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Case Report

Prenatal Diagnosis of Isolated Caroli Disease Caused by a Homozygous *PKHD1* Variant: A Case Report and Literature Review

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Abstract

Background: Caroli disease is a rare ductal plate malformation. While most *polycystic kidney and hepatic disease 1* (*PKHD1*)-related biliary phenotypes arise from compound-heterozygous variants, the prenatal implications of homozygous variants remain unclear. Reporting the first prenatal diagnosis linked to a homozygous *PKHD1* variant, along with the diagnostic workflow, has direct implications for genetic counseling and recurrence prevention strategies. **Case**: A 25-year-old woman, gravida 2, presented with isolated fetal intrahepatic bile duct dilatation at 22^{+5} weeks of gestation. Ultrasound showed arborizing, avascular tubular channels; and fetal magnetic resonance imaging (MRI) confirmed diffuse intrahepatic involvement with normal renal anatomy. Karyotype analysis and chromosomal microarray were normal. Trio-exome sequencing identified a homozygous *PKHD1* c.2507T>C (p.Val836Ala) variant, and Sanger sequencing confirmed parental heterozygosity. Interval surveillance documented enlargement to 47 × 37 × 24 mm. Following multidisciplinary counseling, the pregnancy was electively terminated, and no autopsy was performed. The early, isolated hepatobiliary presentation contrasts with previously reported compound-heterozygous cases. **Conclusions**: Combined ultrasound, fetal MRI, and trio-exome sequencing established an etiologic prenatal diagnosis and refined the differential diagnosis from choledochal cyst and cystic biliary atresia. The homozygous c.2507T>C variant likely confers a dosage-dependent, more severe fetal phenotype, thereby expanding the *PKHD1*-associated spectrum and strengthening genotype–phenotype correlations. These findings provide direct clinical utility and educational value by highlighting key imaging features, outlining a stepwise genomic diagnostic workflow, and emphasizing the utility of preimplantation genetic testing to prevent recurrence.

Keywords: *PKHD1* variants; Homozygote variants; Caroli; prenatal diagnosis

1. Introduction

Caroli disease is a rare congenital malformation of the ductal plate characterized by non-obstructive, cystic dilatation of the intrahepatic bile ducts; when congenital hepatic fibrosis or cirrhosis co-occurs, the phenotype is termed Caroli syndrome [1]. Biallelic variants in *polycystic kidney and hepatic disease 1* (*PKHD1*), which encodes fibrocystin/polyductin expressed in hepatobiliary and renal tubular epithelia, anchor Caroli phenotypes within the hepatorenal fibrocystic disease spectrum. *PKHD1* is the established cause of autosomal recessive polycystic kidney disease (ARPKD), in which biliary abnormalities and congenital hepatic fibrosis are frequent components [2,3].

Across published cohorts, most *PKHD1*-related biliary presentations are compound heterozygous. By contrast, the fetal consequences of homozygous *PKHD1* variants, especially regarding whether they can manifest as an isolated hepatobiliary phenotype without renal involvement, remain poorly defined. This uncertainty has practical consequences for prenatal care. When fetal imaging shows intrahepatic bile-duct dilatation with normal kidneys, clinicians must distinguish Caroli disease from mimics such as choledochal cyst and cystic biliary atresia, and interpret exome findings in support of accurate counseling, perinatal planning, and recurrence-risk management.

Here we describe a fetus with diffuse intrahepatic bile-duct dilatation and normal kidneys in whom trio-based whole-exome sequencing (WES-trio) identified a homozygous *PKHD1* c.2507T>C (p.Val836Ala) variant. By integrating fetal ultrasound, magnetic resonance imaging (MRI), and trio-based WES, this study aimed to define the prenatal presentation of this specific genotype and establish a diagnostic workflow [4]. The findings have direct clinical implications for counseling on prognosis and for informing reproductive decisions, such as recurrence prevention through preimplantation genetic testing.

2. Case Presentation

2.1 Clinical History and Initial Presentation

A 25-year-old gravida 2, para 0 (G2P0) woman was referred to our fetal medicine unit after a suspected hepatobiliary anomaly was noted on the second-trimester anatomic

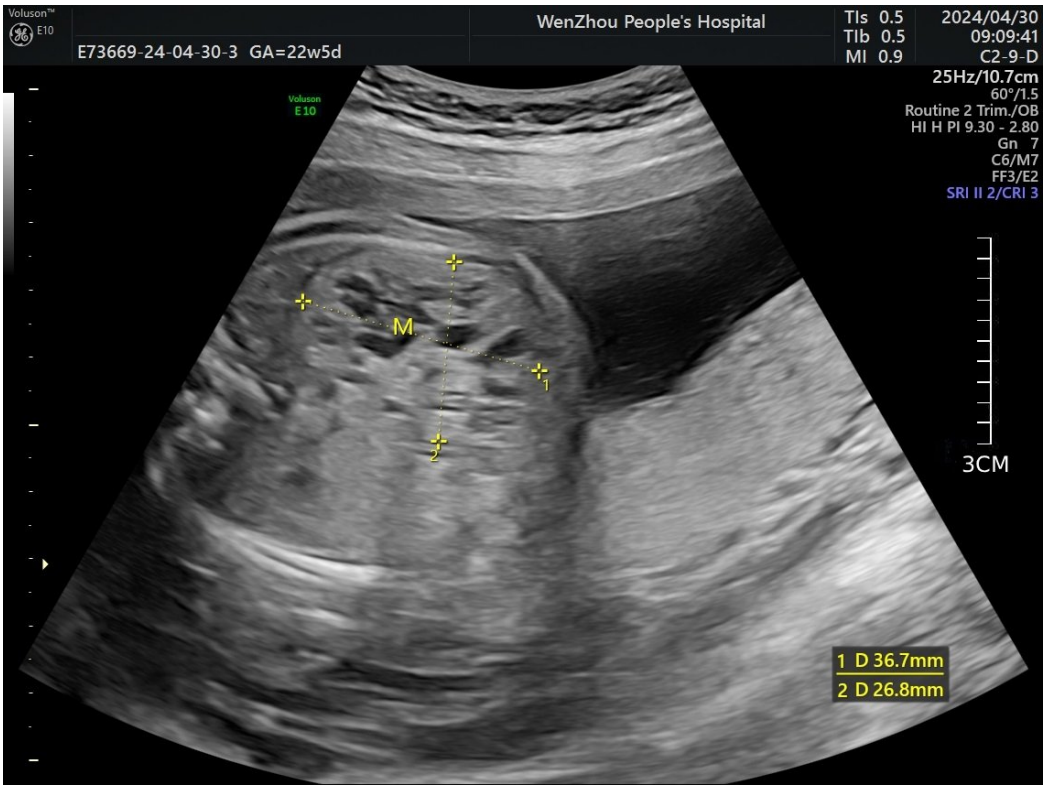

Fig. 1. Fetal ultrasound image demonstrating a dendritic pattern at the intersection of yellow dashed lines within the right lobe of the liver. Image is de-identified.

survey. She and her partner were non-consanguineous Han Chinese. Medical history and medications were unremarkable aside from prenatal vitamins; there was no tobacco, alcohol, or illicit drug exposure. First-trimester screening at 13^{+2} weeks showed a nuchal translucency of 1.5 mm (within normal limits), and cell-free DNA screening at 13^{+2} weeks was low risk for common aneuploidies. A previous pregnancy was electively terminated at 32 weeks after detection of fetal intrahepatic bile duct dilatation; no cytogenetic/genomic testing or post-delivery external examination or autopsy was performed. Fetal sex in the current pregnancy was not disclosed.

2.2 Prenatal Imaging Findings

At 22^{+5} weeks, targeted fetal ultrasound demonstrated a mixed-echogenic lesion in the right hepatic lobe measuring $27 \times 37 \times 26$ mm. Multiple tubular anechoic channels formed a dendritic ("tree-branch") pattern with no internal flow on color Doppler, supporting intrahepatic bile-duct dilatation (Fig. 1). The gallbladder and extrahepatic bile duct appeared unremarkable, and no extrahepatic choledochal cyst was seen. Fetal biometry was appropriate for gestational age, and no additional structural anomalies were identified.

Fetal MRI performed the same week (1.5-T Siemens; predominantly T2-weighted sequences) confirmed ill-defined hilar bile duct structures and diffuse intrahepatic ductal dilatation. The kidneys, bladder, and intestines were normal, with preserved corticomedullary differentiation and no nephromegaly (Fig. 2). The concordant imaging findings supported a ductal-plate malformation within the Caroli spectrum and prompted invasive genetic testing.

2.3 Genetic Analysis

Given the apparently isolated hepatobiliary finding and the couple's adverse obstetric history, amniocentesis (~35 mL) was performed for genetic evaluation. Conventional karyotyping and chromosomal microarray analysis (Affymetrix CytoScan 750K, Lot Number: 901859, Thermo Fisher Scientific, Waltham, MA, US) showed no abnormalities. Trio-based WES-trio identified a homozygous *PKHD1* c.2507T>C (NM_138694.3; p.Val836Ala) variant in the fetus; Sanger sequencing confirmed heterozygosity in both clinically unaffected parents, establishing biparental inheritance (Fig. 3A,B). In-silico prediction tools (SIFT and Condel) supported a deleterious effect. PCR was performed with *PKHD1*-specific primers (forward 5′-CTCCCTTACTGAGTTTCC-3′; reverse 5′-AACAATAAGTCCCTTTCC-3′), and capillary sequencing was undertaken on an ABI 3730XL Genetic Analyzer (Applied Biosystems; Thermo Fisher Scientific, Inc., Foster City, CA, USA) using the BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems; Thermo Fisher Scientific, Inc., Foster City, CA, USA).

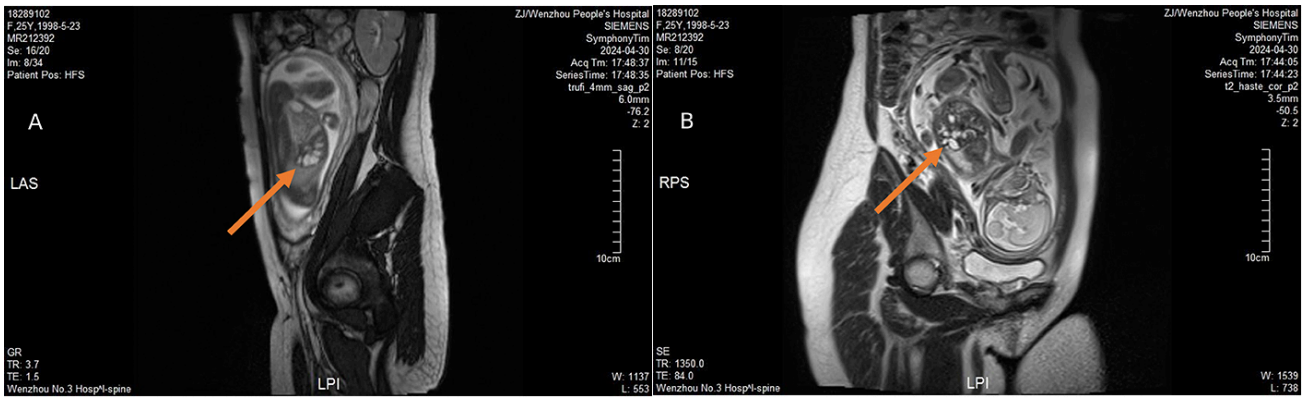

Fig. 2. Fetal MRI findings. (A) MRI shows an ill-defined hilar bile duct (indicated by the orange arrow). (B) MRI reveals dilated intrahepatic bile ducts (indicated by the orange arrow), with no other significant abnormalities detected. Images are de-identified. MRI, magnetic resonance imaging.

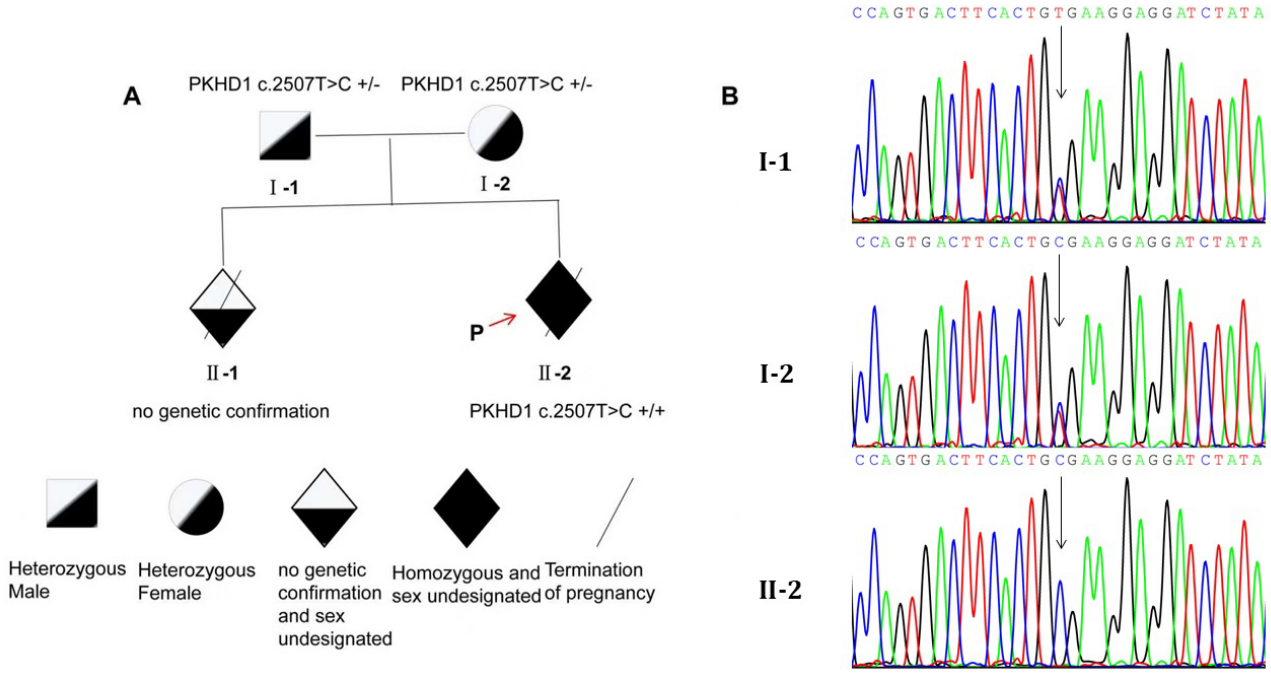

Fig. 3. Pedigree diagram and genetic analysis. (A) Parents are heterozygous carriers (*PKHD1* c.2507T>C, +/–), and fetus (II-2, arrow indicates the proband) carries a homozygous variant (+/+). The red arrow with the letter "P" indicates the proband. (B) Sanger sequencing results of the *PKHD1* gene in I-1, I-2, and fetus II-2; the vertical black arrows indicate the position of the PKHD1 c.2507T>C variant. *PKHD1*, *polycystic kidney and hepatic disease 1*.

2.4 Multidisciplinary Management and Outcome

Upon receipt of the exome result, a multidisciplinary consultation involving maternal-fetal medicine, radiology, and clinical genetics was convened to integrate imaging and genomic data and guide counseling and management. The family received counseling regarding the diagnosis, potential perinatal course, and options for reproductive planning, including preimplantation genetic testing for monogenic disease (PGT-M). Interval surveillance was arranged to monitor lesion evolution and support shared decision-making.

At 25^{+5} weeks, follow-up ultrasound showed interval enlargement of the right-lobe lesion to 47 × 37 × 24 mm, with persistent dendritic anechoic channels and no internal Doppler flow. After further counseling, and in accordance with local regulations, the couple elected termination of pregnancy. No fetal external examination or autopsy/histopathology was performed. Post-test genetic counseling addressed recurrence risk and the option of PGT-M in future pregnancies.

2.5 Diagnostic Synthesis

In summary, the combination of arborizing intrahepatic ductal dilatation without internal vascularity on ultrasound and diffuse intrahepatic involvement with ill-defined hilar ducts on MRI most strongly supported the Caroli spectrum. A choledochal cyst was unlikely, given the predominantly intrahepatic, branching morphology and absence of a solitary extrahepatic cyst. Cystic biliary atresia was less likely in mid-gestation with patent-appearing intrahepatic channels and no ancillary sonographic signs. Hepatic hemangioma was disfavored by the lack of internal Doppler flow and tubular rather than mass-like architecture. Taken together with the homozygous *PKHD1* c.2507T>C result, the findings supported isolated prenatal Caroli disease.

3. Discussion

Variants in the *PKHD1* gene are the primary cause of ARPKD. The *PKHD1*-encoded protein, fibrocystin/polyductin complex (FPC), interacts with NEDD4 ubiquitin ligase-interacting protein 2 (NDFIP2), which interacts with several members of the C2-WWW-HECT domain-containing E3 ubiquitin ligase family. These interactions alter the subcellular localization and function of these ligases, leading to increased activity of transforming growth factor β (TGF-β) and the epithelial sodium channel (ENaC) in bile duct epithelial cells. These molecular changes may ultimately contribute to hepatic and renal fibrosis [5]. Some patients with ARPKD present with clinical features resembling those of Caroli disease [6]. These findings suggest that variants in the *PKHD1* gene not only affect renal development, but also involve the intrahepatic biliary system. Epidemiologically, Caroli disease is exceptionally rare ($\approx$1 per 1,000,000 population), which likely contributes to the scarcity of systematic prenatal series [7]. Furthermore, Caroli disease/Caroli syndrome (CD/CS) lie within the fibropolycystic liver disease spectrum derived from ductal-plate malformations, with phenotype varying by the level and extent of embryologic involvement [8,9].

Caroli disease and ARPKD frequently co-occur, with a reported co-occurrence rate of up to 71% [10]. In addition, studies have reported cases of Caroli disease associated with *PKHD1* gene variants in certain families, even in the absence of overt renal disease [11,12]. Imaging is central to diagnosis. Ultrasonography may reveal cystic dilatation of the intrahepatic bile ducts, particularly in complex cases of Caroli syndrome associated with congenital hepatic fibrosis. In the prenatal setting, the spectrum of isolated congenital hepatobiliary malformations (ICHM) most commonly includes choledochal cysts and cystic biliary atresia, but also encompasses congenital hepatic cysts, gallbladder agenesis/non-visualization, and, less frequently, the Caroli spectrum [13]. A concise, literature-based overview of ICHM entities, prenatal imaging clues, and typical outcomes is provided (Table 1, Ref. [14–18]). Abdominal computed tomography (CT) may demonstrate cystic dilatation with the "central dot sign", or communication between the bile duct and small ductules "tadpole sign" [19–21]. MRI and magnetic resonance cholangiopancreatography (MRCP) are key diagnostic modalities for Caroli syndrome, providing detailed information regarding lesion localization, size, and the presence of intrahepatic bile duct stones [22–24]. Fetal MRI complements ultrasound by delineating the cyst's relationship to the biliary tree and the hepatoduodenal ligament, improving anatomic confidence for choledochal cyst and other ICHM [15]. For suspected CD/CS, prenatal MRI can reveal the central dot sign—the portal fibrovascular bundle within a dilated intrahepatic duct—thereby increasing diagnostic confidence and has been demonstrated in fetuses with ARPKD [14]. A recent prenatal series further reported a consistent central-dot sign across multiple fetuses diagnosed with Caroli disease, underscoring its in-utero utility [25].

ICHM may be subtle in mild cases, and misclassification between choledochal cyst (CC) and cystic biliary atresia (CBA) is common; in a systematic review of prenatal "biliary cysts", approximately 22% proved to be biliary atresia postnatally [26]. Similarly, among perinatally detected subhepatic cysts, 15.4% were ultimately CBA despite sonographic appearances overlapping with CC [27]. Simple biometric cues can assist—cyst width $\leq$2.5 cm strongly favors CBA over CC in early infancy [24]. Beyond the ultrasound, MRI better depicts the cyst's location and continuity with the biliary tree, which helps avoid misdiagnosis and informs perinatal planning (see Table 1). CT and MRCP are important for postnatal confirmation; the central-dot sign is highly suggestive (though not pathognomonic) of the Caroli spectrum [28]. When gallbladder visualization is absent or equivocal, fetal MRI can re-identify a small/contracted gallbladder and help distinguish agenesis from biliary atresia, reducing false-positive NVFGB counseling [18]. By contrast, congenital hepatic cysts typically present late in gestation as isolated unilocular lesions without biliary communication, with generally favorable outcomes [17].

The c.2507T>C variant is a missense variant that results in the substitution of valine (Val) with alanine (Ala) at codon 836 of the *PKHD1* gene. This variant has been associated with Caroli disease. It was first reported in 2014 in a dizygotic twin family in China, in which both twins carried c.2507T>C and c.2341C>T in a compound-heterozygous state and were diagnosed with Caroli disease. The mutations were consistent with familial cosegregation. However, one twin (Patient A) presented with asymptomatic splenomegaly at 1 year of age, was diagnosed with Caroli disease at 5 years due to anorexia and an epigastric mass, and developed cirrhosis and polycystic kidney disease by 7 years. In contrast, the other twin (Patient B) exhibited only intrahepatic biliary dilatation [29]. Liu *et al*. [30] studied three patients with ARPKD. Patient 2 was a 4-year-old male child who presented with polycystic kidney disease spleno-

Table 1. Literature-based overview of ICHM/Caroli spectrum presentations, key imaging features, and complications.

Entity	Typical prenatal presentation (US)	Helpful imaging clues (US/MRI)	Postnatal confirmation/outcome	Representative ref.
Caroli disease/Caroli syndrome	Multiple tubular/branching intrahepatic anechoic channels; often an isolated liver finding	MRI "central dot sign"; assess concomitant ARPKD features	MRCP/CT confirms communication with the biliary tree; risk of cholangitis/portal HTN	[14]
Choledochal cyst	Solitary cyst at porta hepatis; may connect to hepatic/gallbladder ducts	Fetal MRI better defines cyst origin and course along the hepatoduodenal ligament	MRCP + surgery (cyst excision, biliary reconstruction)	[15]
Cystic biliary atresia	Small hilar cyst with non-visualized/small gallbladder	Cyst size threshold ($\leq$2.5 cm) favors CBA over CC in infants; careful GB assessment	Early cholangiography; Kasai portoenterostomy	[16]
Congenital hepatic cyst	Isolated, unilocular intrahepatic cyst discovered in late gestation	No biliary communication on MRCP; often incidental	Many remain asymptomatic; selective resection if growth/pressure	[17]
Gallbladder agenesis/Non-visualization (NVFGB)	GB not seen or very small on US	Fetal MRI can re-identify a small/contracted GB and reduce false-positive NVFGB	Often benign if isolated; evaluate for BA/genetic causes if non-isolated	[18]

ICHM, isolated congenital hepatobiliary malformations; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; CT, computed tomography; HTN, hypertension; GB, gallbladder; ARPKD, autosomal recessive polycystic kidney disease; US, ultrasound; CBA, cystic biliary atresia; CC, choledochal cyst; BA, biliary atresia.

Table 2. Summary of reported cases with the *PKHD1* c.2507T>C variant.

Case	Age (years)	Gender	Genotype	Presentation at detection	Hepatic features	Renal features	Imaging highlights	Diagnosis (Caroli/ ARPKD/Both)	Inheritance pattern	Ref.
1	4	M	c.2507T>C (p.V836A) & c.2278C>T (p.R760C)	Early childhood ARPKD with polycystic kidneys and congenital hepatic fibrosis	Intrahepatic bile duct dilatation; CHF; liver size largely preserved	Bilaterally enlarged kidneys; increased medullary echoes; loss of corticomedullary differentiation; multiple renal cysts	US: enlarged echogenic kidneys with CMD loss; CT/MRI: multiple bilateral renal cysts with intrahepatic bile duct dilatation; spleen normal	Both	AR (compound het.)	Liu *et al*. [30]
2	8 months	M	c.2507T>C (p.V836A) & c.9292G>A (p.G3098R)	Asymptomatic hepatomegaly and nephromegaly were found on routine check	Intrahepatic bile-duct dilatation; serum fibrosis markers elevated; extrahepatic ducts not dilated	Bilaterally enlarged kidneys with loss of corticomedullary differentiation; multiple microcysts; early renal injury (microalbuminuria)	US: enlarged echogenic kidneys with comet-tail; coarse, mesh-like hepatic echotexture; MRCP: mild saccular/branching intrahepatic ductal dilatation	Both	AR (compound het.)	Yang *et al*. [31]
3	5 (Younger of twins)	M	c.2507T>C (p.V836A) & c.2341C>T (p.R781*)	Splenomegaly by 1 y; at 5 y, presented with anorexia and upper abdominal mass, diagnosed as Caroli disease	Progressed to cirrhosis, portal hypertension with hypersplenism; severe anemia; mild jaundice during follow-up	Developed polycystic kidneys later in the course	US/CT/MRI: intrahepatic biliary dilatation; later bilateral renal cysts	Both	AR (compound het.)	Hao *et al*. [29]
4	5 (Older of twins)	M	c.2507T>C (p.V836A) & c.2341C>T (p.R781*)	Detected on family work-up; clinically quiescent at report	Intrahepatic bile-duct dilatation without symptoms	No overt renal disease at the time of report	Imaging showed intrahepatic ductal dilatation; no major extrahepatic findings	Caroli	AR (compound het.)	
5	18	F	c.2507T>C (p.V836A) & c.5935G>A (p.G1979R)	Adolescent evaluated for cystic kidney disease; hepatic abnormalities noted	Hepatic fibrosis; mild intrahepatic bile-duct dilatation reported in the cohort/literature	Bilateral renal cysts; renal function status not detailed in the source summary	US/MRI: renal cysts; intrahepatic ductal changes; no extrahepatic duct dilatation specified	Both	AR (compound het.)	Qiu *et al*. [32]
6	17	M	c.2507T>C (p.V836A) & c.10156G>C (p.V3386L)	Atypical Caroli syndrome with congenital hepatic fibrosis on biopsy; portal hypertension; bile-duct malformation/dilatation; cholestasis	Atypical Caroli syndrome with congenital hepatic fibrosis on biopsy; portal hypertension; bile-duct malformation/dilatation; cholestasis	No polycystic kidney disease; kidneys normal morphology on CT/US	US: dilated third-order intrahepatic bile ducts; CT: hepatosplenomegaly with giant spleen, no intrahepatic cysts; kidneys normal	Caroli	AR (compound het.)	Zhou *et al*. [34]
7	17	M	c.2507T>C (p.V836A) & c.2240dupT (p.A748Gfs*18)	Evaluated for renal cysts with elevated creatinine; hyperuricemia	Not reported at diagnosis	Multiple bilateral renal cysts; creatinine ~276 µmol/L	US/CT: multiple renal cysts; no specific hepatic imaging findings noted	ARPKD	AR (compound het.)	Bi *et al*. [35]
8	54	M	c.2507T>C (p.V836A) & c.572G>C (p.C191S)	Adult-onset renal cysts; clinically stable	Incidental liver cyst	Multiple small (≤2 cm) bilateral renal cysts; creatinine normal	Imaging: small bilateral renal cysts; additional incidental findings (prostate stones; colonic mucinous tubular adenoma; colon polyps)	ARPKD	AR (compound het.)	

CMD, corticomedullary differentiation; AR, autosomal recessive; M, male; F, female; *, stop codon.

megaly at 1 year of age, was diagnosed with Caroli disease at 5 years due to anorexia and an epigastric mass, and developed cirrhosis and polycystic kidney disease by 7 years. In contrast, the other twin (Patient B) exhibited only intrahepatic biliary dilatation [29]. Liu *et al.* [30] studied three patients with ARPKD. Patient 2 was a 4-year-old male child who presented with polycystic kidney disease and intrahepatic biliary dilatation. Genetic analysis identified c.2507T>C and c.2278C>T compound heterozygous variants in the *PKHD1* gene, which were inherited from each parent, respectively. Yang *et al.* [31] reported an 8-month-old child with no abnormalities detected on prenatal ultrasound. At 8 months of age, the child was diagnosed with polycystic kidney disease and intrahepatic bile duct dilatation due to hepatomegaly. Genetic analysis revealed compound heterozygous variants in the *PKHD1* gene (c.2507T>C and c.9292G>A), which were inherited from clinically unaffected parents. Qiu *et al.* [32] conducted a retrospective study on 29 Chinese children with *PKHD1* gene variants, among whom one child was identified with compound heterozygous variants c.2507T>C and c.5935G>A, clinically presenting with mild dilatation of the intrahepatic bile ducts. Ishiko *et al.* [33] studied 32 patients with ARPKD, among whom six carried the c.2507T>C variant, all of whom were compound heterozygotes for c.2507T>C and other *PKHD1* variants. Among these six patients, two had isolated Caroli disease, one had Caroli disease with liver fibrosis, one had liver fibrosis alone, and two developed liver cysts (Table 2, Ref. [29–32,34,35]).

The patient reported in this study is homozygous for the c.2507T>C variant, and to our knowledge, no similar case has been previously documented. In the patient's first pregnancy, fetal bile duct dilatation was detected at 32 weeks of gestation, and bile duct dilatation was again observed at 22^{+5} weeks in the current pregnancy. Taken together with previous literature reports, the onset time and severity of disease vary significantly among patients carrying the same variant—even among twins. Twin A developed asymptomatic splenomegaly at 1 year of age and, two years after the diagnosis of Caroli disease due to liver cirrhosis, presented with hypersplenism, severe anemia, and polycystic kidney disease. In contrast, Twin B exhibited only intrahepatic biliary dilatation [29]. The clinical presentation of this homozygous case appears more severe than many phenotypes described in the literature for compound heterozygous states. A key distinction is the early disease manifestation, with bile duct abnormalities detected at 22^{+5} weeks of gestation in our fetus, whereas other cases typically present at a later age. At the molecular level, the c.2507T>C (p.Val836Ala) variant resides within the transmembrane domain of fibrocystin, a protein encoded by the *PKHD1* gene, which plays a crucial role in maintaining ciliary structure and bile homeostasis in bile duct epithelial cells [36]. An *in vitro* functional study has demonstrated that the localization of fibrocystin to cilia is closely linked to its biological function. The Val836Ala variant may impair fibrocystin function, leading to its mislocalization away from cilia and disruption of ciliary signaling pathways [37]. Unlike compound heterozygous variants, which only partially impair fibrocystin function, homozygous variants may result in a more substantial reduction of biallelic fibrocystin activity. This dose-dependent effect may explain the early embryonic development of bile duct abnormalities in this case. Furthermore, the variant site is located adjacent to a phosphorylation site (Ser833), and the amino acid substitution may interfere with interactions between fibrocystin and other cilia-related proteins, such as hepatocyte nuclear factor 1-beta (HNF1-β) [38], thereby exacerbating the development of bile-duct plate malformations.

Regarding the prognosis of Caroli disease, some patients maintain good long-term health with appropriate medical or surgical management. For example, the literature describes a case in which the patient remained in good health for more than 21 years following surgical intervention [39]. Another study reported four familial cases, in which a male patient presented with acute cholangitis at 6 years of age, while the other three sisters were asymptomatic at diagnosis. All four patients remained alive and asymptomatic for over 22 years at the final follow-up [40]. These findings suggest that, in certain cases, the long-term prognosis for patients with Caroli disease can be favorable. However, Caroli disease can also lead to several serious complications. The most common clinical manifestation is recurrent cholangitis. Additionally, Caroli disease is associated with portal hypertension and cirrhosis, as intrahepatic bile duct dilatation may promote gallstone formation, which can subsequently cause biliary colic, jaundice, and acute pancreatitis [24]. There is also an increased risk of malignancy. A study has shown that approximately 7% of patients who are not candidates for radical surgery develop cancer [41].

In summary, patients with Caroli disease exhibit diverse clinical manifestations and genetic variants. Although all cases involve *PKHD1* gene mutations, the phenotypic expression varies significantly depending on the specific variant location. Despite our effort to collect all reported cases carrying the c.2507T>C variant, no homozygous case has been previously documented. Therefore, our report provides crucial clinical insights by being the first to link a homozygous *PKHD1* variant to an early-onset, isolated prenatal Caroli disease. This finding is significant because it expands the known phenotype and alerts clinicians to consider this diagnosis even with normal fetal kidneys. As the diagnosis was made prenatally and the pregnancy was terminated, long-term clinical follow-up was not possible. Both parents were identified as carriers of the c.2507T>C variant and showed no abnormalities on ultrasound examination. Ultimately, achieving a definitive

molecular diagnosis offers immediate and tangible value for at-risk families by enabling precise recurrence counseling and providing a clear path to prevent recurrence through the use of PGT-M. Recent prenatal reports also emphasize that integrating fetal ultrasound/MRI with trio-based exome sequencing improves recognition of CD/CS and supports tailored counseling [42]. This study provides the first evidence that a homozygous c.2507T>C variant in the *PKHD1* gene can cause isolated fetal Caroli disease.

Limitations

Despite its limitations—including the lack of postmortem pathological data, which limits our understanding of hepatic fibrosis, and a relatively small sample size—further functional studies are warranted to confirm the pathogenicity of this homozygous variant. Our findings highlight the critical role of prenatal WES-trio combined with imaging in early diagnosis and provide essential support for PGT-M intervention in high-risk families. Future research should include functional experiments and long-term cohort studies to further elucidate the dynamic impact of this variant on bile duct development and its long-term clinical outcomes.

4. Conclusions

This study reports the first known prenatal diagnosis of isolated Caroli disease caused by a homozygous *PKHD1* c.2507T>C (p.Val836Ala) variant. It demonstrates how integrated fetal ultrasound, fetal MRI, and WES-trio can resolve challenging hepatobiliary differentials in mid-gestation. The early, liver-limited presentation with normal fetal kidneys refines the prenatal phenotype associated with *PKHD1*. The homozygous state appears to correlate with earlier and more severe ductal involvement, suggesting a potential dosage effect on fibrocystin function. These insights provide immediate clinical utility by enabling precise genetic counseling, guiding perinatal management, and offering families a definitive strategy for recurrence-risk reduction through PGT-M. The case expands *PKHD1* genotype–phenotype correlations and offers practical imaging–genomic teaching points for fetal medicine and clinical genetics. Further functional and longitudinal studies are needed to validate mechanisms and refine prognostication.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to ethical and privacy restrictions related to human genomic data, some raw sequencing data are not publicly available. The publicly accessible data have been deposited in Zenodo https://doi.org/10.5281/zenodo.18263668.

Author Contributions

JZ and HW designed the case report study. HW, HC, ZZ, and HZ acquired and interpreted the clinical and imaging data. XZ and HP performed the genomic sequencing and interpreted the genetic results. YW performed the literature search and data synthesis. ZX interpreted the imaging findings and designed the figures. JZ critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was carried out in accordance with the guidelines of the Declaration of Helsinki. This study was approved by the Ethics Review Committee of Wenzhou People's Hospital (Approval No. KY-202411-009). The authors confirm that written consent for the submission and publication of this case report, including all associated images, clinical data, and other information contained in the manuscript, has been obtained from the patient.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG45794.

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