

PKHD1 biallelic defects caused Severe Hepatic Fibrosis and polycystic kidney: Identification of a novel pathogenic variant in a Chinese family

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Abstract

Background: Autosomal recessive polycystic kidney disease (ARPKD) is a rare hereditary ciliopathy, clinically characterized by fibrocystic changes in the kidneys and liver. The disease is manifested by hepatic fibrosis and significantly enlarged, echogenic kidneys with fusiform dilation of the collecting ducts. ARPKD is predominantly associated with homozygous or compound heterozygous mutations in the PKHD1 gene, which encodes the protein fibrocystin.

Clinical case: In this study, we report a case involving a young Chinese female who presented with recurrent upper gastrointestinal bleeding, abdominal distension, and hepatosplenomegaly. Imaging studies revealed portal hypertension and bilateral renal involvement, while a liver biopsy indicated portal fibrosis with ductal plate malformation. Genetic analysis identified her as a compound heterozygote for a known pathogenic variant, c.2107G>A (p.D703N), and a novel variant, c.4820A>G (p.Y1607C), in the PKHD1 gene.

Conclusion: Family-based studies have shown that individuals carrying the novel variant exhibit a hepatic abnormal phenotype. Bioinformatics analysis suggests that this novel mutation may impact the protein structure by altering hydrogen bond interactions with other amino acids. (*Acta gastroenterol belg.*, 2026, 89, 503-507).

Keywords: PKHD1, Autosomal recessive polycystic kidney disease (ARPKD), A novel pathogenic variant, Hepatic fibrosis, Mutation spectrum.

Introduction

Autosomal recessive polycystic kidney disease (ARPKD) is a rare hereditary ciliopathy, with an estimated incidence of 1 in 20,000 live births (1). This disorder presents a wide range of clinical manifestations affecting multiple organ systems, most notably the kidneys and liver (2). Renal manifestations typically include bilateral kidney enlargement and microcystic dilation, which can begin to manifest during the fetal period and may result in renal insufficiency either prenatally or during the neonatal period. Approximately 30% of affected individuals succumb in the perinatal period, while surviving infants may progress to end-stage renal disease (ESRD) during infancy, early childhood, or adolescence. A large proportion of individuals with ARPKD exhibit clinical signs of liver disease, characterized by dilated biliary ducts, congenital hepatic fibrosis, and portal hypertension (3).

Pathogenic variants in the PKHD1 gene (OMIM *606702) have been implicated as the primary causative

factor of this disease. This gene encodes a large trans-membrane protein known as fibrocystin/polyductin, which is primarily expressed in the kidney (particularly in the collecting ducts and thick ascending loops of Henle), liver (in bile duct epithelia), and pancreas. (4). The precise role of fibrocystin in the clinical phenotype remains elusive; however, it is hypothesized that its localization to the primary cilia of bile ducts may be crucial for maintaining tubular structure (5). Pathogenic mutations have been identified along the entire length of the PKHD1 gene, but there do not appear to be any hotspot mutation except for a missense mutation in exon 3, c.107C>T (p.T36M). (6) Recent studies have suggested that mutations in specific regions of the PKHD1 gene may be associated with the location of symptom onset (7). Nevertheless, the functional effects and underlying mechanisms of individual mutations remain challenging to elucidate, resulting in an unclear genotype-phenotype correlation for ARPKD.

In this study, we present a case involving a 21-year-old female patient diagnosed with ARPKD, characterized by congenital hepatic fibrosis and polycystic kidneys. Through whole exome sequencing (WES), the patient was identified as a compound heterozygote, carrying the established c.2107G>A (p.D703N) variant alongside a novel c.4820A>G (p.Y1607C) variant. This discovery contributes to the expansion of the mutation spectrum associated with the PKHD1 gene and offers new insights into the genotype-phenotype correlation in ARPKD.

Case presentation

A 21-year-old female of Han ethnicity (III, Fig 1A) was admitted with decompensated cirrhosis. Two years earlier, she underwent splenectomy and portal vein dissection due to esophageal and gastric variceal

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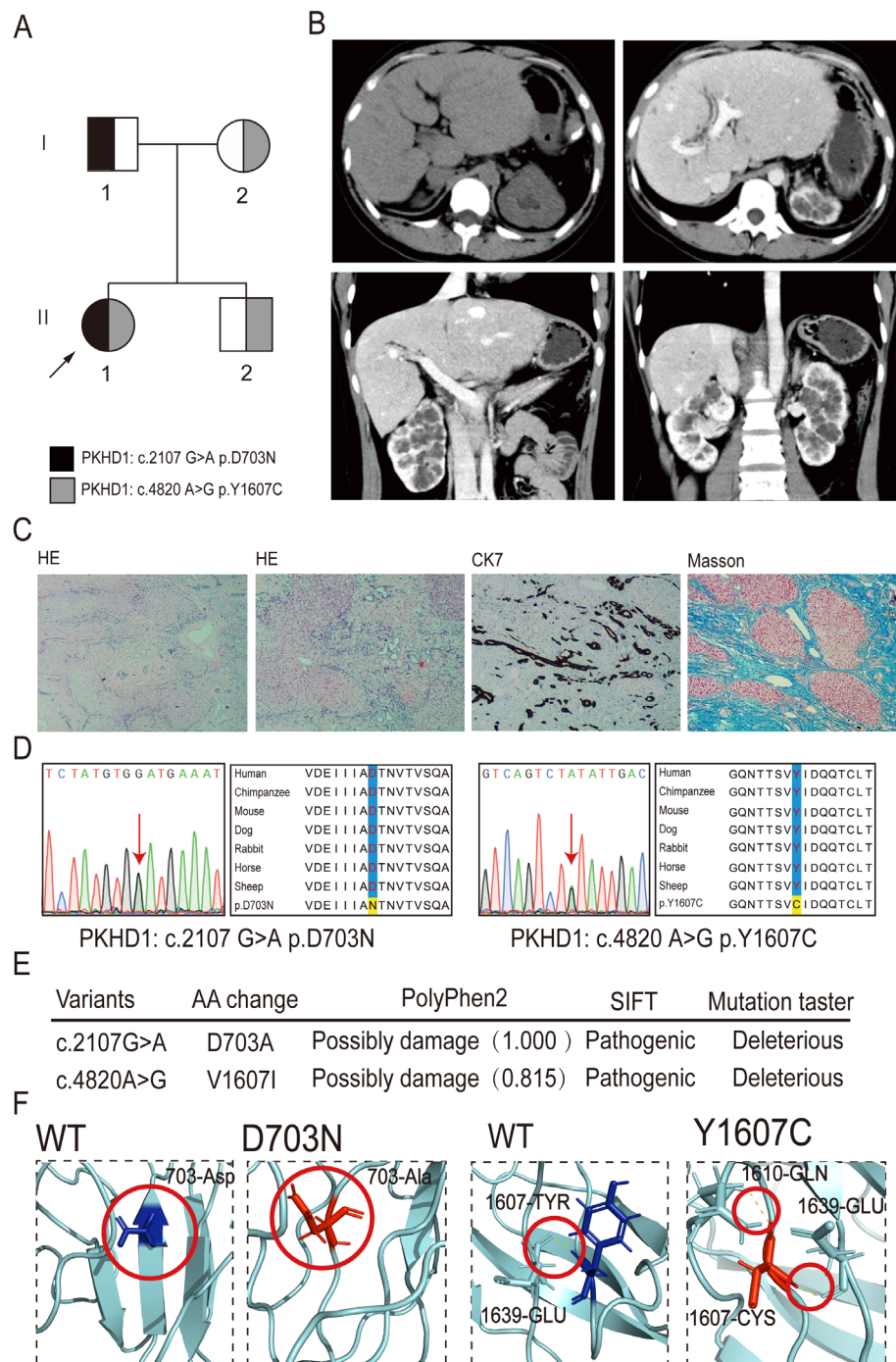


Figure 1. — Identification of a novel PKHD1 variant. (A) Pedigree of the family. II1 was the female patient. (B) Contrast-Enhanced CT Findings: The imaging study identified a narrowing of the intrahepatic segment of the inferior vena cava, atrophy of the right and middle hepatic veins, and the formation of collateral circulation. Hepatomegaly accompanied by hepatic congestion was also observed. Furthermore, esophagogastric varices and dilation of the intrahepatic bile ducts were noted. A vascular tumor or focal nodular hyperplasia (FNH) was suspected in liver segment S2, and gallstones were detected in the neck of the gallbladder. (C) Liver Biopsy Findings: Histopathological analysis revealed mild fibrous thickening of the liver capsule and disorganized lobular architecture, characterized by bridging fibrosis and pseudolobule formation. The bile ducts appeared irregular, with evidence of cholestasis and ductular proliferation. Hepatocytes exhibited mild edema, ballooning degeneration, necrosis, and accumulation of cholestatic pigment. Immunohistochemical analysis demonstrated positive CK7 expression in the bile ducts, a sparse presence of activated Kupffer cells, and a low number of α -SMA-positive hepatic stellate cells. Special staining confirmed the presence of bridging fibrosis. (D) Sanger sequencing and conservation analysis: Sanger sequencing was conducted to validate the two PKHD1 mutations identified in the proband. Conservation analysis revealed that the mutated sites within the PKHD1 protein are highly conserved across multiple species, including humans, chimpanzees, dogs, mice, rabbits, horses, and sheep, indicating their potential functional significance. (E) Results from various predictive software tools: (F) Three-Dimensional Modeling of wild-type (WT) and mutant PKHD1: The partial structure of the PKHD1 protein was modeled using I-TASSER-MTD. This analysis elucidated the spatial positions and conformational alterations associated with the two missense variants, D703N and Y1607C.

bleeding complicating cirrhosis with pancytopenia (white blood cell count $1.48 \times 10^9/L$, hemoglobin 75 g/L, platelet count $37 \times 10^9/L$) in the other hospital. Postoperative histopathological examination revealed chronic congestive splenomegaly in the splenic tissue and cirrhosis in the hepatic tissue. She took anticoagulant medication for half a year after the surgery. Additionally, she took propranolol to prevent variceal bleeding. Upon admission, she was 162 cm tall, weight of 51 kg, and BMI of 19.4 kg/m^2 . She had no obstetric history and reports no history of hypertension, diabetes, hyperlipidemia, or other related conditions. Laboratory investigations showed a white blood cell count (WBC) of $9.68 \times 10^9/L$, hemoglobin (HGB) level of 113 g/L, and an elevated platelet count (PLT) of $565 \times 10^9/L$, consistent with post-splenectomy status. Coagulation profiles were within normal limits. Biochemical assessments indicated compromised renal function, with an estimated glomerular filtration rate (eGFR, CKD-EPI) of 83.19 mL/min (reference value: $>90 \text{ mL/min}$ for normal kidney function, with 60–89 mL/min suggesting mild kidney damage). Liver function tests indicated a mild reduction in albumin (ALB) level of 38.7 g/L (reference value: 35–50 g/L), while other hepatic parameters remained within normal ranges: alanine aminotransferase (ALT) 13.36 U/L (reference value: 7–56 U/L), aspartate aminotransferase (AST) 18.28 U/L (reference value: 8–48 U/L), alkaline phosphatase (ALP) 68.93 U/L (reference value: 44–147 U/L), gamma-glutamyl transferase (GGT) 29.98 U/L (reference value: 9–48 U/L), globulin (GLB) 32.24 g/L (reference value: 20–40 g/L), total bilirubin (TBIL) $10.15 \mu\text{mol/L}$ (reference value: $5.1\text{--}19.0 \mu\text{mol/L}$), and direct bilirubin (DBIL) $2.95 \mu\text{mol/L}$ (reference value: $0\text{--}5.1 \mu\text{mol/L}$). The etiology of chronic liver disease was investigated, and common causes such as HBV, HCV, alcohol, drugs, metabolic dysfunction-associated steatotic liver disease, autoimmune liver disease, and Wilson disease were excluded.

Further diagnostic evaluation included radiological and histopathological analyses. Contrast-enhanced computed tomography (CECT) revealed nodular enhancement in the arterial phase of liver segment S2, along with multiple slightly hypodense lesions in the left hepatic lobe. Thickening of the left branch of the portal vein was observed, suggesting portal hypertension. Numerous small cysts were identified in the liver, accompanied by mild dilation of the bile ducts. Multiple lymph nodes were observed in the right diaphragmatic crus, supra-diaphragmatic region, porta hepatis, and retroperitoneum, some of which were slightly enlarged, with the largest measuring approximately $11 \times 13 \text{ mm}$. A high-density shadow was noted in the gallbladder duct. The bilateral kidneys exhibited multiple cysts, calcifications, and small stones (Fig 1B). Re-examination of the liver biopsy revealed significant disruption of the lobular architecture, extensive bridging fibrosis, and the formation of pseudolobules.

Hematoxylin and eosin (HE) staining demonstrated mild hepatocellular edema, focal necrosis, and irregular bile duct proliferation. Immunohistochemical analysis for CK7 was positive for cholangiocyte markers, indicating extensive cholangiolar-like proliferation with variable morphology and disordered arrangement, suggestive of abnormal bile duct development. Masson's trichrome staining confirmed extensive fibrosis deposition (Fig 1C).

Based on the above results, she was diagnosed with congenital hepatic fibrosis. Given the patient's young age but severe hepatic fibrosis and combined polycystic kidney phenotype, whole exome sequencing (WES) was conducted. Two variants in the PKHD1 gene were identified: a known pathogenic variant, c.2107G>A (p.D703N), and a novel mutation, c.4820A>G (p.Y1607C). These findings were subsequently confirmed through Sanger sequencing (Fig 1D).

Family members were recruited for a family-based genetic analysis with informed consent. Their clinical and genotype data summarized in Table 1. The proband's father (I1) was found to be heterozygous for the known D703N variant and exhibited bilateral renal cysts and multiple small stones as observed via color Doppler ultrasound. The proband's mother (I2) and brother (II2) were carriers of the novel Y1607C variant, displaying distinct phenotypes: the mother presented with fatty liver, while the brother, despite being only 22 years old, had small stones in the intrahepatic bile ducts.

Furthermore, we employed various bioinformatics approaches to assess the pathogenicity of the novel Y1607C variant. Conservation analysis across multiple species revealed that this position is highly conserved (Fig. 1D). According to online predictive tools, the variant is anticipated to be deleterious, as indicated by three different software packages (Fig. 1E). This missense mutation results in the substitution of tyrosine (Y) with cysteine (C) at position 1607 in the PKHD1 protein. Three-dimensional structural modeling demonstrated that this alteration modified hydrogen bond interactions with other amino acids, leading to changes in the protein's tertiary structure (Fig. 1F).

Discussion

ARPKD is a complex disorder characterized by significant phenotypic variability and multi-organ involvement, primarily affecting the kidneys and liver. Clinical studies have demonstrated that patients with ARPKD exhibit a range of clinical manifestations: some present with kidney involvement alone, others with liver involvement alone, and some with both (8, 9, 10). Blyth and Ockenden (11) documented cases illustrating a reciprocal relationship between renal and hepatic involvement. In one group of patients, congenital liver fibrosis was observed with the subsequent development of renal cysts later in life, whereas another group primarily exhibited renal involvement, with visible

Table 1.

	Proband (III)	Father (II)	Mother (I2)	Brother (II2)	Reference
PKHD1 Genotype	D703N/Y1607C	D703N/WT	Y1607C/WT	Y1607C/WT	
Kidney					
- Creatinine (CR) (μmol/L)	86(↓)	/	/	/	52–92
-Glomerular Filtration Rate (GFR, CKD-EPI formula) (ml/min)	83.19 (↓)	/	/	/	≥ 90
- Ultrasound	Multiple hyperechoic lesions in both kidneys	Renal cysts; multiple renal calculi	/	/	
- CT	Multiple renal cysts; calcified sediment and renal calculi	/	/	/	
Liver					
-Albumin (ALB) (g/L)	38.7 (↓)	/	/	/	40–55
- Ultrasound	Hepatomegaly; portal vein dilatation	/	Mild hepatic steatosis	Small intrahepatic bile duct stones	
- CT	Liver cirrhosis; scattered hepatic cysts; mild intrahepatic bile duct dilatation	/	/	/	

liver fibrosis manifesting much later. The multisystemic and severe manifestations of ARPKD necessitate comprehensive multidisciplinary management strategies, which are crucial for improving patient outcomes.

Our case study involves a young female presenting with clinical features affecting both the kidneys (polycystic kidney) and the liver (severe hepatic fibrosis). The complexity of symptoms poses significant challenges for diagnosis and treatment. The final diagnosis of ARPKD was achieved through collaboration among hepatologists, nephrologists, medical geneticists, and other specialists. Molecular diagnosis played a pivotal role in this process. Through the application of molecular genetic testing, precise diagnoses can be achieved at an earlier stage, thereby circumventing the need for unnecessary invasive procedures and facilitating the early detection of kidney and liver complications during disease progression. Furthermore, the results of genetic testing can assist families affected by ARPKD in making informed decisions regarding testing for asymptomatic siblings or considering preimplantation genetic diagnosis for future pregnancies (6).

Individuals diagnosed with Autosomal Recessive Polycystic Kidney Disease (ARPKD) typically possess two pathogenic mutations within the PKHD1 gene. As of now, the NCBI mutation database (<https://www.ncbi.nlm.nih.gov/clinvar>) has documented 649 pathogenic mutations. A substantial number of these mutations are unique to individual pedigrees, with the majority of patients demonstrating compound heterozygosity, which contributes to the genetic heterogeneity observed in

ARPKD. In the present case, the patient is a compound heterozygote, carrying two missense variants: c.2107G>A (p.D703N) and c.4820A>G (p.Y1607C). The D703N variant has been previously linked to renal enlargement and is classified as a pathogenic mutation. (12). In contrast, the pathogenicity of the Y1607C variant has not been conclusively determined. However, bioinformatic analyses suggest that the Y1607C mutation is likely pathogenic (Fig 1E). Three-dimensional structural analysis has indicated that the Y1607C mutation results in alterations to the protein structure (Fig 1F). Examination of the family history revealed that two heterozygous carriers of the Y1607C variant exhibited distinct hepatic phenotypes: the mother was diagnosed with fatty liver, and the brother developed small stones in the intrahepatic bile ducts. Considering the brother's relatively young age and lack of detrimental habits, it is plausible that this hepatic phenotype is associated with the Y1607C variant. These findings strongly suggest that the Y1607C variant is a pathogenic mutation with potential links to liver involvement.

The PKHD1 gene, which is notably large, consists of 67 exons encoding a protein of 4,074 amino acids. Pathogenic variants are distributed throughout the gene, with most mutations being unique to individual families. Despite numerous reported cases, establishing a genotype-phenotype correlation for ARPKD remains a challenge due to significant allelic heterogeneity and the high rate of different compound heterozygotes. Current research has identified the following associations

between PKHD1 genotypes and clinical phenotypes (7, 13): (1) Patients with two truncating mutations typically exhibit a severe phenotype, often resulting in perinatal or neonatal demise (2). Missense mutations exhibit a wide range of effects on protein function and are more commonly identified in patients with a milder clinical presentation. (3) Specific regions within the PKHD1 protein may be associated with distinct phenotypes. Amino acid substitutions in the 709–1837 region have been linked to a slower progression of renal dysfunction, whereas missense mutations in the 2831–2840 and 3051–3209 regions are typically associated with a predominant liver phenotype.

In this study, the female patient, who carries two mutations, presented with symptoms affecting both the kidney and liver. Her father, a heterozygote for the D703N mutation, exhibits renal abnormalities, including bilateral renal cysts and multiple small calculi. This observation aligns with the earlier assertion that the 709–1837 region is more frequently associated with renal manifestations. Conversely, her mother and brother, both carriers of the Y1607C variant, displayed either asymptomatic or mild liver abnormalities, suggesting that this missense mutation may result in reduced protein function, thereby contributing to a clinically milder course.

Conclusion

In summary, through the integration of clinical, radiological, histopathological, and genetic test results, a diagnosis of ARPKD was established in an adult patient, and a novel pathogenic variant, Y1607C, was identified, thereby expanding the known spectrum of PKHD1 mutations. Furthermore, family members carrying the D703N and Y1607C mutations exhibited symptoms affecting the kidney and liver, respectively. This observation suggests that specific regions of the PKHD1 protein may correspond to distinct organ-specific manifestations, thereby enhancing the understanding of genotype-phenotype correlations in ARPKD.

Declarations

Conflict of interests: Authors state no conflict of interest.

Author's contributions: Xuan Shang: Conceptualization; Project administration; Supervision; Writing – original draft. Ganwei Zheng: Data curation; Formal analysis; Methodology; Writing – original draft. Jiameng Si: Data curation. Hammouche Feryel: Formal analysis; Investigation. Miaoxia Liu: Formal analysis; Resources; Methodology; Investigation; Writing – review & editing.

Ethics declarations: This study adhered to ethical standards set forth in the Declaration of Helsinki. All participants provided informed consent before taking part in the research.

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References

1. Zerres K, Mücher G, Becker J, Steinkamm C, Rudnik-Schöneborn S, Heikkilä P, et al. Prenatal diagnosis of autosomal recessive polycystic kidney disease (ARPKD): molecular genetics, clinical experience, and fetal morphology. *Am J Med Genet* 1998;76:137–44.
2. Büscher R, Büscher AK, Weber S, Mohr J, Hegen B, Vester U, et al. Clinical manifestations of autosomal recessive polycystic kidney disease (ARPKD): kidney-related and non-kidney-related phenotypes. *Pediatr Nephrol* 2014;29:1915–25.
3. Hoyer PF. Clinical manifestations of autosomal recessive polycystic kidney disease. *Curr Opin Pediatr* 2015;27:186–92.
4. Menezes LFC, Cai Y, Nagasawa Y, Silva AMG, Watkins ML, Da Silva AM, et al. Polyductin, the PKHD1 gene product, comprises isoforms expressed in plasma membrane, primary cilium, and cytoplasm. *Kidney International* 2004;66:1345–55.
5. Courcet J-B, Minello A, Prieur F, Morisse L, Phelip J-M, Beurdeley A, et al. Compound heterozygous PKHD1 variants cause a wide spectrum of ductal plate malformations. *Am J Med Genet A* 2015;167A:3046–53.
6. Hartung EA, Guay-Woodford LM. Autosomal recessive polycystic kidney disease: a hepatorenal fibrocystic disorder with pleiotropic effects. *Pediatrics* 2014;134:e833–e45.
7. Burgmaier K, Brinker L, Erger F, Beck BB, Benz MR, Bergmann C, et al. Refining genotype-phenotype correlations in 304 patients with autosomal recessive polycystic kidney disease and PKHD1 gene variants. *Kidney International* 2021;100:650–9.
8. Lasagni A, Cadamuro M, Morana G, Fabris L, Strazzabosco M. Fibrocystic liver disease: novel concepts and translational perspectives. *Transl Gastroenterol Hepatol* 2021;6:26.
9. Gunay-Aygun MAT, Baris I, A Bryant, Joy A Daryanani, Kailash T. A Gerstein, Maya Tuchman A Piwnicka-Worms, Katie A Choyke, Peter A Heller, Theo A Gahl, William A. Hepatorenal findings in obligate heterozygotes for autosomal recessive polycystic kidney disease. *Mol Genet Metab* 2011;104:677–81.
10. Guay-Woodford LM, Desmond RA. Autosomal recessive polycystic kidney disease: the clinical experience in North America. *Pediatrics* 2003;111:1072–80.
11. Blyth H, Ockenden BG. Polycystic disease of kidney and liver presenting in childhood. *J Med Genet* 1971;8:257–84.
12. Bergmann C, Senderek J, Sedlacek B, Pegiazoglou I, Puglia P, Eggermann T, et al. Spectrum of mutations in the gene for autosomal recessive polycystic kidney disease (ARPKD/PKHD1). *J Am Soc Nephrol* 2003;14:76–89.
13. Bergmann C, Senderek J, Windelen E, Küpper F, Middeldorf I, Schneider F, et al. Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). *Kidney International* 2005;67:829–48.