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【 CASE REPORT 】

Medullary Cystic Kidney Disease and Focal Segmental Glomerulosclerosis Caused by a Compound Heterozygous Mutation in *TTC21B*

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Abstract:

Mutations in the *TTC21B* gene have been identified in patients with nephronophthisis and were recently found in some patients with focal segmental glomerulosclerosis. We herein report a Japanese boy with end-stage renal disease due to medullary polycystic kidney disease and primary focal segmental glomerulosclerosis. Next-generation sequencing detected a new compound heterozygous missense mutation in the *TTC21B* gene. His renal pathological findings and gene mutations have not been previously reported in patients with ciliopathy. For children with severe renal dysfunction, mutations in the *TTC21B* gene cause both ciliopathy characterized by bilateral polycystic kidney disease and primary focal segmental glomerulosclerosis.

Key words: *TTC21B*, polycystic kidney disease, focal segmental glomerulosclerosis, end-stage renal disease

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Introduction

Mutations in the *TTC21B* gene have been identified in patients with nephronophthisis (NPHP) and NPHP-related ciliopathy (1-3). Recently, some patients with focal segmental glomerulosclerosis (FSGS) were also described (4, 5). Most of them presented with a homozygous p.Pro209Leu mutation or a compound heterozygous missense mutation in the *TTC21B* gene (1-3, 4, 5).

We herein report a Japanese boy who presented with severe renal dysfunction as an infant due to bilateral medullary polycystic kidney disease (PKD) and primary FSGS. We detected new compound heterozygous missense mutations in his *TTC21B* gene. His renal histopathological findings were reminiscent of ciliopathy; however, they clearly differed from NPHP. To our knowledge, this is the first case with both ciliopathy and glomerular disease caused by a new mutation in the *TTC21B* gene.

Case Report

The patient was a Japanese boy whose parents were not consanguineous with no family history of similar symptoms or terminal renal failure. He was born at 38 gestational weeks without oligohydramnios or fetal distress. From the early infantile period, he presented with renal dysfunction and polyuria with urinary concentration defects. Ultrasonography and magnetic resonance imaging showed multiple renal cysts of various sizes, several small liver cysts, and dilated bile ducts. His kidneys were not enlarged, and no other extra-renal manifestation was noted. By three months of age, he had presented with recurrent bacterial cholangitis three times. Hypertension was not noted during the infantile period. At 15 months of age, he was transferred to our hospital for the management of chronic renal failure.

Upon admission, his physical examination showed a height of 67.4 cm [-4.1 standard deviations (SD)] and body weight of 7,155 g (-2.9 SD). His creatinine level and 24-h creatinine clearances were 0.68 mg/dL and 40.9 mL/min/

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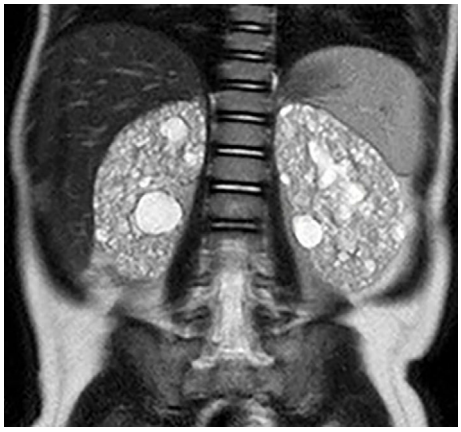

Figure 1. Magnetic resonance imaging at two years of age. Magnetic resonance imaging shows bilateral multiple renal cysts of various sizes located from the surface to the medullary area of the kidneys. The kidney is not enlarged in size.

1.73 m^2, respectively. A urinalysis revealed no hematuria. His proteinuria level and spot urine protein-to-creatinine ratio were 240 mg/day and 1-2 g/gCr, respectively. In addition, the urine β2-microglobulin level was 14,468 μg/L. After admission, only one episode of cholangitis occurred. He was treated with ursodeoxycholic acid and trimethoprim-sulfamethoxazole as prophylaxis. Figure 1 shows the multiple renal cysts that developed at two years of age. His renal dysfunction gradually progressed over several years. Furthermore, the proteinuria increased to 5-6 g/gCr of spot urine protein-to-creatinine ratio without hypoalbuminemia. At eight years of age, peritoneal dialysis was initiated, and left nephrectomy was performed because of polyuria. Subsequently, he received living-donor kidney transplantation with his mother as the donor. Right nephrectomy was performed at 9 years and 7 months of age.

Regarding the pathological findings of right kidney resection during transplantation, macroscopically, the cut surface showed both large and small multiple cysts from the surface to the inside area of the bilateral kidneys (Fig. 2A). Furthermore, microscopically, two major diagnoses were made. The first pathological diagnosis was medullary cystic kidney disease. CK7 staining proved that the dilated distal tubules and collecting ducts in the medulla had multiple cysts (Fig. 2B, C). In the cortex, renal tubular atrophy and interstitial fibrosis were observed. The surviving proximal tubules that were positive for CD10 were dilated, but no cystic changes were noted (Fig. 2D). The second diagnosis was primary FSGS. A large part of the glomeruli showed sclerotic lesions that were characteristic features of secondary FSGS caused by ischemic damage (Fig. 2E) as well as of the primary FSGS (Fig. 2F).

We performed a genetic analysis as the next diagnostic step. Using next-generation sequencing, a compound heterozygous mutation was identified in the *TTC21B* gene, termed NM_024753.4:c.1685A>G, p.Tyr562Cys and NM_024753.4:c.2569G>A, p.Ala857Thr. This was also confirmed by Sanger sequencing. His mother and father had p.Tyr562Cys and p.Ala857Thr, respectively (Fig. 3). Other genetic abnormalities causing ciliopathies, such as PKD, NPHP, and NPHP-RC, were not identified.

Discussion

A number of cystic kidney diseases, such as PKD and NPHP, are classified as ciliopathies caused by abnormalities of the primary cilia function or structure (6). Recently, several genetic abnormalities causing ciliopathy have been identified, involving genes encoding proteins localized in each ciliary compartment and maintaining the structure (6, 7). The differential diagnosis of ciliopathy is based on a combination of clinical manifestations and genetic and renal pathological diagnoses. The clinical manifestations include the following: the age at the onset of cysts and renal dysfunction, cyst shape, kidney size, renal dysfunction severity, and extra-renal complications. Autosomal dominant PKD (ADPKD), autosomal recessive PKD (ARPKD), and NPHP are major ciliopathies that can be diagnosed by confirming their phenotype and genotype. NPHP-related ciliopathies (NPHP-RC) present with extra-renal manifestations, and their diagnoses, which are confirmed by genetic analyses, include encephalocele (Meckel syndrome), retinal degeneration (Senior-Løken syndrome), and cerebellar vermis aplasia (Joubert syndrome) (7, 8). The present patient's clinical manifestation was bilateral PKD with renal dysfunction from the infantile period complicated with liver cysts and cholangitis, which was similar to ARPKD, including the lack of any family history. However, the imaging findings, which were characterized by multiple cysts of various sizes and normal-sized kidney, suggested ADPKD rather than ARPKD. Furthermore, his progressive proteinuria was not similar to tubulointerstitial disease with PKD. The patient's clinical manifestations and imaging findings are uncommon among known ciliopathies.

The patient's pathological finding of multiple cysts derived from the medullary distal tubules and collecting ducts was not similar to that of ADPKD, in which renal cysts form in the glomeruli and all tubular segments (9). The finding of medullary cystic kidney disease suggested ARPKD, NPHP, and NPHP-RC. ARPKD associated with severe renal dysfunction often presents with multiple tiny cysts in the enlarged kidney from the infantile period (10). NPHP is typically characterized by interstitial fibrosis; several-millimeter-sized cysts arise from the medullary distal tubules and collecting ducts with irregular thickening or disruption of the tubular basement membrane (11, 12). Although the patient's progressive proteinuria did not resemble the tubulointerstitial damage associated with medullary cystic kidney disease, the primary FSGS is a possible pathological diagnosis as the cause of his progressive proteinuria and renal dysfunction.

Mutations in the *TTC21B* gene have been identified in patients with NPHP and NPHP-RC carrying the homozygous p.Pro209Leu mutation (1-3). Recently, a total of 23 patients

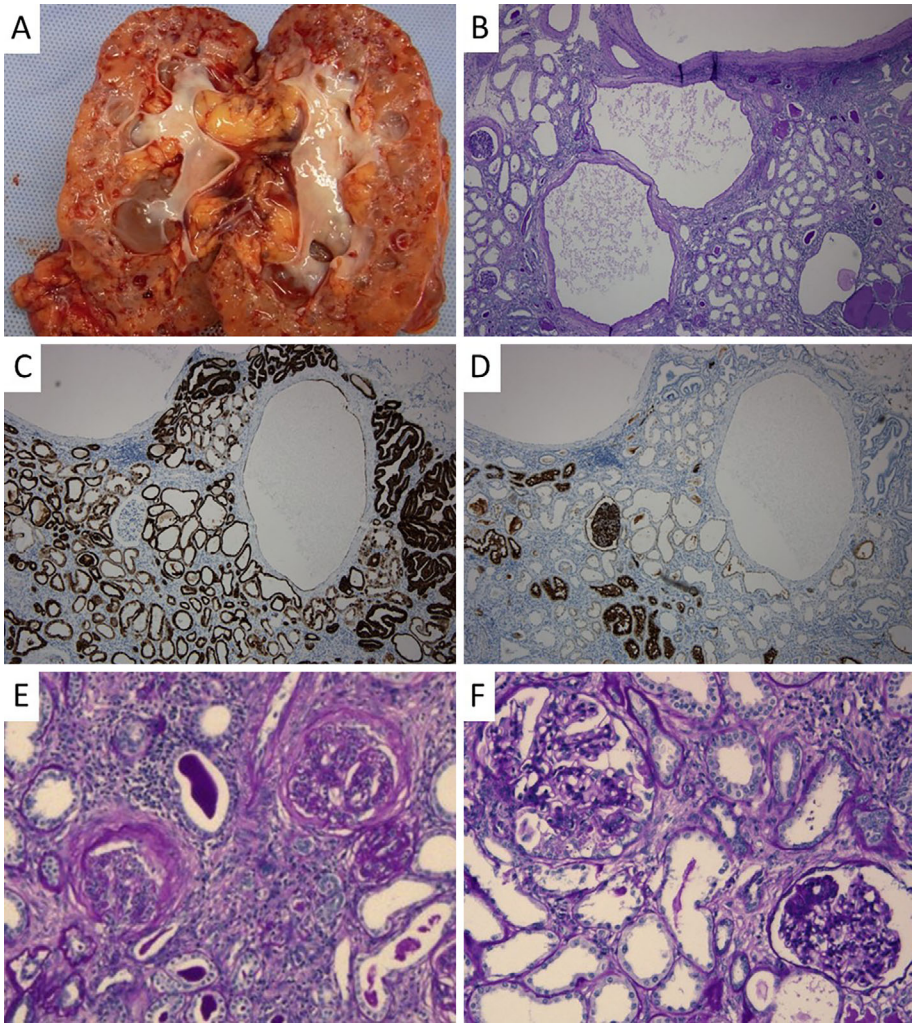

Figure 2. **Renal biopsy findings. (A) The cut surface demonstrated both large and small multiple cysts from the surface to the inside area of the bilateral kidneys. (B) Multiple cysts are present in the medulla (periodic acid-Schiff staining, original magnification). (C) Multiple cysts are present in the distal tubules and collecting ducts because they are positive for CK7 staining. (D) Renal tubular atrophy and interstitial fibrosis are observed in the cortex. The surviving proximal tubules that were positive for CD10 were dilated, but no cystic change was noted. (E) Secondary focal segmental glomerulosclerosis caused by ischemic damage (periodic acid-Schiff staining, original magnification). (F) Primary focal segmental glomerulosclerosis (periodic acid-Schiff staining, original magnification).**

(13 families) with FSGS and tubulointerstitial lesions due to homozygous or compound heterozygous missense mutations in the *TTC21B* gene were described (4, 5). Most of them presented with a homozygous p.Pro209Leu mutation, and their tubulointerstitial lesions were characterized by tubulointerstitial fibrosis, atrophic tubules, a thickened tubular basement membrane, and medullar cysts, that were consistent with the pathological findings of NPHP (4, 5). The *TTC 21B* gene encodes the ciliary protein IFT139, a component of the intraflagellar transport complex A required for retrograde intraflagellar transport in the cilium (13). IFT139 is expressed at the base of the primary cilium in developing podocytes in human fetal tissues and undifferentiated podocytes. In addition, it relocalizes along the microtubule network in mature and differentiated podocytes (5). In human mature podocytes, the p.Pro209Leu mutation has been demonstrated to cause a partial alteration in the microtubule network that may affect the cytoskeleton dynamics and destabilize the podocyte architecture (5). It was suggested that the *TTC21B* mutation leads to a novel hereditary kidney disorder with both glomerular and tubulointerstitial damage.

Most of the reported patients presented with a homozygous mutation of p.Pro209Leu (4, 5), but our patient had a heterozygous mutation. Furthermore, several of these patients were diagnosed with FSGS and NPHP (4, 5), and in our patient, large-sized renal cysts were found. Clinically, the reported patients presented with the childhood or adult onset of proteinuria (in the nephrotic or non-nephrotic range) and progression to end-stage renal disease (ESRD). Interestingly, the two affected siblings carrying the p.Pro209 Leu and p.His426Asp mutation in the *TTC21B* gene showed the onset of proteinuria at a younger age (4 and 6 years old)

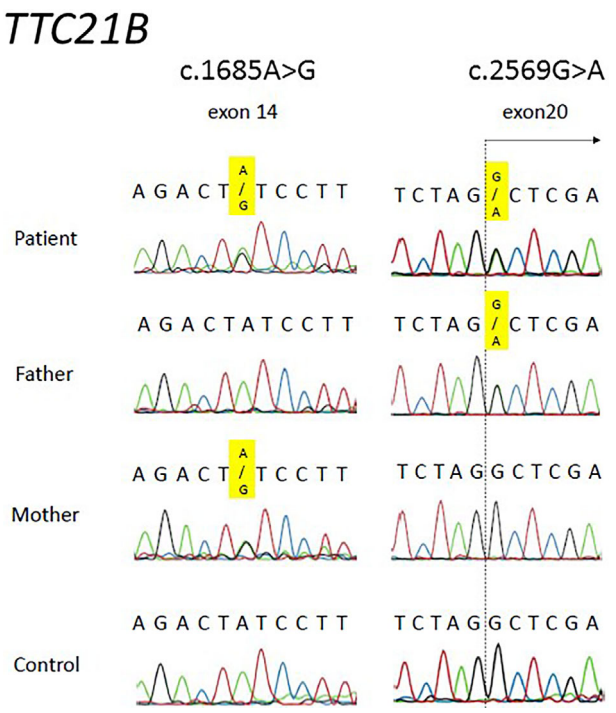

Figure 3. Mutations in the *TTC21B* gene. An electropherogram of the c.1685A>G and c.2569G>A heterozygous *TTC21B* mutations.

than patients with the homozygous p.Pro209Leu mutation (8-30 years old; median, 16 years old) (5). Given the rapid renal dysfunction progression in our patients, determining whether the tubuloglomerular involvement is the primary lesion or the consequence of this rapid deterioration in the renal function is difficult, but the focal and segmental aspect of the glomerular lesion and the interstitial infiltrate point to a specific pathological setting for our patient's compound heterozygous mutation in the *TTC21B* gene. Due to our patient showing a new heterozygous mutation, the pathogenesis of the genetic abnormality cannot be fully comprehended at present. Its pathogenicity may be demonstrated through similar case reports or a predictive analysis of the gene or protein.

In conclusion, the compound heterozygous mutation in the *TTC21B* gene results in the complication of medullary cystic kidney disease and primary FSGS associated with severe renal dysfunction from the infantile period.

The authors state that they have no Conflict of Interest (COI).

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