Adult Nephronophthisis – An Overlooked Cause of Chronic Kidney Disease: Two Case Reports and Literature Review

Vitória Paes de Faria[*#1], *Joana Dias*[#1]; *Claúdia Falcão Reis*; *Sofia Santos*[4] *Ana Marta Gomes*[1,5,6,7]

[#]Equal contributions

1. Nephrology Department, Unidade Local de Saúde Gaia/Espinho, Vila Nova de Gaia, Portugal
2. Medical Genetics Department, Unidade Local de Saúde de Santo António, Porto, Portugal
3. ERKnet – European Rare Kidney Reference Center (ERKNet), Unidade Local de Saúde de Santo António, Porto, Portugal
4. Nephrology Department, Hospital das Forças Armadas – Pólo Porto, Porto, Portugal
5. Centro Académico Clínico Egas Moniz Health Allianace Campus Universitário Santiago, Aveiro, Portugal
6. ITR- Laboratory for Integrative and Translational Research in Population Health, Porto, Portugal.
7. Unit for Multidisciplinary Research in Biomedicine, School of Medicine and Biomedical Sciences, University of Porto, Porto, Portugal.

https://doi.org/10.71749/pkj.136

Abstract

Nephronophthisis is the most common monogenic cause of chronic kidney failure within the first three decades of life. Adult-onset disease remains largely underdiagnosed because of its subtle and nonspecific clinical presentation.

We report two families with adult-onset chronic kidney disease (CKD), of undetermined aetiology who were subsequently diagnosed with a homozygous pathogenic variant in *TTC21B*, c.626C>T (p.Pro209Leu) associated with nephronophthisis type 12. Pathogenic variants in *TTC21B* are associated with heterogenous renal phenotypes, including both tubulointerstitial and glomerular involvement, and are rarely reported in adult patients.

With the increasing availability and comprehensive genetic testing, a paradigm shift has occurred in the diagnostic approach to CKD of unknown origin in young adults. Our findings suggest that *TTC21B*-nephronophthisis represents and underrecognized cause of end-stage kidney disease, characterized by combined tubulointerstitial fibrosis and focal segmental sclerosis.

These cases underscore the importance of pursuing a definitive etiological diagnosis in young adults with CKD, given the significant implications for prognosis, clinical management and long-term genetic counselling.

Keywords: Adult; Ciliopathies/genetics; Genetic Testing; Kidney Diseases, Cystic/genetics; Kidney Failure, Chronic/genetics

What's Already Known About this Topic?

- Nephronophthisis is the most common genetic cause of CKD in the first 3 decades of life;
- Adult-onset disease nephronophthisis remains widely underdiagnosed

What Does this Study Add?

- We provide rare reports of adult-onset *TTC21B*-nephronophthisis.

Learning Points

- Contrarily to other genes causing nephronophthisis, variants in *TTC21B* may cause both tubulo-interstitial and glomerular phenotype.
- Genetic testing as major role diagnosing CKD of unknown cause in younger patients.
- Perseverance in studying underlying cause of CKD, especially at younger ages, is important for prognostic implications and long-term counselling.

Received: 01/02/2026 **Accepted:** 09/03/2026 **Published Online:** 15/03/2026 **Published:** 16/03/2026

* **Corresponding Author:** Vitória Paes de Faria | victoria.paesdefaeria@gmail.com | Nephrology Department, Street, s/n, R. Conceição Fernandes, 4434-502 Vila Nova de Gaia

INTRODUCTION

Nephronophthisis (NPHP) is the most common genetic cause of kidney failure in the first three decades of life. It results from pathogenic variants in genes encoding proteins involved in the structure and function of the primary cilium.[1] Although increasingly recognized as a monogenic cause of chronic kidney disease (CKD) in adults, NPHP remains widely underdiagnosed due to its subtle, insidious clinical presentation and lack of specific early findings. Here, we report two cases of adult-onset CKD secondary to n *TTC21B*-nephronophthisis, traditionally described as nephronophthisis type 12, highlighting their clinical features and emphasizing key diagnostic clues that may facilitate earlier recognition.

CASE REPORTS

Case 1

A 44-year-old Caucasian Portuguese male (Figs. 1 and 2, patient 1a) with a past medical history of hypertension, dyslipidaemia, and active smoking was referred to the nephrology outpatient clinic for evaluation of CKD of undetermined aetiology, initially diagnosed at the age of 36. At presentation, he was asymptomatic, with blood pressure of 140/90 mmHg. Laboratory evaluation revealed a serum creatinine (sCr) level of 1.5 mg/dL (estimated glomerular filtration rate (epi-eGFR) of 61 mL/min/1.73 m²). A 24-hour urine collection showed slightly increased albuminuria (42.5 mg/24 h), a urinary protein-to-creatinine ratio (uP/Cr) of 0.5 g/g, and a normal urinary sediment. Renal ultrasound demonstrated kidneys of normal size, cortical thickness, and echogenicity, with two simple cysts and foci of bilateral microlithiasis.

His blood count was unremarkable, showing only mild polycythaemia with Hb 18.3 mg/dL. The remaining analytical study revealed normal ion levels, mildly elevated cholesterol, normal liver enzymes (including alkaline phosphatase, GGT) and bilirubin, normal serum protein electrophoresis and immunoglobulin levels. Viral HIV, HBV, and HCV makers were negative, as was screening for Fabry disease by measurement of alpha-galactosidase by dried blood spot.

There was no history of protein supplement use, non-steroidal anti-inflammatory drug exposure, or herbal product consumption.

Regarding family history, his brother (patient 1b) was followed at another centre for CKD of unknown aetiology and had been on renal replacement therapy since the age of 51. He had been diagnosed at the age of 48, at the time with sCr of 4 mg/dL (epi-eGFRof 18 mL/min/1.73 m²), proteinuria of 2 g/24h and ultrasonographic features consistent with advanced CKD. A kidney biopsy revealed focal segmental glomerulosclerosis (FSGS) with high-grade interstitial fibrosis and tubular atrophy. His past medical history was notable for early-onset hypertension, biliary cirrhosis of unknown etiology diagnosed at age 30, and recently identified bull's eye maculopathy.

Their parents were consanguineous (third degree cousins) and had no known kidney disease.

During nephrology follow-up, patient 1a maintained stable kidney function, with sCr levels around 1.5 mg/dL and a uP/Cr of approximately 0.5 g/g while receiving antiproteinuric therapy with an angiotensin-converting enzyme inhibitor.

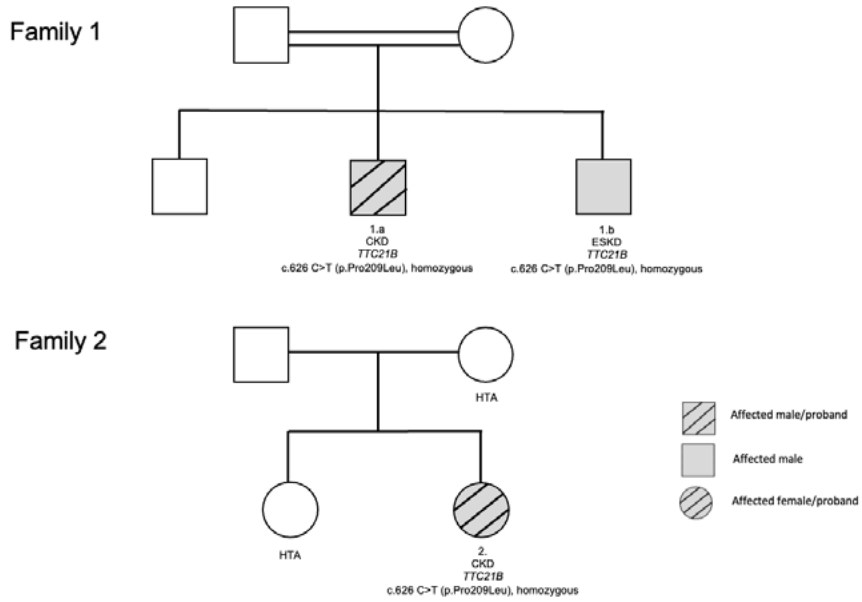

Figure 1. Pedigree of families presented. Family 1 – case 1; family 2 – case 2.

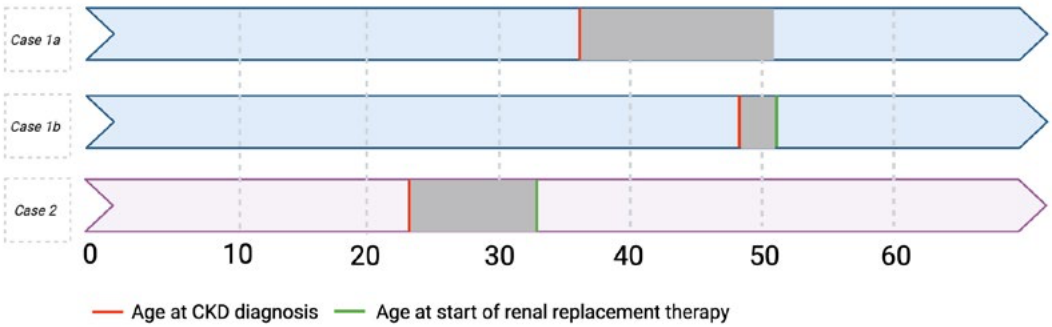

Figure 2. Graphical representation of timeline of kidney events of the patients presented. On the on the horizonal scale the numbers (years) represent the age of patients at each event.

Kidney biopsy was subsequently performed, revealing glomeruli with no evident alterations on light microscopy, tubular atrophy in 5%-10% with a scarce chronic inflammatory infiltrate, and an estimated 5% interstitial fibrosis. Direct immunofluorescence was negative for IgA, IgG, IgM, C3, C1q, and κ and λ light chains. Immunohistochemical staining for κ and λ chains was also negative.

Ultrastructural study by electron microscopy identified diffuse podocyte foot-processes effacement, increased mesangial matrix, and areas of mesangial and glomerular basement membrane sclerosis, without evidence of immune deposits (Fig. 3.)

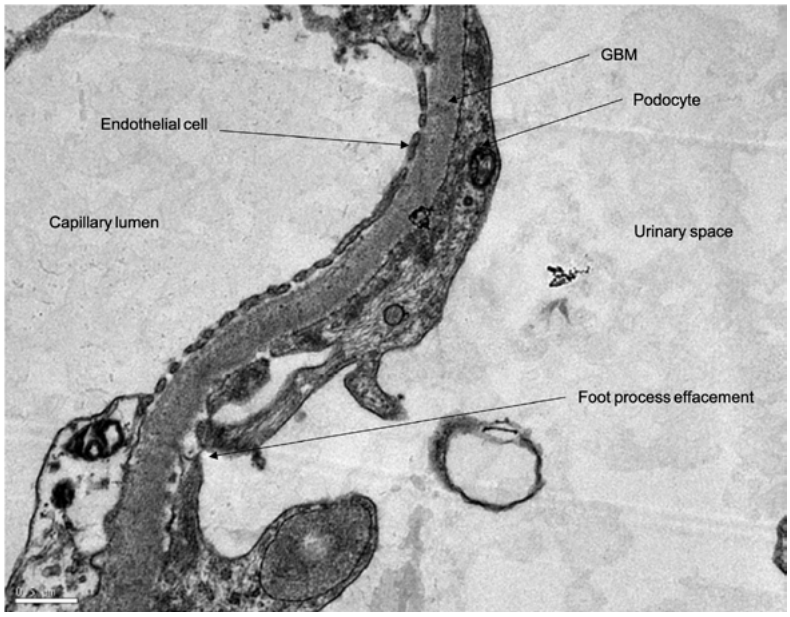

Figure 3. Electron Microscopy of patient 1a. Diffuse fuse process effacement is evident. GBM – glomerular basement membrane.

By the second year of follow-up, he maintained stable GFR, with a uP/Cr of 1.0, without other systemic manifestations. Due to suspicion of hereditary podocytopathy, genetic study was requested using a next-generation sequencing (NGS) panel associated with FSGS. A homozygous pathogenic variant NM_024753.5(*TTC21B*): c.626C>T (p.Pro209Leu) was identified leading to the diagnosis of *TTC21B*-NPHP. Other organ involvement was excluded. In light of this finding, targeted genetic testing was offered to his brother, who was found to carry the same homozygous pathogenic variant.

Case 2

A 34-year-old Caucasian Portuguese female (patient 2) with a past medical history of asthma and allergic rhinitis was referred to the nephrology clinic at the age of 23 for evaluation of CKD and hypertension.

At this time, she presented no medical complaints. Her average blood pressure was 140/90 mmHg on 3 different antihypertensive medications. Initial laboratory evaluation revealed a sCr level of 1.2 mg/dL (epi-eGFR of 65 mL/min/1.73 m²). Urinalysis showed an unremarkable urinary sediment and no proteinuria. Renal ultrasound

demonstrated symmetric kidneys measuring 9 cm in length, with preserved cortical thickness and corticomedullary differentiation. Mild pyelocalyceal prominence of the right kidney was noted, without renal cysts or evidence of nephrolithiasis.

Patient 2 had no family history of kidney disease and denied parental consanguinity.

An extensive clinical and laboratory evaluation failed to identify the aetiology of CKD. Complete blood count, serum electrolytes, albumin, protein electrophoresis, and liver enzymes were within normal ranges. Immunological testing, including antinuclear antibodies, was negative.

Secondary causes of hypertension were excluded: normal serum TSH and T4 levels excluding hyperthyroidism, renin and angiotensin levels excluding hyperaldosteronism, plasma free metanephrines and 24-hour urine fractionated catecholamines and metabolites excluding pheochromocytoma. Computed tomography (CT) renal angiography showed no evidence of renovascular hypertension. Renal biopsy was not performed.

Over a 10-year follow-up period, the clinical course was marked by resistant hypertension, eventually requiring six classes of antihypertensive medications, and progressive decline in kidney function.

Five years after initial presentation, at the age of 28, kidney function had declined by nearly 50%, with an sCr of 1.9 mg/dL (epi-eGFR of 36 mL/min/1.73 m²). Low-grade proteinuria (<500 mg/24 h) was detected, while urinary sediment remained unremarkable.

By the age of 32, she reached CKD stage 4. The following year, she presented a hypertensive emergency resulting in a haemorrhagic stroke with no neurological sequelae and acute kidney injury (sCr 12 mg/dL) with partial recovery to a sCr of 6 mg/dL. Workup during this episode revealed normal ECG, chest X-ray, head CT, and fundoscopy. She began kidney replacement therapy shortly after and received live donor transplant from her partner in the following year.

During workup for CKD of unknown aetiology, genetic testing revealed a homozygous pathogenic variant NM_024753.5(*TTC21B*):c.626C>T (p.Pro209Leu), compatible with the diagnosis of *TTC21B*-Nephronophthisis.

DISCUSSION

Nephronophthisis (NPHP) is a ciliopathy classically characterized by impaired urinary concentrating ability, chronic tubulointerstitial nephritis, corticomedullary cyst formation, and progression to end-stage renal disease (ESRD). Based on age at presentation, NPHP is traditionally classified into infantile, juvenile, and adolescent/adult forms. Approximately 80%-90% of individuals do not present any extra-renal phenotype, and both inter and intrafamilial phenotypic heterogeneity have been extensively reported.[1-3]

The *TTC21B* gene (tetratricopeptide repeat domain 21B), located on chromosome 2, encodes a component of the intraflagellar transporter (IFT139), essential for bidirectional protein trafficking within primary cilia. IFT139 is predominantly expressed in distal renal tubules and developing podocytes, but is also involved in maintaining the microtubular network of mature podocytes.[1,4-6]

Biallelic loss-of-function variants of the *TTC21B* gene cause NPHP 12, an autosomal recessive inherited ciliopathy.[7-10] Within the NPHP spectrum, NPHP due to *TTC21B* gene pathogenic variants is quite rare. A total of 45 pathogenic variants in *TTC21B* have been found, of which c.626C>T(p.Pro209Leu) is the most common.[6,9] In a single centre cohort of 834 patients from 694 families with clinically suspected NPHP submitted to genetic testing, biallelic *TTC21B* p.Pro209Leu variant was present in 5%.[3]

Adult-onset NPHP remains exceptionally uncommon. To the best of our knowledge, this report represents only the second description of adult-onset *TTC21B*-NPHP. The first case, reported by Wang D, *et al* – a 33-year-old male, with KD stage 3, tubular proteinuria without extra-renal manifestations or family history of disease, with a pathogenic heterozygous *TTC21B* non-sense mutation of c.264_267dup (p.E90*).[9]

Genes encoding podocyte cytoskeletal proteins are well-established causes of familial focal segmental glomerulosclerosis (FSGS). In contrast, pathogenic variants in ciliary genes expressed in tubular epithelial cells have traditionally been associated with predominant tubulointerstitial injury, without significant glomerular involvement. However, since IFT139 also plays a role in podocyte cytoskeletal regulation, *TTC21B* dysfunction provides a mechanistic link between ciliary defects and podocyte injury, explaining the coexistence of glomerular and tubulointerstitial pathology.[5,9]

Notably, the *TTC21B* c.626C>T (p.Pro209Leu) variant represents the first pathogenic variant in a ciliary gene implicated in the pathogenesis of both NPHP and FSGS. This variant has been identified in families diagnosed with NPHP, FSGS, or overlapping phenotypes.[5,7,10,11] It appears to be mainly found in individuals of Portuguese and North African ancestry.[1,7,10]

The late-onset and isolated renal presentation observed in affected individuals is thought to result from a hypomorphic effect of the c.626C>T (p.Pro209Leu) variant, leading to partial reduction—rather than complete loss—of IFT139 function.[3,5]

This mechanism likely underlies the broad phenotypic spectrum and variable disease severity observed both within and between affected families.[7]

We describe two families with adult-onset CKD due to NPHP 12, initially considered of undetermined aetiology. In case 1, family history of CKD and parental consanguinity suggested a monogenic disease with autosomal recessive inheritance. Because the ultrastructural examination of the renal biopsy indicated podocytopathy, genetic investigation was directed through an NGS panel of genes associated with FSGS, establishing the etiological diagnosis of NPHP associated with the *TTC21B* gene (type 12). The patient

was referred to medical genetics outpatient clinic for better genetic counselling for both himself and his family, including reproductive counselling as safeguarded by Portuguese law.[12] His brother was also re-evaluated considering this diagnosis and other comorbidities presented such as biliary cirrhosis (prior to CKD diagnosis) and bull's eye maculopathy were considered as extra-renal manifestations of the ciliopathy spectrum of disease. In fact, eye involvement represents a predominant extra-renal feature, as reported in this case.[3] Liver fibrosis, along with skeletal abnormalities and neurodevelopmental delay are also part of the extra-renal spectrum of manifestations in NPHP.[8]

In case 2, the patient's prominent clinical feature was severe hypertension. Severe early-onset hypertension, where secondary causes have extensively been excluded has been described in many patients with *TTC21B* pathogenic variants. Cases that have undergone renal biopsy have showed severe hypertensive nephrosclerosis with arterial thrombotic microangiopathy.[13] A case series by Doreielle *et al* reports 7 patients presenting severe early onset hypertension and CKD of unknown cause were found to have genetically confirmed NPHP, 6 of which affected by the same homozygous variant in TTC21B (NM_024753.5:c.626C>T, p.Pro209Leu). Four of the patients underwent kidney biopsy revealing features of arteriolar thrombotic microangiopathy (TMA), and no usual histologic aspects of NPHP (kidney tubular cysts and tubular membrane disruption). Before genetic diagnosis, all patients had been thoroughly studies for causes of secondary hypertension.

Hypertension is thought to be absent at initial presentation of NPHP because of salt wasting. As seen in Case 2, 3 patients described in this case series had diagnosed severe hypertension before any kidney dysfunction.[13] Although the precise pathogenic mechanism remains unclear, these findings raise speculation that hypertension in NPHP can reflect endothelial cilium dysfunction. Ciliary protrusions in endothelial cells appear to function as vascular mechano-sensors, potentially playing a significant role in blood pressure regulation.[14] We believe that future research may expand the known phenotypic spectrum of NPHP.

In the diagnostic evaluation of patients with hypertensive emergency or thrombotic microangiopathy of unclear aetiology in individuals of Portuguese and North African ancestry, *TTC21B* gene analysis may be relevant.

The phenotypes described in these cases have few characteristics of classical NPHP. In fact, it is unlikely that NPHP would have been diagnosed if not for genetic testing within the workup of CKD of unknown origin. The spectrum of manifestations caused by *TTC21B*-related disease seem to exceed the classical NPHP phenotype and therefore the term NPHP type 12 seems to be misleading.

Although no disease-specific therapy currently exists for *TTC21B*-NPHP early recognition allows for optimized supportive management, which may delay progression to ESRD. Moreover, establishing a molecular diagnosis is crucial for accurate prognostication, family screening, and appropriate preconception and reproductive counselling.

This report is limited by the small number of cases and the lack of functional studies; however, the consistent genotype–phenotype correlation and detailed clinical characterization strengthen the causal association.

Table 1. Summary of clinical data of the patients presented

Family	Patient	Origin	Sex	Consanguinous parents	Age at Diagnosis	Kidney Features at diagnosis	Others Features	Kindey Biopsy	Age at ESKD
1	a	Portugal	M	1	36	Low-grade proteinúria; CKD stage 3		FSGS	N/A
	b		M			Subnephrotic proteinuria; CKD stage 5	Bull's eye; Biliary Cirrosis	FSGS	51
2	-	Portugal	F	0	24		Hypertension	Not performed	34

CONCLUSION

With the increasing availability and integration of genetic testing into nephrology practice, a paradigm shift is occurring in the evaluation of chronic kidney disease of unknown aetiology in young adults. Due to its insidious course, lack of specific imaging findings, and variable extra-renal manifestations, adult-onset nephronophthisis is highly susceptible to misdiagnosis or delayed recognition. Pathogenic variants in *TTC21B*, particularly the c.626C>T (p.Pro209Leu) variant, are likely an underrecognized cause of end-stage kidney disease with a combined tubulointerstitial and glomerular phenotype, manifesting as NPHP, FSGS, or overlapping presentations.

These cases further highlight the evolving role of next-generation sequencing in the diagnostic workup of unexplained chronic kidney disease, particularly in younger patients, in whom genetic testing may be more informative than histopathology alone. Moreover, the cases presented underscore the importance of persistent investigation into the aetiology of CKD, given the significant implications for prognosis, therapeutic decision-making, and long-term genetic counselling for affected individuals and their families.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship.
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.
Patient Consent: Consent for publication was obtained.
Provenance and Peer Review: Not commissioned; externally peer-reviewed.

Contributorship Statement

VPF and JD: Conception and design of the work; data aquisition; manuscript draft; figures and tables.
CFR: Conception and design of the work and manuscript review.
SS: Data aquisition and manuscript review.
AMG: Concenption and design of the work, data aquisition and manuscript review.
All authors approved the final version to be published.

REFERENCES

1. Stokman M, Lilien M, Knoers N. Nephronophthisis-Related Ciliopathies. 2016 Jun 23 [Updated 2023 Mar 2]. In: Adam MP, Bick S, Mirzaa GM, et al, editors. GeneReviews®. Seattle: University of Washington, Seattle;2026.
2. Gupta S, Ozimek-Kulik JE, Phillips JK. Nephronophthisis-Pathobiology and Molecular Pathogenesis of a Rare Kidney Genetic Disease. Genes. 2021; 12:1762. doi:10.3390/genes12111762
3. Petzold F, Billot K, Chen X, Henry C, Filhol E, Martin Y, et al.The genetic landscape and clinical spectrum of nephronophthisis and related ciliopathies. Kidney Int. 2023;104:378-87. doi: 10.1016/j.kint.2023.05.007
4. Online Mendelian Inheritance in Man [Internet]. [Updated 2018 Jun18] Available from: https://www.omim.org/entry/612014#0001
5. Huynh Cong E, Bizet AA, Boyer O, Woerner S, Gribouval O, Filhol E, et al. A homozygous missense mutation in the ciliary gene TTC21B causes familial FSGS. J Am Soc Nephrol. 2014;25:2435-43. doi: 10.1681/ASN.2013101126.
6. Abo El Fotoh WMM, Al-Fiky AF. A Compound Heterozygous Mutation in the Ciliary Gene TTC21B Causes Nephronophthisis Type 12. J Pediatr Genet. 2020;9:198-202. doi:10.1055/s-0039-1700804
7. Gambino G, Catalano C, Marangoni M, Geers C, Moine AL, Boon N, et al. Case report: homozygous pathogenic variant p209l in the TTC21B gene: a rare cause of end stage renal disease and biliary cirrhosis requiring combined liver-kidney transplantation. a case report and literature review. Front Med. 2021;8:795216. Published 2021 Dec 10. doi:10.3389/fmed.2021.795216
8. Wang D, Chen X, Wen Q, Li Z, Chen W, Chen W, et al. A single heterozygous nonsense mutation in the TTC21B gene causes adult-onset nephronophthisis 12: A case report and review of literature. Mol Genet Genomic Med. 2022;10:e2076. doi:10.1002/mgg3.2076
9. Davis EE, Zhang Q, Liu Q, Diplas BH, Davey LM, Hartley J, et al. TTC21B contributes both causal and modifying alleles across the ciliopathy spectrum. Nat Genet. 2011;43:189-96. doi:10.1038/ng.756
10. Bullich G, Vargas I, Trujillano D, Mendizábal S, Piñero-Fernández JA, Fraga G, et al. Contribution of the TTC21B gene to glomerular and cystic kidney diseases. Nephrol Dial Transplant. 2017;32:151-6. doi: 10.1093/ndt/gfv453.
11. Zhang H, Su B, Liu X, Xiao H, Ding J, Yao Y. Mutations in TTC21B cause different phenotypes in two childhood cases in China. Nephrology. 2018;23:371-6. doi:10.1111/nep.13008
12. Law nº 12/2005 January 26 [cited 2026 Jan 20]. Available: https://www.pgdlisboa.pt/leis/lei_mostra_articulado.php?nid=1660&tabela=leis
13. Doreille A, Raymond L, Lebre AS, Linster C, Saraeva Lamri R, Karras A, et al. Nephronophthisis in young adults phenocopying thrombotic microangiopathy and severe nephrosclerosis. Clin J Am Soc Nephrol. 2021;16:615-7. doi:10.2215/CJN.11890720
14. Abdul-Majeed S, Nauli SM. Dopamine receptor type 5 in the primary cilia has dual chemo- and mechano-sensory roles. Hypertension. 2011; 58: 325–31. doi: 10.1161/HYPERTENSIONAHA.111.172080