A single heterozygous nonsense mutation in the \textit{TTC21B} gene causes adult-onset nephronophthisis 12: A case report and review of literature

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**Abstract**

**Background:** Nephronophthisis type 12 (NPHP 12) is a rare cilia-related cystic kidney disease, caused by \textit{TTC21B} mutation, mainly involving the kidneys, which generally occurs in children. Our study aimed to illustrate its clinical, pathological and genetic characteristics by reporting an adult-onset case of NPHP 12 caused by a single heterozygous nonsense mutation of \textit{TTC21B} confirmed by renal histology and whole exome sequencing and reviewing related literature with a comparative analysis of the clinical features of each case. It will further increase the recognition of this rare kidney genetic disease, which sometimes can manifest as an adult disease.

**Results:** A 33-years-old man showed a chronic disease course, and he exhibited slight renal dysfunction (CKD stage 3, eGFR = 49 ml/\text{min} \times 1.73 \text{m}^2) with renal tubular proteinuria, without any extrarenal manifestations, congenital malformation history of kidney disease, or family hereditary disease. Renal histological findings showed substantial interstitial fibrosis with some irregular and tortuous tubules with complex branches and segmental thickening and splitting of the tubular basement membrane. The patient was diagnosed with chronic interstitial nephritis for an unknown reason clinically. Further genetic analysis revealed a single heterozygous nonsense mutation in the \textit{TTC21B} gene and NPHP 12 was diagnosed finally.

**Conclusion:** A single heterozygous mutation in the \textit{TTC21B} gene may cause atypical NPHP12, which had a relatively later onset and milder clinical symptoms without developmental abnormalities. Therefore, for unexplained adult-onset chronic interstitial nephritis with unusual changes of renal tubules and interstitial fibrosis, even without a clear history of hereditary kidney disease, genetic testing is still recommended. The correct diagnosis of this rare adult-onset hereditary nephropathy can avoid unnecessary treatment.
BACKGROUND

Nephronophthisis (NPHP) is an autosomal recessive cilia-related cystic kidney disease, with genetic heterogeneity, mainly involving the kidneys, but about 15% of patients can have extrarenal involvement, including retinal abnormalities, liver fibrosis, skeletal anomalies, and neurodevelopmental delay. At present, 27 pathogenic genes have been identified. According to the different mutation genes, the disease is divided into NPHP1-27 (Table 1).

NPHP accounts for about 15% of end-stage renal disease (ESRD) in children and is an important cause of renal failure in children. Although adult-onset NPHP is very rare, with the popularization of genetic testing in recent years, more and more adult-onset NPHP have been discovered which were mainly NPHP type 1 (Snoek et al., 2018). Other subtypes of NPHP were relatively less

| NPHP type | Gene | Disorders and clinical features | References |
|-----------|------|--------------------------------|------------|
| 1         | NPHP1| NPHP/SLSN/JBTS                 | Snoek et al. (2018) |
| 2         | INVS | NPHP/SLSN/situs inversus        | Moalem et al. (2013); Raina et al. (2021) |
| 3         | NPHP3| NPHP/SLSN/MKS                  | Olinger et al. (2021); Sun et al. (2016); Tang et al. (2022) |
| 4         | NPHP4| NPHP/SLSN                      | Fujimaru et al. (2021) |
| 5         | IQCB1| NPHP/SLSN/LCA                  | Hussain et al. (2018); Tong et al. (2013) |
| 6         | CEP290| JBTS/BBS/MKS/LCA/SLSN           | Chaki et al. (2011) |
| 7         | GLIS2| NPHP                           | Halbritter, Porath, et al. (2013) |
| 8         | RPGRIP1L| NPHP/JBTS/MKS               | Chaki et al. (2011) |
| 9         | NEK8 | NPHP                           | Otto et al. (2008) |
| 10        | SDCCAG8| NPHP/SLSN/BBS                | Otto et al. (2010); Watanabe et al. (2019) |
| 11        | TMEM67| NPHP/MKS/JBTS/COACH syndrome  | Iannicelli et al. (2010); Tkemaladze et al. (2017) |
| 12        | TTC21B| NPHP/JBTS                     | Davis et al. (2011); Jian et al. (2019); Strong et al. (2021) |
| 13        | WDR19| NPHP/JBTS                      | Lee et al. (2015) |
| 14        | ZNF423| NPHP/JBTS                      | Chaki et al. (2012) |
| 15        | CEP164| NPHP/SLSN/JBTS                | Fujimaru et al. (2021) |
| 16        | ANKS6| NPHP                           | Fang et al. (2020) |
| 17        | IFT172| NPHP/Jeune/Mainzer-Saldino syndrome | Halbritter, Bizet, et al. (2013) |
| 18        | CEP83| NPHP                           | Failler et al. (2014); Yue et al. (2020) |
| 19        | DCDC2| NPHP/liver fibrosis            | Schueuer et al. (2015) |
| 20        | MAPKBP1| NPHP                        | Schonauer et al. (2020) |
| 21        | ADAMTS9| NPHP/deafness/short stature    | Choi et al. (2019) |
| 22        | NPHPL1/XPNPEP3| NPHP/essential tremor/bearing loss/seizure/mental or development delay | O’Toole et al. (2010) |
| 23        | SLC41A1| NPHP/bronchiectasis           | Hurd et al. (2013) |
| 24        | TRAF3IP1| NPHP/retinal degeneration     | Bizet et al. (2015) |
| 25        | CC2D2A/MKS6| NPHP/JBTS                  | Chaki et al. (2011); Fleming et al. (2017) |
| 26        | AH11  | NPHP/JBTS                      | Chaki et al. (2011); König et al. (2017); Utsch et al. (2006) |
| 27        | ATXN10| NPHP/JBTS                      | Sang et al. (2011) |

KEYWORDS
chronic kidney disease, ciliopathy, nephronophthisis, TTC21B
reported. NPHP 12 is caused by the pathogenic mutation of gene TTC21B (OMIM accession number * 612014). Up to recently, only 5 childhood-onset cases have been reported in Chinese (Jian et al., 2019; Yue et al., 2020; Zhang et al., 2018). According to literature retrieved in PubMed, there is no report of adult-onset NPHP 12 yet. This article compares and analyzes the generalities and differences between this adult-onset NPHP 12 and previously reported cases of early-onset NPHP 12 to improve the overall understanding of this rare genetic kidney disease.

2 RESULTS

2.1 Case presentation

2.1.1 Clinical data

A 33-year-old male patient was admitted to the hospital in 2021, with the main complaint of “Elevated serum creatinine for more than 7 months”. Seven months before, he did a regular physical examination and found increased creatinine (112 μmol/L, reference range 59–104 μmol/L), increased blood uric acid (428 μmol/L, reference range 202–416 μmol/L), and increased fasting blood glucose (13.24 mmol/L). He had no other symptoms including foamy urine, hematuria, nocturia, joint pain, rash, polydipsia, or polyuria. But the patient has lost about 10 kg in weight without any known reason during the past 7 months. He had a high blood pressure history for 5 years without any discomfort. His BP was around 150–160/80–90 mmHg and began treatment 2 months earlier with amlodipine 2.5 mg/d. His father was diagnosed with both “diabetes” and “uremia” at the same time and passed away a month ago. His mother and his 3 children are all healthy (Figure 1). He has no family history of genetic disease or kidney disease. No abnormalities were found on physical examination. After admission, routine examinations including blood and urine tests were conducted, showing increased serum creatinine (159 μmol/L), increased serum uric acid (462 μmol/L), and increased low-density lipoprotein cholesterol (LDL-c, 3.31 mmol/L). Urine analysis showed urine protein was negative, with 24-h urine protein quantitative: 0.147–0.170 g, urine volume 2400–3400 ml. Further urine microprotein analysis showed only tubular proteinuria was found. Other examination results included glycosylated hemoglobin 5.5%, glucose tolerance OGTT (0, 30 min, 2 h: 4.3, 9.3, 10.0 mmol/L). The level of renin (192 pg/ml, normal range 4–38 pg/ml) and aldosterone (691.77 pg/ml, normal range 40–310 pg/ml) in the upright position were all increased with an aldosterone-to-renin ratio of about 3.6. The amount of VMA in 24h urine, serum ACTH, and cortisol levels were all in a normal range. Serum autoantibodies, including ANA, ANCA, dsDNA, and Rh factor, were all negative. Renal ultrasound examinations showed both kidneys in normal size and shape with slightly increased echogenicity and no hydronephrosis. Only unremarkable findings could be found in Chest CT.

2.1.2 Kidney pathology

There were 21 glomeruli and among which 9 were globally sclerotic. The remaining glomeruli were slightly enlarged with mildly mesangial proliferation. Several glomerular capsules were thickened and stratified, with occasional synechia. The main significant changes were found in the renal interstitium, with renal tubule atrophy (about 30%), significant tubule dilation, tubular basement membrane thickening, and some bizarre tortuous renal tubules with obvious “sprouting” performance. Microcysts can also be seen at the junction of the cortex and medulla (Figure 2a–d). Immunofluorescence showed IgA + + +, C3 + + +, C1q + + +, diffuse spherical distribution, and granularly deposited in the mesangial area. IgG, IgM, and Fg were all negative. Electron microscopy results showed the irregularly thickened tubular basement membrane consistent with the finding of light microscopy (Figure 2e–g). The initial pathological diagnosis was chronic tubulointerstitial nephritis and IgA nephropathy.

2.1.3 Genetic diagnosis

Whole exome capture and sequencing were performed on the tested genomic DNA, and single nucleotide variation (SNV), small insertion-deletion (indel) mutation, and copy number variation (CNV) were analyzed based on next-generation sequencing data. Sequencing and analysis were supported by Guangzhou KingMed Diagnostics. There were two mutations in total. First, was a missense mutation, NM-000384.3:c.5828C>T (p.Ser1943Phe), in the APOB gene on chromosome 2: 1233912. Mutation in
the APOB gene can lead to familial hypercholesterolemia type 2 (FHCL2), which is autosomal semi-dominant inheritance. Although this mutation has not been reported in the large-scale population database gnomAD, his mildly elevated LDL-c is consistent with the autosomal semi-dominant inheritance.

The second variation is a heterozygous mutation of c.264_267dup (p.E90*) in the TTC21B gene. This nonsense
mutation was expected to change the 90th amino acid of the encoded protein from glutamic acid to a stop codon and premature termination of the protein translation, which could generate truncation of the encoded protein or loss of normal function due to nonsense-mediated mRNA degradation. According to the previous literature, the mutation was detected in 1 patient with NPHP12, which had renal failure at 3 years old and with situs inversus (SI), polysplenia, gastrointestinal tract (GIT) malformation, and polydactyly [6]. According to the American College of Medical Genetics and Genomics (ACMG) classification of gene mutations, the mutation is considered a suspected pathogenic mutation.

2.1.4 | Diagnosis and differential diagnosis

This case is an adult-onset male patient (more than 30 years old). The only complaint was increased creatinine with no obvious reason. He was admitted to the hospital with decreased morning urine specific gravity, mildly increased uric acid, and LDL-c levels without any extrarenal manifestations, such as situs inversus, polysplenia, GIT malformation, and polydactyly [6]. According to the American College of Medical Genetics and Genomics (ACMG) classification of gene mutations, the mutation is considered a suspected pathogenic mutation.

The proband presented hypertension at age 27 years, 5 years before renal dysfunction. Through the detection of renin and aldosterone in the upright and supine positions, it was found that both renin and aldosterone were significantly increasing in the upright position, which ruled out primary aldosteronism. 24-h urine VMA determination measured the content of catecholamines and excluded pheochromocytoma. Due to renal dysfunction, no enhanced CT was performed, so reninoma and renal artery stenosis which may cause secondary aldosteronism cannot be ruled out.

On the other hand, a review of the previous literature found that pathogenic mutations in TTC21B can also manifest as early-onset hypertension with elevated systolic blood pressure, with an average onset age of 23 years (Doreille et al., 2021), similar to the characteristics of this case, but it is worth noting that in many TTC21B-related hypertension patients, the renal biopsy pathology has always been dominated by FSGS, which was not lined with the feature of our patients. Our whole exome assay did not identify other genetic mutations, so it does not support early-onset hypertension caused by other genetic mutations.

2.1.5 | Analysis of clinical characteristics of NPHP12 with different gene mutation types

The clinical manifestations of NPHP12 vary greatly due to different mutation sites and different mutation types, though all of them have elevated creatinine and proteinuria, as well as interstitial nephritis in renal pathology. Based on reported cases of NPHP12 (Table 2), there are 3 types of gene mutation. The first type is homozygous mutations (P1–P4), which suggest that NPHP12 is an autosomal recessive genetic disease. While there were more compound heterozygous mutations (P5–P16) and single heterozygous mutations (P17–P26), which suggests that NPHP12 is an autosomal dominant/semi-dominant mutation disease. For a single site, e.g., mutation of p.E90*, the patient (P2) with homozygous mutations has an earlier age of onset (3 years old when ESRD) and more severe clinical manifestations than patients with heterozygous mutation (P25, P26). Most compound heterozygous mutations cases, except P3, P4, P8, and P13, have obvious extrarenal manifestations (situs inversus, gastrointestinal malformations, polysplenia, polydactyly, liver fibrosis), and tend to have earlier onset age (<=10 years old). In a large-scale genetic screening study (Halbritter, Porath, et al., 2013) of NPHP-related ciliopathies patients diagnosed by
### TABLE 2 NPHP12 gene mutations and clinical features

| Patient ID | Mutation type         | Genes  | Mutation site (AA changes)                                                                 |
|------------|-----------------------|--------|-------------------------------------------------------------------------------------------|
| P1²        | Hom                   | TTC21B | c.2211 + 3A > G                                                                          |
| P2²        | Hom                   | TTC21B | c.264_267dup (p.E90*)                                                                     |
| P3³        | Hom                   | TTC21B | P209L                                                                                     |
| P4⁴        | Hom                   | TTC21B | P209L                                                                                     |
| P5⁵        | compound Het          | TTC21B | c.1552T > C (p.C518R)/c.1456dupA (p.R486KfsX22)                                           |
| P6³        | compound Het          | TTC21B | c.1552T > C (p.C518R)/c.752T > G (p.M251R)                                                |
| P7⁴        | compound Het          | TTC21B | c.380C > T (p.A127V)/c.267_268insTAGA (p.E90_A91delins*)                                  |
| P8⁴        | compound Het          | TTC21B | c.880G > T (p.A294S)/c.3622A > G (p.I1208V)                                              |
| P9⁵        | compound Het          | TTC21B | c.626C > T (p.P209L)/c.1240G > T (p.E414*)                                              |
| P10⁵       | compound Het          | TTC21B | c.626C > T (p.P209L)/c.3923A > G (p.D1308G)                                            |
| P11⁵       | compound Het          | TTC21B | c.1231C > T (p.R411*)/c.1445dupA (p.T483Dfs*25)                                       |
| P12⁵       | compound Het          | TTC21B | c.93delG (p.R32Gfs*17)/NFPH1 (p.S466fs*7)                                             |
| P13⁵       | compound Het          | TTC21B | c.1274dupT (p.R426Qfs*7)                                                                 |
| P14⁵       | compound Het          | TTC21B | P209L/c.2758-2A > G                                                                      |
| P15⁵       | compound Het          | TTC21B | P209L/C552X                                                                              |
| P16⁵       | compound Het          | TTC21B | W150R/c.3264-3C > G                                                                      |
| P17⁵       | single Het            | TTC21B | P753L                                                                                     |
| P18⁵       | single Het            | TTC21B | L1002V                                                                                   |
| P19⁵       | single Het            | TTC21B | K31fsX48                                                                                 |
| P20⁵       | single Het            | TTC21B | c.2322 + 3A > G                                                                          |
| P21⁵       | single Het            | TTC21B | T231S                                                                                     |
| P22⁵       | single Het            | TTC21B | T231S                                                                                     |
| P23⁵       | single Het            | TTC21B | H566R                                                                                     |
| P24⁵       | single Het            | TTC21B | Y1167C                                                                                   |
| P25⁵       | single Het            | TTC21B | c.264_267dup (p.E90*)                                                                     |
| P26 (this report) | single Het | TTC21B | c.264_267dup (p.E90*)                                                                     |

| Patient ID | Age* | Proteinuria | Scr (µmol/L) | Renal size/cysts/CMD | Renal biopsy | Extrarenal manifestations                                                                 |
|------------|------|-------------|--------------|----------------------|--------------|------------------------------------------------------------------------------------------|
| P1²        | 8    | 1728 mg/d   | 618          | Normal/no/not clear | Chronic interstitial nephritis and FSGS | Situs inversus, short phalanges, physical retardation, bronchitis or pneumonia, hypertension, elevated liver enzymes, neutropenia |
| P2³        | 3    | –           | –            | –                    | –            | Situs inversus, polydactyly, GIT malformation, polypsplenia                                |
| Patient ID | Age* | Proteinuria | Scr (μmol/L) | Renal size/cysts/ CMD | Renal biopsy | Extrarenal manifestations |
|-----------|------|-------------|-------------|-----------------------|-------------|---------------------------|
| P3        | –    | –           | –           | –                     | –           | no                        |
| P4        | –    | –           | –           | –                     | –           | no                        |
| P5        | 1    | 158 mg/kg/d | 249         | Enlarged/no/not clear | Chronic interstitial nephritis and FSGS | Hypertension, elevated liver enzymes, hepatomegaly and splenomegaly, anemia |
| P6        | 3.9  | 556 mg/d    | 462         | Normal right kidney, small left kidney | –           | Situs inversus, anemia, short phalanges |
| P7        | 6.7  | + ~ ++      | 517.5       | Normal                | Interstitial nephritis, corticomedullary cysts, glomerulosclerosis, no thickened and multilayered TBM | anemia, enuresis |
| P8        | 6.5  |             | 687         | Small/yes             | Interstitial nephritis, corticomedullary cysts, glomerulosclerosis, no thickened and multilayered TBM | no |
| P9        | 2    | –           | –           | –                     | –           | Liver fibrosis             |
| P10       | 3    | –           | –           | –                     | –           | Liver fibrosis, cone-shaped epiphysis (hands/feet) |
| P11       | 10   | –           | –           | –                     | –           | Situs inversus, hepatopathy |
| P12       | >8   | –           | –           | –                     | –           | Chondrodysplasia, Bell’s palsy, hypertension |
| P13       | 16   | –           | –           | –                     | –           | no                        |
| P14       | –    | –           | –           | –                     | –           | yes                       |
| P15       | –    | –           | –           | –                     | –           | yes                       |
| P16       | –    | –           | –           | –                     | –           | yes                       |
| P17       | –    | –           | –           | –                     | –           | yes                       |
| P18       | –    | –           | –           | –                     | –           | yes                       |
| P19       | –    | –           | –           | –                     | –           | no                        |
| P20       | –    | –           | –           | –                     | –           | no                        |
| P21       | –    | –           | –           | –                     | –           | no                        |
| P22       | –    | –           | –           | –                     | –           | no                        |
| P23       | –    | –           | –           | –                     | –           | no                        |
| P24       | –    | –           | –           | –                     | –           | no                        |
| P25       | >19  | –           | –           | –                     | –           | no                        |
| P26 (this report) | –    | 170 mg/d    | 159         | Normal/no/clear | Interstitial nephritis IgA nephropathy, glomerulosclerosis | – |

* Refers to age at ESRD in years.

Abbreviations: CMD, corticomedullary differentiation; FSGS, Focal segmental glomerulosclerosis; GIT, gastrointestinal tract; Het, heterozygous; Hom, homozygous; Scr, serum creatinine; TBM, tubular basement membrane; ‘-‘, no data.
published clinical criteria (Chaki et al., 2011), multiple cases of single heterozygous mutations in the TTC21B gene were found (P17–25). Unfortunately, these cases have not described the clinical and pathological changes clearly. Our case for the first time gave a detailed picture of NPHP12 patient with TTC21B single heterozygous mutation, which suggested a late age of onset with only tubular proteinuria, and relatively slow progression to ESRD without any extrarenal manifestations. Pathological findings, such as some bizarre tortuous renal tubules with obvious “sprouting” performance and cysts at the junction of the cortex and medulla, may give clinicians clues for further gene testing.

3 | DISCUSSION

By describing the clinical and pathological characteristics of an adult-onset single heterogeneous mutant NPHP12 patient, and retrospectively analyzing the relationship between the gene mutation types and clinical characteristics of previously reported NPHP12 cases, our research suggests that TTC21B gene mutations can be manifested in both recessive inheritance and dominant/semi-dominant inheritance. Homozygous mutations at a single site and heterozygous mutations at multiple sites lead to earlier onset, more severe clinical manifestations, and more extrarenal involvement. Single heterozygous mutations may also cause kidney injury, but the onset is usually late, the progression is relatively slow, and extrarenal involvement is also rare. Although Gemma Bullich et al revealed heterozygous deleterious TTC21B variants may exacerbate other glomerular and cystic kidney diseases as a disease modifier (Bullich et al., 2017), we believe that single heterozygous TTC21B can also cause NPHP in our case since the whole exome test did not find mutations in other kidney disease-related genes.

NPHP is characterized by chronic tubular interstitial disease, which generally occurs in infants and adolescents, and quickly progresses to end-stage renal failure. Clinically, NPHP is divided into infantile type (less than 5 years old), juvenile type (5–15 years old), and adolescent type (greater than 15 years old), based on the onset age of ESRD. The infantile type manifests as an enlarged cyst kidney, severe hypertension, and rapid disease progression. The pathological manifestations are cortical cysts, with no obvious changes in the tubular basement membrane, and the degree of renal fibrosis is mild (Waldherr et al., 1982). Some patients have extrarenal diseases, including retinal damage, liver cirrhosis, skeletal abnormalities, and abnormal cerebellar development (Luo & Tao, 2018). The juvenile type is the most common and is mainly caused by mutations in the NPHP1 gene. The average median onset age of ESRD is 13 years. The clinical features of the adolescent NPHP are similar to those of the juvenile NPHP. Kidney ultrasound reveals the normal or reduced renal size and enhanced parenchyma echo, and the renal pathology is characterized by prominent tubulointerstitial fibrosis, thickening or delamination of the tubular basement membrane, and cortical-medullary junction cysts in the distal tubules can be seen in less than 50% of cases in the advanced stage of the disease. Immunofluorescence change was non-specific or negative. The impaired urine concentration function of the patient leads to anemia, polyuria, polydipsia, then proteinuria in the advanced stage (Bergmann, 2019). The renal function continues to deteriorate and progresses to end-stage renal disease (ESRD) before the age of 30. The adult-onset nephrophthisis is very rare, including this case, only 34 cases have been reported (Fujimaru et al., 2021; Georges et al., 2000; Haghjhi et al., 2016; Snoek et al., 2018).

At present, 27 pathogenic genes of NPHP have been found, as shown in Table 1 (Luo & Tao, 2018; Srivastava et al., 2017). Among them, homozygous deletion mutations in the NPHP1 gene account for the most NPHP1 type (about 21%), but there are still about 70% without a clear causative gene. The NPHP12 type is caused by pathogenic mutations in the gene TTC21B, which is relatively rare. Only more than 40 confirmed cases have been reported internationally. A total of 45 mutations have been found, of which c.626C>T (p.P209L) is the most common one, mainly discovered in cases of Europe and North Africa, and cases in Asia are very rare (El Fotoh & Al-Fiky, 2020). Our case is the first reported case of NPHP12 in adulthood caused by mutations in the TTC21B gene. Although the patient is already 33 years old, he has not yet progressed to ESRD. The patient’s clinical characteristics are consistent with the characteristics of adult-onset NPHP reported in the literature (Snoek et al., 2018). Due to the few extra-renal abnormalities as well as non-specific clinical and imaging manifestations, adult-onset NPHP is very likely to be misdiagnosed. It is different from autosomal dominant tubulointerstitial kidney disease (ADTKD), which has an obvious family history, often accompanied by early-onset hyperuricemia or gout (Olinger et al., 2020), which could attract the attention of clinicians and lead to genetic screening. Besides, autosomal dominant polycystic kidney disease also manifests as renal cysts, but most of them with clear family history and the number and size of kidney cysts slowly increase which makes the characteristic ultrasound images (Raina et al., 2021). A Japanese study analyzed the characteristics of adult-onset NPHP and found that thickened tubular basement membrane (greater than 10 μm) is a more specific pathological manifestation (Fujimaru et al., 2021). However, the pathology of this patient showed obvious tortuous tubules and
“sprouting” phenomenon, which may be a more specific pathological manifestation of NPHP12.

NPHP gene products are mainly located in the primary cilia, basal body, and centrosomes of kidney epithelial cells (McConnachie et al., 2021). The protein IFT139 encoded by the TTC21B gene is one of the components of the cell cilia transporter A complex, which mainly regulates the material transport in the primary cilia (El Fotoh & Al-Fiky, 2020). It is mainly expressed in the distal renal tubules and glomerular podocytes, and its mutations affect multiple signal pathways in renal tubular epithelial cells, resulting in tubular and interstitial lesions, but the specific molecular mechanism is still unclear (McConnachie et al., 2021).

Although typical NPHP is characterized by renal tubular lesions, recent studies have found that TTC21B gene mutations have been detected in patients with Focal Segmental Glomerular Sclerosis (FSGS) (Hibino et al., 2020). It also found that pathogenic variants in TTC21B can simultaneously cause glomerular lesions characterized by FSGS and tubular lesions characterized by interstitial damage, which is considered as “tubuloglomerular kidney disease” (Olinger et al., 2022). This is in line with the fact that IFT139, the protein encoded by TTC21B exists not only in the ciliated structure of distal tubules but also along the intracellular microtubule network in non-ciliated human podocytes. In vitro experiments have found that IFT139 plays an important role in podocyte function, and its mutation can lead to podocyte dysfunction (Cong et al., 2014), which may be related to glomerular sclerosis in patients with NPHP12.

Furthermore many patients with TTC21B mutations have been found to have early-onset hypertension and the causes of secondary hypertension have not been identified. Renal pathology of some cases showed severe hypertensive nephrosclerosis with arteriolar thrombotic microangiopathy (TMA) (Doreille et al., 2021). Although there is insufficient evidence for a direct pathogenic mechanism of TTC21B and hypertension, it was speculated that TTC21B may lead to endothelial cell dysfunction, thereby affecting blood pressure regulation.

So far, there is no specific drug for NPHP and the main intervention is routine treatment to delay the progression of CKD. Supportive treatment can only delay the progression of renal function and improve the quality of life of patients, but it cannot prevent the occurrence of ESRD (Hildebrandt et al., 2009; Stokman et al., 2021). Kidney transplantation is the only effective cure, as there is no recurrence of NPHP in the kidneys after transplantation (Devlin & Sayer, 2019; Tayfur et al., 2011). Therefore, for unexplained adult interstitial nephritis, even if there is no clear history of hereditary kidney disease, it is recommended to perform genetic testing to exclude rare hereditary nephropathy onset in adults once there are characteristic findings in the pathology.

4 | CONCLUSIONS

NPHP12 can be manifested as a single heterozygous mutation disease, which is clinically manifested as an adult-onset, relatively slowly progressive chronic interstitial nephritis. Patients with unexplained interstitial nephritis and abnormal renal tubules deserve further gene testing to avoid misdiagnosis.

5 | METHODS

5.1 | Participant and clinical data

The clinical data of this case including the results of renal pathology and electron microscopy were collected by enquiry of clinical records and telephone interviews. Pathology and electron microscopy images at the time of diagnosis were obtained from the pathology department. Written consent was received from the participant.

5.2 | Whole exome sequencing

DNA was extracted from a blood sample of this case and whole exome capture and sequencing were performed on the tested genomic DNA, and single nucleotide variation (SNV), small insertion–deletion (indel) mutation, and copy number variation (CNV) were analyzed based on next-generation sequencing data. Sequencing and analysis were supported by Guangzhou KingMed Diagnostics. GenBank reference sequence and version number for the TTC21B is NC_000002.12 (REGION: complement [165873362.0.165953776]).

AUTHOR CONTRIBUTIONS

Dan Wang: writing-original draft preparation, investigation. Xionghui Chen: original draft preparation, investigation. Qiong Wen: collection of case characteristics. Zhijian Li: collection of case characteristics. Wei Chen: writing–reviewing and editing. Wenfang Chen: analysis of pathological results. Xin Wang: supervision, project administration. All authors read and approved the final manuscript.

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