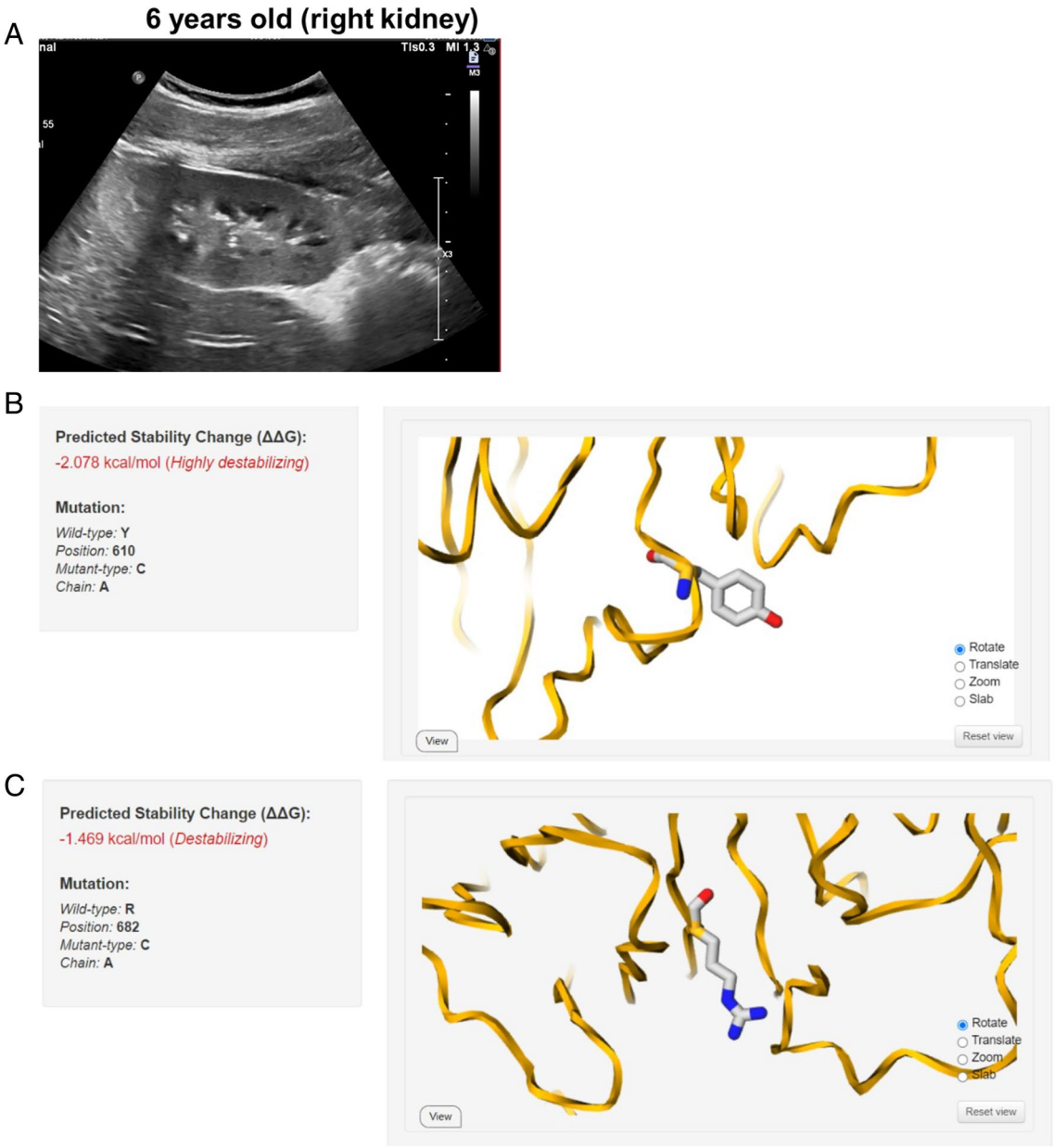


**Fig. 1** **A** Echography: image illustrating the patient's right kidney at the age of 6 years, observing normal size, shape, and positioning. Small (< 3 mm) well-defined hyperechogenic foci in the renal pyramids, suggestive of medullary nephrocalcinosis, and an increased echogenicity were observed in the cortex. (**B**) mCSM energy-based prediction of the PKHD1 Y610C variant. (**C**) mCSM energy-based prediction of the PKHD1 R3482C variant

and – 1.469 kcal/mol, respectively (Fig. 1B, C). Missense3D predicted no structural damage for both variants (Supplemental Fig. 1A–D).

Based on the findings, genetic counseling was offered to the parents considering that the case involved the birth of their first child. The patient is currently 7.5 years old and is under the supervision of a pediatric nephrologist. She undergoes regular blood and urine analyses and is not receiving any pharmacological interventions due to the absence of symptoms.

## Discussion

NC in newborns and infants is generally regarded as a rare condition, but its incidence is rising among preterm infants or those with specific metabolic conditions, such as hypercalciuria and hypocitraturia, which increase the susceptibility to the development of calcium stones in the kidney [1]. Although the urinary calcium-to-creatinine ratio observed in our patient was at the upper limit at the age of 6, it normalized at the age of 7. Continuous monitoring is necessary due to its potential to trigger the formation of kidney stones. It is crucial to rule out other potential disorders through comprehensive analyses. In our patient, an increased medullary echogenicity was incidentally discovered, leading to an early NC diagnosis, preserving kidney function up to the age of 7. It is essential to remember that what may appear as NC on imaging could indicate genuine histopathological NC or other conditions mimicking NC. Depending on the clinical context, the following conditions should be considered: nephrolithiasis, medullary sponge kidney (MSK), hyperparathyroidism, distal renal tubular acidosis, primary hyperoxaluria, Bartter syndrome, vitamin D intoxication, infection-related calcifications, among others. Given that genetic testing is increasingly becoming part of the routine care in nephrology, the identification of a pediatric case with multiple suspected etiologies could potentially be resolved through genetic analysis during early stages.

MSK (ORPHA: 1309) is characterized by dilated malformation of the medullary collecting ducts between 1 and 7 mm in size. Typically, MSK is diagnosed in adulthood and is considered benign, with an undetermined prevalence in the general population. However, recent reports have highlighted two adult cases with MSK features who unexpectedly developed progressive kidney disease without liver abnormalities. Whole-exome sequencing revealed that both individuals carried compound heterozygous *PKHD1* variants predicted to have a missense and a truncating effect. The variants found in these MSK cases had previously been independently reported in autosomal recessive polycystic kidney disease (ARPKD) patients [2].

PKHD1 is a large transmembrane protein involved in the cell differentiation within kidney tubules and bile ducts. Biallelic *PKHD1* variants are known to cause ARPKD, manifesting as a severe childhood disorder characterized by enlarged kidneys and liver involvement, often resulting in high mortality rates, especially in those carrying at least one PKHD1-truncating variant. It has been estimated that approximately 1/70 individuals in the general population carry a single-altered *PKHD1* allele. A study involving 110 obligate *PKHD1* heterozygote carriers revealed bilateral medullary hyperechogenicity in six women, without hypercalciuria or kidney function impairment [3]. These observations suggest that monoallelic *PKHD1* variants may underlie MSK in certain cases. Furthermore, a mouse model with a truncating heterozygous *Pkhd1* variant developed cystic liver and late-onset MSK-like features [4]. Of note, none of these reports describes an increased echogenicity at the cortex, and the explanation of this finding in our patient remains unknown but deserves monitoring.

On the basis of the close and long follow-up, our patient supports the hypothesis that biallelic *PKHD1* variants may lead to a phenotype beyond ARPKD, resembling MSK in early childhood. Both variants, Y610C and R3482C, are situated in highly conserved extracellular domains. They have been reported in population databases, with a frequency of 0.008% (Y610C) and 0.02% (R3482C). R3482C has been described in individuals with ARPKD-related conditions. Additionally, mCSM predicted significant stability changes for these variants, which were inherited from her parents, who did not exhibit echographically relevant findings. Consequently, it appears more likely that the combined presence of *PKHD1* variants is associated with the observed MSK phenotype.

At 7 years of age, the patient exhibited no relevant symptoms, and her estimated glomerular filtration rate was 129 ml/min/1.73 $m^2$. Generally, treatment or intervention is directed to the underlying cause of NC and associated risk factors. Our patient experienced early-onset kidney alterations and preserved kidney function until the age of 7, excluding pharmacological measures so far. However, NC is a condition that is rarely reversible and may lead to kidney failure in 10% of patients if recurrent urinary infections or kidney stones occur [5].

## Conclusion

Medullary NC can result from various etiologies, including MSK associated with *PKHD1*. When medullary NC is diagnosed early in life, it often suggests an underlying inherited condition that may progress to kidney failure. While a family history of affected relatives is frequently absent, physicians need to consider genetic analysis in sporadic NC during

childhood to enable early diagnosis and regular monitoring, to anticipate progression and to provide genetic counseling.

## Summary

### What is new?

This case report unveils a phenotype beyond ARPKD associated with *PKHD1* variants, highlighting the need for genetic analysis in atypical phenotypes in children due to the risk of progressive kidney disease.

- Biallelic *PKHD1* variants may lead to a kidney phenotype beyond ARPKD, resembling MSK in early childhood with an uncertain prognosis.
- Interpretation of missense variants can be supported by web-based stability predictive tools.
- In asymptomatic MSK patients, regular clinical supervision with biochemical analyses should be performed to evaluate pharmacological interventions.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s00467-024-06348-y.

**Data availability** The data supporting the findings of this clinical case are available upon justified request. For inquiries regarding more information, interested parties may contact Paola Krall at paola.krall@uchile.cl. We are committed to transparency and facilitating further research endeavors.

## Declarations

**Consent for publication** The patient's legal guardians, represented by her parents, have provided consent to publish the clinical and genetic data.

**Conflict of interest** The authors declare no competing interests.

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