Heliyon 10 (2024) e28985

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Case report

Renal cell carcinoma in an adult-onset ESRD patient with nephronophthisis harboring *NPHP3* deletion: A case report

Zuo-Lin Li, Feng-Mei Wang, Yi Wen, Hai-Feng Ni, Xiao-Liang Zhang **, Bin Wang *

Department of Nephrology, Zhong Da Hospital, Southeast University School of Medicine, Nanjing, Jiangsu, China

ARTICLE INFO

Keywords:
Nephronophthisis
Renal cysts
Renal cell carcinoma
Adult-onset ESRD
NPHP3 gene

ABSTRACT

Background: Nephronophthisis (NPHP) is a rare autosomal recessive inherited tubulointerstitial nephropathy, the most prevalent genetic cause of end-stage renal disease (ESRD) in children. Convincing evidence indicated that the overall prevalence of NPHP in adult-onset ESRD is very likely to be an underestimation. Therefore, understanding the genetic background and clinicopathologic features of adult-onset NPHP is warranted.

Case presentation: we reported one intriguing case with concurrent *NPHP3* c.2694-2_2694-1delAG (splicing) variant and c.1082C > G (p.S361C) variant. A 48-year-old male was admitted to our hospital, complained about renal dysfunction for 10 years, and found right renal space-occupying lesion for 1 week. One of the most interesting clinical features is adult-onset ESRD, which differs from previous cases. Another discovery of this study is that the NPHP harboring *NPHP3* deletion may be associated with clear cell renal cell carcinoma.

Conclusion: In conclusion, we report two mutations in the *NPHP3* gene that cause NPHP with adult-onset ESRD and renal clear cell carcinoma in a Chinese family, enriching the clinical features of NPHP.

1. Introduction

Nephronophthisis (NPHP), a rare autosomal recessive inherited tubulointerstitial nephropathy (incidence of 0.1–0.2 per 10,000 live births), represents the most prevalent genetic cause of end-stage renal disease (ESRD) in children [1]. In the past few years, causal mutations in more than 25 genes (including *NPHP3*) have been identified in understanding the molecular mechanisms [2]. NPHP is characterized by clinical and genetic heterogeneity, especially for patients carrying NPHP3 mutations [3]. Based on ESRD onset age, NPHP divides into infantile, juvenile, and adolescent forms.

Generally, NPHP starts around mid-childhood with nonspecific and mild symptoms, which always progresses to ESRD in general around age 13 years old [4]. Ultrasonography is one of the most useful imaging techniques. Typical ultrasound features include echogenicity with loss of corticomedullary differentiation and corticomedullary cysts. Cortical microcysts and tubulointerstitial abnormalities characterize the histopathology of NPHP. Of note, due to the nonspecific and variable features, genetic analysis is the vital method to diagnose NPHP with certainty [5].

Although the incidence of NPHP is considered to be rare in adults, convincing evidence indicated that the overall prevalence of NPHP in adult-onset ESRD is very likely to be an underestimation [6,7]. Understanding the genetic background and clinicopathologic

* Corresponding author
** Corresponding author.
E-mail addresses: tonyxlz2020@163.com (X.-L. Zhang), wangbinhewei@126.com (B. Wang).

https://doi.org/10.1016/j.heliyon.2024.e28985
Received 14 August 2023; Received in revised form 12 March 2024; Accepted 27 March 2024
Available online 29 March 2024

features of adult-onset NPHP is warranted. In the current report, we report two novel mutations in the *NPHP3* gene that cause adult NPHP with renal clear cell carcinoma and late-onset ESRD in a Chinese family.

2. Case description

A 48-year-old male was admitted to our hospital on September 8, 2021, complained about renal dysfunction for 10 years and finding right renal space-occupying lesion for 1 week. He presented no foamy urine, gross hematuria, or low back pain. He had a past medical history of hypertension and multiple renal cysts for ten years. His blood pressure was 130/90 mmHg, without further abnormal findings in physical examination. He also had no hearing loss or ocular abnormalities.

Regarding the family history, the 18-year-old son of the proband has presented with renal cysts. The elder brother of the proband has a history of renal dysfunction and renal cysts and died of ESRD in his 40th year of age. The son of his elder brother has had proteinuria and mild renal dysfunction. Meanwhile, his maternal uncle also died of renal dysfunction at the age of 55. And the son of his maternal uncle also presented with renal dysfunction and renal cysts. Furthermore, his grandmother and grandmother's two brothers all had kidney diseases and died (Fig. 1).

Biochemistry analysis revealed serum total protein 60.5 g/L, albumin 36.4 g/L, and creatinine 751 μmol/L (57–111 μmol/L). By urinalysis, proteinuria was presented (1.994 g/24h), and red blood cells were 20/HPF. Serology for liver anomalies, cardiac and gastrointestinal defects, tumor markers, anti-nuclear, anti-double-stranded DNA, anti-phospholipase A2 receptor antibodies, anti-glomerular basement membrane, and anti-neutrophilic cytoplasmic antibodies were also negative. Meanwhile, there was no serological evidence of hepatitis B and C or HIV infections. Abdominal enhanced computed tomography scanning and renal artery CTA revealed scattered cysts of both kidneys and right renal space-occupying lesion (3.0 cm × 2.2 cm) with rich blood supply, and the possibility of renal clear cell carcinoma is considered (Fig. 2a and b). Ultrasound scans showed that the right kidney is 10.54 cm × 5.65 cm, and the left kidney size is 9.9 cm × 4.9 cm. Both kidneys lost corticomedullary differentiation while showing multiple cortical microcysts. We observed an echogenicity of cystic solid mass (3.16 cm × 2.95 cm) and blood flow signal inside. Echocardiography and ultrasound examination of liver, pancreas, and spleen have no abnormal findings.

A right nephrectomy was performed duo to the potential malignant space-occupying lesions. Grossly, the tumor was located in the lower pole of the right kidney and exhibited a 2.5 cm × 2 cm × 2.7 cm unclear boundary spheroid mass with golden yellow, tender texture, no bleeding and necrosis, and no satellite nodule. The section of other renal tissues showed cystic change, with a diameter of 0.2 cm–0.6 cm. The inner wall was smooth with 0.1 cm thickness, and there was no content (Fig. 3a). Pathological diagnosis of clear cell renal cell carcinoma G2I (T1a, N0, M0) was made (Fig. 3b). Histological findings of noncancerous tissues showed mild glomerular mesangial hyperplasia, segmental collapse of the glomerular capillary loops, moderate renal tubules atrophy, thickened tubular basement membrane, significantly cystic dilated of some tubules, and diffuse renal interstitial fibrosis with lymphocyte infiltration (Fig. 3c).

The Next-generation sequencing was performed using proband blood samples. The result demonstrated *NPHP3* c.26 94-2_2694-1delAG (splicing) variant (located in the intron19) and *NPHP3* c.1082C > G (p.S361C) variant (located in the exon6). In silico analysis, the pathogenic nature of the c.2694-2_2694-1delAG (splicing) genetic variant in *NPHP3* gene. The American College of Medical Genetics and Genomics (ACMG) also predicted the variant as "pathogenic", which has an impact on splice site changes and protein features might be affected. Additionally, as for c.1082C > G (p.S361C) variant, this novel mutation was predicted to be "uncertain" using the ACMG analysis. Thus, a diagnosis of NPHP was made.

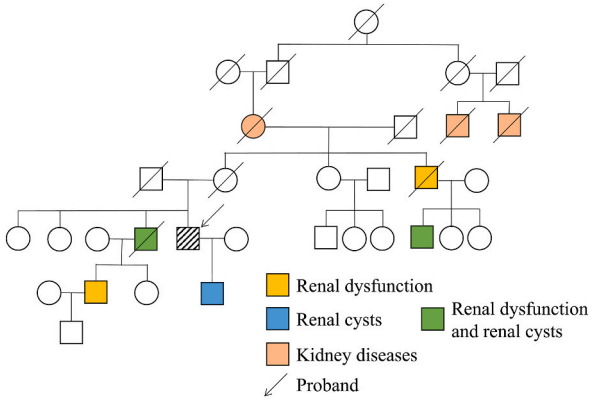

Fig. 1. The pedigrees of the family. Orange indicates the patients with renal dysfunction; Green indicates the patients with renal dysfunction and renal cysts; Blue indicates the patients with renal cysts; Pink indicates the patients with kidney diseases. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

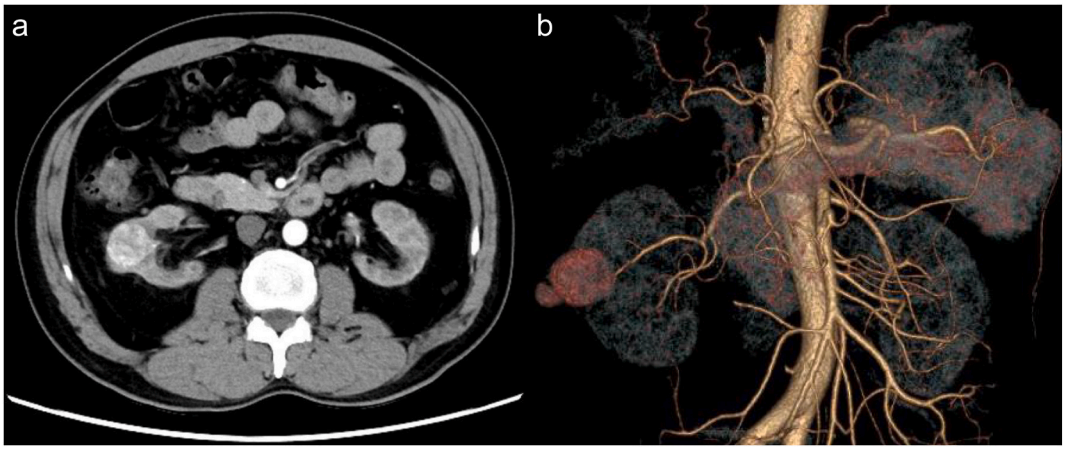

Fig. 2. Imaging finding. a). Contrast-enhanced computed tomography scan showing the renal mass. b). Renal artery CTA revealed scattered cysts of both kidneys and right renal space occupying lesion (3.0 cm × 2.2 cm) with rich blood supply.

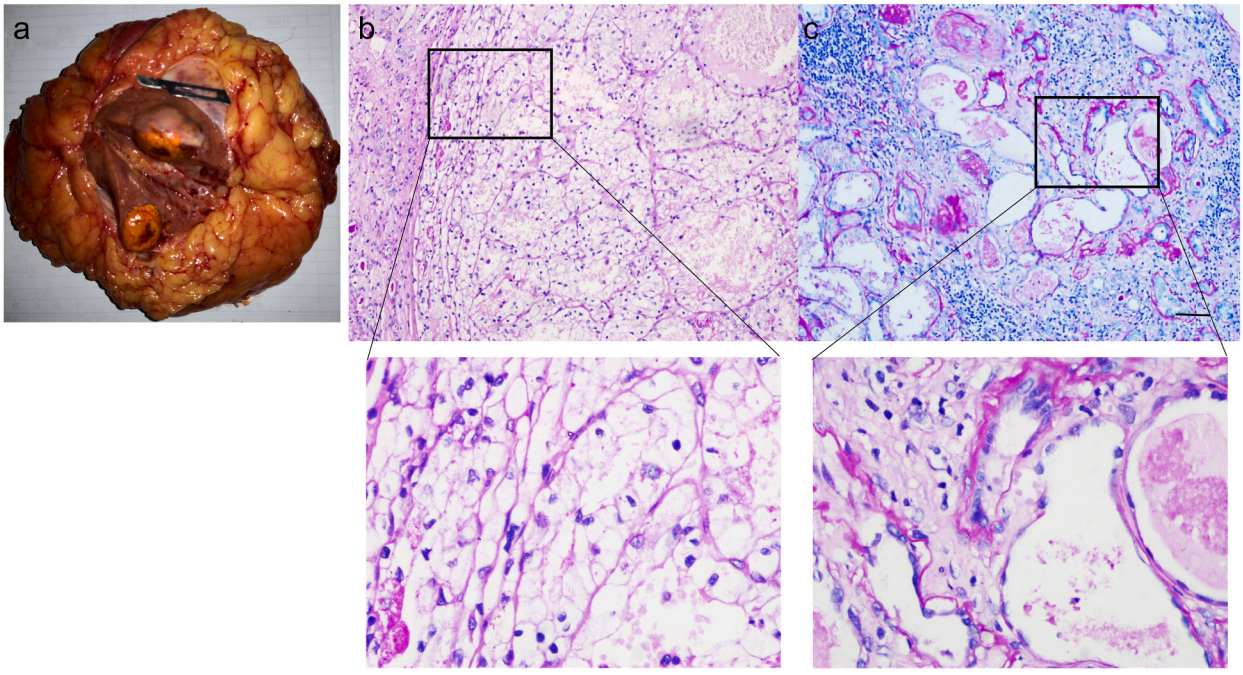

Fig. 3. Kidney specimen findings. a). Gross pathology of the right kidney; b). Light microscopy demonstrating the clear cell renal cell carcinoma (periodic acid-Schiff staining); c). Histological findings of noncancerous tissues showed mild glomerular mesangial hyperplasia, segmental collapse of the glomerular capillary loops, moderate renal tubules atrophy, thickened tubular basement membrane, significantly cystic dilated of some tubules, and diffuse renal interstitial fibrosis with lymphocyte infiltration (periodic acid-Schiff staining).

3. Discussion

NPHP is an autosomal recessive genetic disorder with high genetic, phenotypic, and clinical heterogeneity. Currently, the NPHP is divided into 3 clinical subtypes based on the median age of onset of ESRD: infant type (approximately 5 years old), juvenile type (approximately 13–14 years old), and adolescent type (approximately 19 years old). Recently, a genome-wide association study using adult renal transplant recipients from five cohorts indicated that the median age at ESRD onset was 30 years old [6], suggesting that the overall prevalence of NPHP in adult-onset ESRD is very likely to be an underestimation. Although, in the literature, the oldest NPHP patient with ESRD onset is 61 years old, adult-onset patients have always been described with NPHP1 mutations (the most common *NPHP* mutation) [6]. Therefore, to our knowledge, we reported the oldest patient with *NPHP3* variant. Recently, Hudson et al. [8] reported that a patient with *NPHP4* variants has chronic kidney disease stage 4 at 39 years old, identifying *NPHP4* as an appreciable

genetic cause for adult-diagnosed nonsyndromic NPHP. Although the genotype-phenotype correlation in patients with NPHP is poorly understood [9], NPHP is no longer considered a pediatric kidney disease.

Another discovery of this study is that the mutation of *NPHP3* gene may be associated with tumor. As we know, nephrocystins, encoded by *NPHP* genes, are essential for maintaining ciliary function [10]. Mutations in *NPHP* genes result in ciliopathy. Recently, Lee et al. [11] demonstrated that cancer cell viability is regulated by NPHP3-mediated primary cilium formation, suggesting a close correlation between NPHP3 and tumor. Although the role of primary cilia in cancer is still debated, the effects of the primary cilium on tumor microenvironments and different cancers have been observed, highlighting novel possibilities for therapeutic targets in cancer that have been systemically reviewed and summarized [12]. However, there is no clinical literature on NPHP gene mutation leading to tumorigenesis.

Previously, Olbrich et al. [13] reported hypomorphic mutations in *NPHP3* to be responsible for the adolescent type of NPHP (MIM 604387). Mutations of *NPHP3* result in a broad clinical spectrum of early embryonic patterning defects comprising situs inversus, polydactyly, central nervous system malformations, structural heart defects, preauricular fistulas, and a wide range of renal and urinary tract anomalies. *NPHP3* mutations can result in isolated NPHP, Senior-Loken syndrome, renal-hepatic-pancreatic dysplasia, Meckel-Gruber-like syndrome, and embryonic lethality [14]. In addition, other potential mechanisms may also be involved in the NPHP mutation-mediated tumorigenesis. The expression of phosphorylated p38 mitogen-activated protein kinase (p-p38 MAPK) increases in an NPHP2 mouse model [15]. It is well-known that p38 MAPK pathways represent ubiquitous signal transduction pathways that play a vital role in cancer [16].

Mutation of c.2694-2_2694-1delAG (splicing) is a pathogenic acceptor splice site mutation (located in the intron19) that results in gene dysfunction and contributes to a specific clinical phenotype, which has been reported previously [3,17,18]. However, the c.1082C > G (p.S361C) (located in the exon6) mutation has not been reported, and the clinical significance of the mutation is "uncertain" according to ACMG guidelines. In this case, according to the evidence of the detailed family history and pedigree, pathological findings of the kidney, and the results of next-generation sequencing, the proband seems to present with a compound heterozygosity of two mutations, c.2694-2_2694-1delAG (splicing) and c.1082C > G (p.S361C), which is different from previously reported cases. Of note, the heterozygous variants may also cause different clinical phenotypes.

As for the differential diagnosis of this case, von Hippel-Lindau syndrome, a relatively common cystic kidney disease and always accompanied by renal clear cell carcinoma [19], needs to be considered. Considering the high heterogeneity of NPHP, it is important to discriminate NPHP from other tubulointerstitial diseases or cystic kidney disease. Genetic analysis is essential for definitive diagnosis, providing evidence for clarifying the exact mechanisms and new insights into the molecular landscape for precision medicine.

In summary, a "pathogenic" mutation of c.2694-2_2694-1delAG (splicing) and an "uncertain" mutation of c.1082C > G (p.S361C) in *NPHP3* were identified causing adult NPHP in a Chinese family. Accompanying renal cell carcinoma may be one of the features of patients with NPHP3. Further, the prevalence of NPHP in adult-onset ESRD is very likely to be an underestimation, and differential diagnosis of NPHP is critical, even in cases with tumor. This case also helps to understand the genotype-phenotype correlation in patients with NPHP.

Ethical approval

Ethical approval was obtained from the Human Research Ethics Committee of Southeast University.

Informed consent statement

Informed consent was obtained from the proband.

Data availability statement

The data presented in this study are available on request from the corresponding author.

Funding

This work was supported by grants from the National Natural Science Foundation of China (82000648, 82070735, 82241047); the Natural Science Foundation of Jiangsu Province (BK20200363), Jiangsu Province Key Research and Development Program-Social Development (BE2021737), Nanjing Health and Scientific Technology Development Program (YKK20237, YKK21268), the Innovative and Entrepreneurial Talent (Doctor) of Jiangsu Province, and the Fundamental Research Funds for the Central Universities (2242023K40046).

CRediT authorship contribution statement

Zuo-Lin Li: Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization, Writing – original draft, Writing – review & editing. **Feng-Mei Wang:** Writing – review & editing, Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation. **Yi Wen:** Writing – review & editing. **Hai-Feng Ni:** Writing – review & editing, Validation, Methodology, Investigation, Data curation, Conceptualization. **Xiao-Liang Zhang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Funding

acquisition, Conceptualization. **Bin Wang:** Writing – review & editing, Writing – original draft, Visualization, Validation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors are grateful to the family for their cooperation and permission to publish the data and photographs.

References

[1] M. Levy, J. Feingold, Estimating prevalence in single-gene kidney diseases progressing to renal failure, Kidney Int. 58 (3) (2000) 925–943.
[2] F.L. Luo, Y.H. Tao, Nephronophthisis: a review of genotype-phenotype correlation, Nephrology 23 (10) (2018) 904–911.
[3] X. Tang, C. Liu, X. Liu, J. Chen, X. Fan, J. Liu, et al., Phenotype and genotype spectra of a Chinese cohort with nephronophthisis-related ciliopathy, J. Med. Genet. 59 (2) (2022) 147–154.
[4] J. König, B. Kranz, S. König, K.P. Schlingmann, A. Titieni, B. Tönshoff, et al., Phenotypic spectrum of children with nephronophthisis and related ciliopathies, Clin. J. Am. Soc. Nephrol. 12 (12) (2017) 1974–1983.
[5] N. Sakakibara, K. Nozu, T. Yamamura, T. Horinouchi, C. Nagano, M.J. Ye, et al., Comprehensive genetic analysis using next-generation sequencing for the diagnosis of nephronophthisis-related ciliopathies in the Japanese population, J. Hum. Genet. 67 (7) (2022) 427–440.
[6] R. Snoek, J. van Setten, B.J. Keating, A.K. Israni, P.A. Jacobson, W.S. Oetting, et al., NPHP1 (Nephrocystin-1) gene deletions cause adult-onset ESRD, J. Am. Soc. Nephrol. 29 (6) (2018) 1772–1779.
[7] M. Akira, H. Suzuki, A. Ikeda, M. Iwasaki, D. Honda, H. Takahara, et al., Atypical histological abnormalities in an adult patient with nephronophthisis harboring NPHP1 deletion: a case report, BMC Nephrol. 22 (1) (2021) 261.
[8] R. Hudson, C. Patel, C.M. Hawley, S. O'Shea, P. Snelling, G. Ho, et al., Adult-diagnosed nonsyndromic nephronophthisis in Australian families caused by biallelic NPHP4 variants, Am. J. Kidney Dis. 76 (2) (2020) 282–287.
[9] T. Fujimaru, K. Kawanishi, T. Mori, E. Mishima, A. Sekine, M. Chiga, et al., Genetic background and clinicopathologic features of adult-onset nephronophthisis, Kidney Int Rep 6 (5) (2021) 1346–1354.
[10] S. Gupta, J.E. Ozimek-Kulik, J.K. Phillips, Nephronophthisis-pathobiology and molecular pathogenesis of a rare kidney genetic disease, Genes 12 (11) (2021) 1762.
[11] J.W. Lee, J.Y. Cho, P.X. Thuy, E.Y. Moon, HeLa cervical cancer cells are maintained by nephronophthisis 3-associated primary cilium formation via ROS-induced ERK and HIF-1α activation under serum-deprived normoxic condition, Int. J. Mol. Sci. 23 (23) (2022) 14500.
[12] B. Wang, Z. Liang, P. Liu, Functional aspects of primary cilium in signaling, assembly and microenvironment in cancer, J. Cell. Physiol. 236 (5) (2021) 3207–3219.
[13] H. Olbrich, M. Fliegauf, J. Hoefele, A. Kispert, E. Otto, A. Volz, et al., Mutations in a novel gene, NPHP3, cause adolescent nephronophthisis, tapeto-retinal degeneration and hepatic fibrosis, Nat. Genet. 34 (4) (2003) 455–459.
[14] C. Bergmann, M. Fliegauf, N.O. Brüchle, V. Frank, H. Olbrich, J. Kirschner, et al., Loss of nephrocystin-3 function can cause embryonic lethality, Meckel-Gruber-like syndrome, situs inversus, and renal-hepatic-pancreatic dysplasia, Am. J. Hum. Genet. 82 (4) (2008) 959–970.
[15] N. Sugiyama, M. Kohno, T. Yokoyama, Inhibition of the p38 MAPK pathway ameliorates renal fibrosis in an NPHP2 mouse model, Nephrol. Dial. Transplant. 27 (4) (2021) 1351–1358.
[16] L. García-Hernández, M.B. García-Ortega, G. Ruiz-Alcalá, E. Carrillo, J.A. Marchal, M.Á. García, The p38 MAPK components and modulators as biomarkers and molecular targets in cancer, Int. J. Mol. Sci. 23 (1) (2021) 370.
[17] E. Molinari, E. Decker, H. Mabillard, J. Tellez, S. Srivastava, S. Raman, et al., Human urine-derived renal epithelial cells provide insights into kidney-specific alternate splicing variants, Eur. J. Hum. Genet. 26 (12) (2018) 1791–1796.
[18] T. Fiskerstrand, G. Houge, S. Sund, D. Scheie, S. Leh, H. Boman, et al., Identification of a gene for renal-hepatic-pancreatic dysplasia by microarray-based homozygosity mapping, J. Mol. Diagn. 12 (1) (2010) 125–131.
[19] M.A. Perazella, R. Dreicer, M.H. Rosner, Renal cell carcinoma for the nephrologist, Kidney Int. 94 (3) (2018) 471–483.