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Hypersplenism Accompanying a PKD-Like Nephropathy Associated with a Heterozygous *TTC21B* Mutation

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ABSTRACT

Background: Ciliary dysfunction is increasingly recognized as a genetic basis of cystic kidney diseases. Although homozygous *TTC21B* mutations are classically associated with nephronophthisis type 12, emerging evidence suggests that heterozygous variants may also produce clinical phenotypes. We report a case of PKD-like cystic nephropathy with hypersplenism associated with a heterozygous *TTC21B* mutation.

Case Report: A 51-year-old man was evaluated for thrombocytopenia and renal dysfunction detected during routine testing. Magnetic resonance imaging revealed enlarged kidneys with numerous cysts. Bone marrow biopsy findings were consistent with secondary hypersplenism. Genetic analysis identified a heterozygous *TTC21B* frameshift variant (c.125dupA; p.Tyr42fs*), while no pathogenic variants were detected in *PKD1*, *PKD2*, or *GANAB*.

Conclusion: Heterozygous *TTC21B* variants may be associated with adult-onset PKD-like nephropathy with systemic features, potentially expanding the phenotypic spectrum of *TTC21B*-related ciliopathies.

Keywords: Ciliopathy, hypersplenism, nephronophthisis, polycystic kidney disease, *TTC21B*.

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INTRODUCTION

Diseases within the ciliopathy spectrum may exhibit a wide range of clinical and morphological features due to genetic heterogeneity. Within this spectrum, nephronophthisis (NPHP) and polycystic kidney disease (PKD) represent two phenotypic extremes; however, intermediate presentations between these entities have also been reported. This suggests that mutations in ciliary genes can result in both cystic renal morphology and extrarenal manifestations. NPHP is an autosomal recessive primary ciliopathy characterized by tubulointerstitial fibrosis, corticomedullary microcysts, and progressive kidney failure. To date, 27 genes associated with NPHP have been identified, most of which are involved in maintaining the structural or functional integrity of the primary cilium. Ciliary dysfunction disrupts intracellular signaling pathways and may lead to pathological changes affecting multiple organs, including the kidneys, retina, liver, and skeleton.[1]

Table 1. Laboratory findings at the initial presentation

Category	Parameter	Result	Unit	Reference range
Renal function	Creatinine	1.3	mg/dL	0.5–1.2
	eGFR (CKD-EPI)	68.6	mL/min/1.73 m^2	90–130
	BUN	28	mg/dL	6–20
	Uric acid	6.6	mg/dL	3.4–7.0
	Calcium	9.47	mg/dL	8.6–10.2
	Phosphorus	3.72	mg/dL	2.5–4.5
	Magnesium	0.87	mmol/L	0.66–1.07
	Sodium	139	mmol/L	136–145
	Potassium	4.92	mmol/L	3.5–5.1
	Chloride	101	mmol/L	98–107
Liver function	AST	11	U/L	0–40
	ALT	13	U/L	0–41
	ALP	59	U/L	40–130
	GGT	20	U/L	10–71
	Total bilirubin	0.46	mg/dL	0–1.4
	Direct bilirubin	0.22	mg/dL	0–0.3
	Total protein	7.02	g/dL	6.4–8.3
	Albumin	4.11	g/dL	3.5–5.2
Complete blood count	WBC	6.1	$\times 10^3/\mu L$	4.8–10.7
	HGB	13.2	g/dL	14–18
	PLT	75	$\times 10^3/\mu L$	130–400
Urinalysis	Appearance	Clear	–	–
	Specific gravity (SG)	1.014	–	1.005–1.020
	pH	6.0	–	5–6
	Protein	75 (trace)	mg/dL	0–10
	Blood (RBC)	250	RBC/µL	0–10
	RBC microscopy	44	/HPF	0–3
	WBC	1	/HPF	0–4

eGFR: Estimated glomerular filtration rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; BUN: Blood urea nitrogen; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; WBC: White blood cell; HGB: Hemoglobin; PLT: Platelet; SG: Specific gravity; RBC: Red blood cell; HPF: High-power field.

The *TTC21B* gene is located on chromosome 2q24.3 and encodes the IFT139 protein, a component of the intraflagellar transport complex A. This protein is essential for retrograde transport from the ciliary tip to the basal body. Disruption of this process leads to loss of tubular epithelial polarity, ciliary disorganization, and cystic degeneration. *TTC21B* mutations are classically associated with NPHP type 12, typically presenting in childhood and usually involving homozygous or compound heterozygous variants. Renal failure, retinopathy, and hepatic fibrosis are common extrarenal findings.[2]

Recent literature suggests that heterozygous *TTC21B* variants may be associated with variable clinical phenotypes and may act as modifiers of other ciliopathy-related genes. Adult-onset cases with isolated renal involvement have been described, some of which exhibit PKD-like radiological features. In these cases, numerous small corticomedullary cysts result in a morphology distinct from classic PKD but phenotypically similar. Therefore, *TTC21B*-associated conditions may represent an intermediate phenotype within the spectrum of cystic kidney diseases.[3]

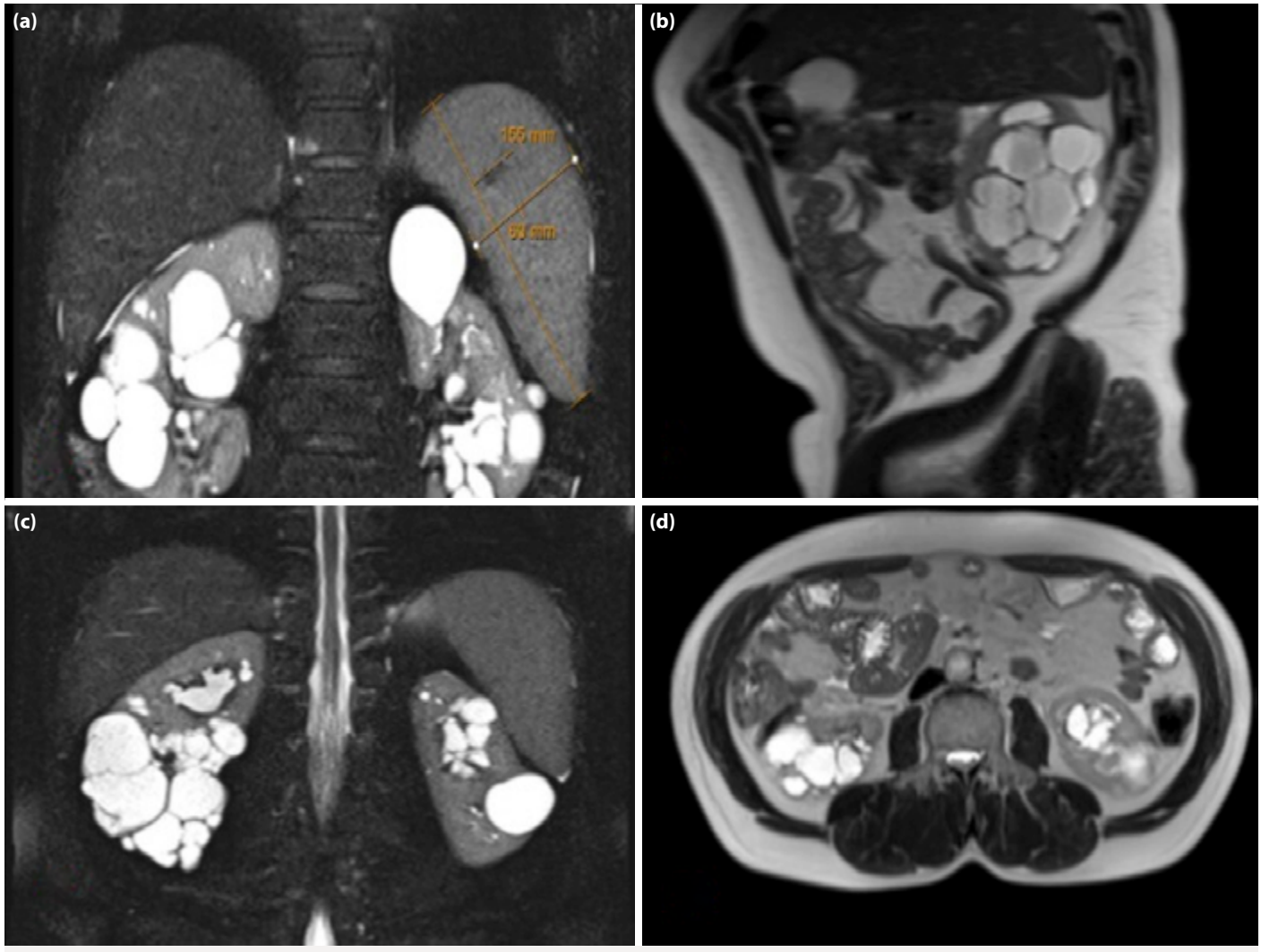

Figure 1. (a) Coronal T2-weighted magnetic resonance (MR) image showing splenomegaly, with the spleen measuring approximately 155 mm in craniocaudal and 69 mm in anteroposterior diameter. The enlarged spleen is consistent with hypersplenism observed in the patient. **(b)** Sagittal T2-weighted MR image demonstrating multiple well-defined cortical cysts in the left kidney, consistent with a polycystic kidney disease-like phenotype. The cysts vary in size and show homogeneous hyperintense signal characteristics. **(c)** Coronal T2-weighted MR image revealing multiple bilateral cortical and medullary cysts of varying sizes in both kidneys, consistent with a polycystic kidney disease-like phenotype. The renal parenchyma between the cysts appears thinned. **(d)** Axial T2-weighted MR image demonstrating multiple bilateral renal cortical cysts of varying sizes, compatible with a polycystic kidney disease-like morphology. The cysts exhibit high signal intensity, and the intervening parenchyma shows mild thinning.

PKD is typically associated with *PKD1* or *PKD2* mutations and is characterized by large cortical cysts. In contrast, ciliopathy-related PKD-like cases usually present with smaller, limited-number corticomedullary cysts; a family history is absent in most patients, and disease progression tends to be slower.[4] These observations suggest that *TTC21B* mutations may result not only in the classical NPHP phenotype but also in PKD-like cystic nephropathy. Adult-onset phenotypes associated with heterozygous *TTC21B* variants are rare, and cases accompanied by hematological manifestations have not been previously reported.

CASE REPORT

A 51-year-old male was referred for evaluation of thrombocytopenia and chronic kidney dysfunction identified during routine testing. He had no history of chronic disease

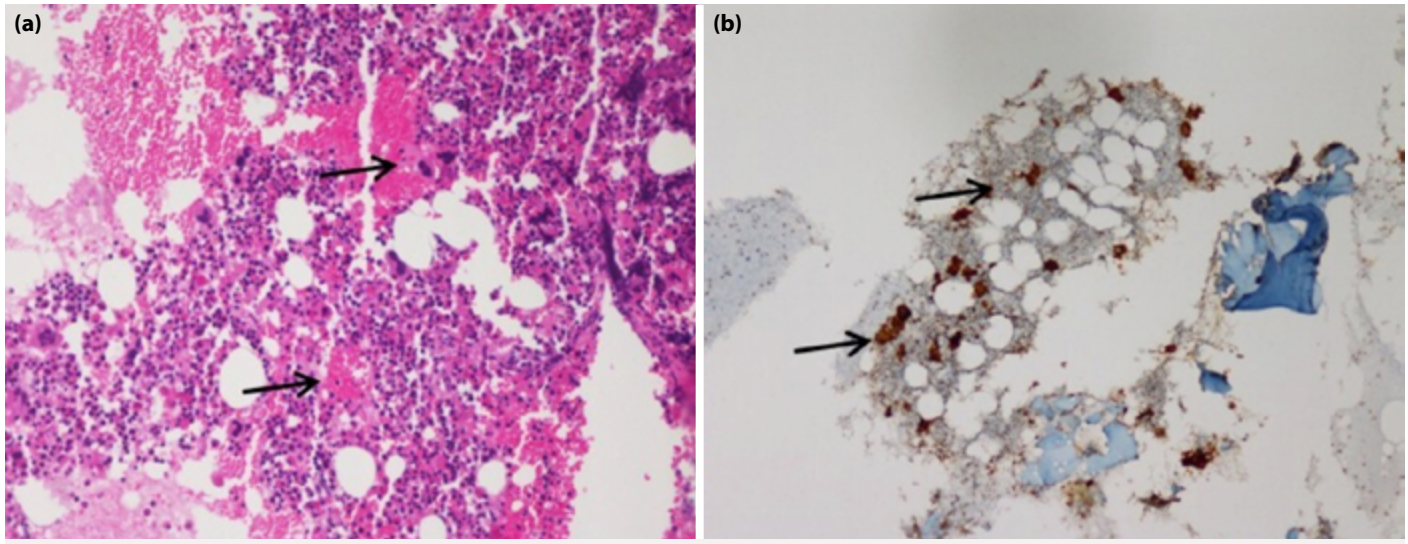

Figure 2. (a) Hematoxylin and eosin (H&E) staining shows normocellular marrow with increased megakaryocytes (black arrows). **(b)** CD61 immunohistochemical staining highlights megakaryocytes (black arrows), confirming megakaryocytic proliferation consistent with hypersplenism-related compensatory changes.

or hepatotoxic medication use. There was no family history of kidney failure. Physical examination revealed obliteration of Traube's space and a blood pressure of 120/75 mmHg. Laboratory findings showed hemoglobin 13.2 g/dL, leukocytes 6.1×10^9/L, platelets 75×10^9/L, urea 28 mg/dL, and creatinine 1.3 mg/dL. Liver function tests, coagulation parameters, and viral serologies were normal (Table 1).

Abdominal magnetic resonance imaging demonstrated numerous cortical and corticomedullary cysts in both kidneys, with increased renal volumes (right kidney, 858 mL; left kidney, 667 mL), findings compatible with PKD. Hepatic steatosis and splenomegaly (154 mm) were also observed, without clear radiological evidence of clinically significant portal hypertension (Fig. 1). Bone marrow biopsy performed for thrombocytopenia showed normocellular marrow with mild megakaryocytic hyperplasia, consistent with hypersplenism (Fig. 2). Ophthalmological evaluation revealed retinopathy, whereas cardiac assessment was normal.

Next-generation sequencing using a 44-gene nephropathy panel identified a heterozygous c.125dupA (p.Tyr42fs*) frameshift variant in *TTC21B*, classified as a variant of uncertain significance according to ACMG criteria.[5] The same classification was reported in ClinVar. No pathogenic variants were detected in *PKD1*, *PKD2*, or *GANAB*. Pedigree analysis across three generations identified a sibling with a similar cystic renal phenotype; there was no consanguinity or history of kidney disease among the parents.

Taken together, these findings suggested a diagnosis of adult-onset multisystem ciliopathy characterized by PKD-like cystic nephropathy associated with a heterozygous *TTC21B* variant, accompanied by hypersplenism and thrombocytopenia. Partial improvement in thrombocytopenia was observed after empirical corticosteroid therapy. Nephroprotective treatment was initiated for renal management.

DISCUSSION

The IFT139 protein encoded by *TTC21B* is essential for retrograde intraflagellar transport. Disruption of this system may impair intracellular signaling, leading to loss of apical–basal polarity and tubular cystic degeneration.[5,6] In the present case, the detection of numerous corticomedullary cysts and multisystem findings in an adult patient carrying a heterozygous frameshift mutation suggests that reduced *TTC21B* function may contribute to the observed phenotype.

Although *TTC21B* mutations are most commonly described in recessive NPHP12, recent studies indicate that heterozygous variants may also exert clinical effects and modify disease phenotypes.[3] This supports a potential modifier role for the gene. In our patient, the apparent association between a single-allele frameshift mutation and the clinical presentation raises the possibility of a gene dosage effect.

Radiological findings demonstrating small NPHP-like cysts together with renal enlargement resemble PKD features. While PKD typically presents with large, smooth-walled cysts, ciliopathy-associated cases often exhibit numerous small

cysts with irregular borders. According to the Mayo imaging classification, atypical morphology includes asymmetric, focal, segmental, or non-diffuse cystic involvement patterns that differ from classical ADPKD morphology. In the present case, the radiological findings and accompanying extrarenal manifestations were considered more compatible with an adult-onset atypical PKD-like ciliopathy phenotype rather than conventional *PKD1*/*PKD2*-associated ADPKD. Therefore, the prognostic applicability of the Mayo classification may be limited in this setting.[7] These differences support the concept that *TTC21B*-related disorders represent an intermediate phenotype within the NPHP–PKD spectrum.

One of the most notable features of this case is hematological involvement. Although retinal findings have been frequently reported in *TTC21B*-related disease, hypersplenism has rarely been described. The role of ciliary structures in hematopoietic organ function remains unclear; however, the influence of the IFT complex on cytoskeletal organization may theoretically affect splenic stromal architecture and blood cell circulation.[8] This observation suggests that the phenotypic spectrum of *TTC21B*-associated disease may be broader than previously recognized. Although no clear radiological evidence of clinically significant portal hypertension was identified, elastography and endoscopic evaluation were not performed. Therefore, subclinical portal hypertension could not be completely excluded. Microscopic hematuria and mild proteinuria may reflect cyst-related microhemorrhage, tubulointerstitial involvement, or possible glomerular pathology. Although *TTC21B*-associated disease has primarily been linked to ciliopathy-related renal phenotypes, glomerular and tubulointerstitial involvement have also been reported.[9] However, renal biopsy was not performed because urinary abnormalities were mild and there was no strong clinical indication. Although renal function was relatively preserved at presentation, the long-term renal prognosis of atypical *TTC21B*-associated ciliopathy remains uncertain. Previous reports suggest variable phenotypic expression and possible progression to chronic kidney disease in some patients. Therefore, close long-term nephrological follow-up is warranted.[10]

CONCLUSION

Heterozygous *TTC21B* variants may be associated with adult-onset multisystem ciliopathy phenotypes, including atypical PKD-like nephropathy. However, because the identified variant is classified as a variant of uncertain significance and functional validation and segregation analyses were unavailable, a definitive causal relationship cannot be established. Taken together, the current findings should be interpreted cautiously and viewed primarily as a hypothesis-generating observation that may expand the spectrum of atypical ciliopathy-associated renal phenotypes.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

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