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Adult Congenital Hepatic Fibrosis and Autosomal Dominant Polycystic Kidney Disease with PAX2 and PKD1 Variants: A Case Report

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Case Report

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Abstract

Purpose

Congenital hepatic fibrosis (CHF) is a rare ductal plate malformation typically associated with autosomal recessive polycystic kidney disease. Its co-occurrence with autosomal dominant polycystic kidney disease (ADPKD) in adults is exceptionally rare and poses diagnostic challenges. This study reports a case of a 39-year-old female diagnosed with CHF and ADPKD and investigate its genetic underpinnings.

Methods

The patient underwent a comprehensive diagnostic evaluation, including laboratory testing, abdominal imaging (computed tomography/ultrasonography), transient elastography (FibroScan), and histopathological analysis of a liver biopsy. Genetic analysis was performed using targeted next-generation sequencing (NGS) to identify potential mutations and pedigree analysis was conducted.

Results

The 39-year-old patient presented with thrombocytopenia and hepatosplenomegaly. Imaging revealed multiple renal cysts and intrahepatic bile duct dilatation with evident signs of portal hypertension, including splenorenal shunts and varices, despite preserved liver synthetic function. Liver biopsy confirmed CHF through characteristic histology. Targeted NGS identified a heterozygous *PKD1* mutation (c.2534T > C, p.Leu845Ser) and a maternally inherited *PAX2* mutation (c.95C > G, p.Pro32Arg). Notably, the patient lacked ocular anomalies typical of *PAX2*-related syndromes. She is currently stable under conservative management.

Conclusions

This case suggests that the *PAX2* variant may act as a genetic modifier, influencing the phenotypic expression of *PKD1*-mediated disease to include hepatic fibrosis. Our findings underscore the phenotypic variability of hepatorenal fibrocystic diseases and highlight the utility of genetic profiling in diagnosing atypical presentations in adult patients.

Introduction

Congenital hepatic fibrosis (CHF) is a rare developmental liver disorder characterized by ductal plate malformation (DPM), which results in the persistence of embryonic bile duct structures and progressive periportal fibrosis.(Zhu et al., 2020) While hepatic function often remains preserved, the disease typically manifests in childhood or adolescence with sequelae of portal hypertension, such as splenomegaly and esophageal varices.(Zhu et al., 2020) CHF is most commonly associated with autosomal recessive

polycystic kidney disease (ARPKD), caused by mutations in the *PKHD1* gene encoding fibrocystin/polyductin, a key protein in ciliary function and tubulogenesis.(Ward et al., 2002) In ARPKD, the liver phenotype is invariably present, ranging from DPM to severe fibrosis.(Gunay-Aygun et al., 2013, Burgmaier et al., 2023)

In contrast, Autosomal Dominant Polycystic Kidney Disease (ADPKD), caused by mutations in *PKD1* or *PKD2*, typically presents with polycystic liver disease characterized by non-communicating cysts, rather than hepatic fibrosis.(O'Brien et al., 2012, Brancatelli et al., 2005) The co-occurrence of CHF in patients with ADPKD is exceptionally rare, and the mechanisms driving this phenotypic overlap remain poorly understood.(Liu et al., 2024, Sila et al., 2023) Recent studies suggest that phenotypic variability in fibrocystic diseases may be influenced by genetic modifiers or oligogenic inheritance patterns rather than a single gene defect.(Bergmann et al., 2005)

One candidate modifier is the paired box 2 (*PAX2*) gene, encoding a transcription factor critical for urogenital development. *PAX2* is expressed in the collecting duct lineage and is essential for branching morphogenesis.(Saifudeen et al., 2012) Although *PAX2* mutations are classically associated with Renal-Coloboma Syndrome, experimental data demonstrate that *Pax2* haploinsufficiency significantly modifies cystogenesis progression in *Pkd1*-mutant mouse models.(Stayner et al., 2006) suggesting a potential epistatic interaction between *PAX2* and *PKD*-associated pathways.

Diagnosing CHF in adults with ADPKD poses significant challenges due to delayed diagnosis from non-specific symptoms.(Liu et al., 2024, Loeb et al., 2024) Herein, we report a rare case of an adult female presenting with CHF and ADPKD features, confirmed by histopathology and genetic analysis. Targeted next-generation sequencing (NGS) identified a pathogenic *PKD1* variant and a potentially modifying *PAX2* variant. This case underscores the importance of considering genetic modifiers in atypical hepatorenal phenotypes and highlights the utility of comprehensive genetic profiling in adult patients.

Case presentation

A 39-year-old female presented for evaluation of a suspected familial genetic disorder. She had no prior history of liver disease or significant alcohol consumption. Her visit was prompted by the identification of *PAX2* and *PKD1* mutations in her children. Family history was notable for renal disease: her father had PKD requiring dialysis, and her mother had undergone kidney transplantation for renal failure. The pedigree suggested autosomal dominant inheritance (Fig. 1).

Upon admission, the patient reported a history of intermittent diarrhea following the consumption of fatty or cold foods, as well as symptoms suggestive of coagulopathy, including gingival bleeding and abnormal uterine bleeding over the past year. She also noted recurrent episodes of urticaria-like rashes. Physical examination revealed pale conjunctivae and palpable splenomegaly. Given the potential association with *PAX2* mutations, an ophthalmic examination was performed, which revealed no evidence of optic nerve coloboma or other visual defects.

Laboratory findings revealed persistent thrombocytopenia (platelet count: 77–113 × 10^9/L; reference: 150–450 × 10^9/L) present since adolescence. Platelet-associated antibodies were negative. Liver biochemistry showed low-normal alkaline phosphatase (ALP: 35 U/L; reference: 40–129 U/L) and mildly decreased ceruloplasmin (14.6 mg/dL; reference: 16–45 mg/dL). Serum protein electrophoresis revealed mild hypergammaglobulinemia (gamma-globulin: 15.6%; reference: 11.1–18.8%). Viral hepatitis markers were negative except for anti-hepatitis A virus (HAV) immunoglobulin G (IgG), indicating past immunity. Autoimmune markers—antinuclear antibody (ANA), antimitochondrial antibody (AMA), and perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA)—were negative.

Abdominal computed tomography (CT) and ultrasonography revealed findings consistent with cirrhosis and portal hypertension. Axial CT scans demonstrated multiple bilateral renal cysts, consistent with the diagnosis of ADPKD (Fig. 2A, **white arrows**). Coronal imaging identified extensive collateral circulation secondary to portal hypertension, including paraesophageal varices at the gastroesophageal junction (Fig. 2B, **red arrow**) and a prominent splenorenal shunt (Fig. 2B, **blue arrow**). Additionally, intrahepatic bile duct (IHD) dilatation (0.6 cm) was observed in the absence of mechanical obstruction (Fig. 2C, **green arrow**). Significant splenomegaly, with a maximal diameter of 14.1 cm, was further documented (Fig. 2D). No hepatocellular carcinoma or portal vein thrombosis was identified. Liver stiffness measurement (FibroScan) was 14 kPa, indicative of advanced fibrosis. Although magnetic resonance imaging (MRI) raised suspicion for primary sclerosing cholangitis (PSC) or primary biliary cholangitis (PBC), these were excluded based on negative serologic markers. Upper gastrointestinal endoscopy revealed mild chronic superficial gastritis without varices requiring intervention.

To investigate the structural cause of portal hypertension and differentiate the condition from cryptogenic cirrhosis, a liver biopsy was performed. Histopathological examination provided definitive evidence of congenital hepatic fibrosis (CHF). At low magnification, the liver architecture exhibited a characteristic "jigsaw" pattern, where dense fibrous septa partitioned the hepatic parenchyma into irregularly shaped islands (Fig. 3A, 3B; **blue arrows**). Notably, these islands lacked regenerative nodules, and the hepatic plates within them remained well-preserved, a finding that explains the maintained synthetic function despite advanced fibrosis.

Intermediate-magnification imaging revealed ductal plate malformation (DPM), manifested by numerous irregularly dilated and branched bile ducts forming complex networks within the expanded portal tracts (Fig. 3C, 3D; **green arrows**). Functional bile stasis was evidenced by the presence of inspissated bile plugs within these dilated biliary lumens (Fig. 3C; **black arrows**). The developmental nature of these biliary structures was confirmed at higher magnifications. Specifically, malformed ducts exhibited a characteristic interrupted linear arrangement at the fibro-lobular interface (Fig. 3E; **green arrows**). At the highest magnification (400x), these ducts were found to be lined by a single layer of well-differentiated cuboidal epithelium, a definitive hallmark of DPM (Fig. 3F; **green arrows**). These comprehensive pathological findings, combined with the imaging and genetic data, confirmed the diagnosis of CHF associated with ADPKD.

Targeted NGS identified two heterozygous variants: a *PKD1* missense variant (NM_001009944.3:c.2534T > C, p.Leu845Ser; rs199476100), classified as "likely pathogenic" per American College of Medical Genetics and Genomics (ACMG) guidelines, and a maternally inherited *PAX2* missense variant (c.95C > G, p.Pro32Arg).

Based on clinical, histological, and genetic findings, the patient was diagnosed with CHF associated with ADPKD. Management included strict blood pressure control with renin-angiotensin system (RAS) inhibitors for renal protection and surveillance for portal hypertension complications. Bleeding risk monitoring was prioritized given hypersplenism-associated thrombocytopenia. Genetic counseling was recommended for family members. At recent follow-up, the patient remained clinically stable without variceal bleeding or renal function deterioration.

Discussion

CHF is a hereditary DPM disorder typically manifesting in childhood and frequently associated with ARPKD caused by *PKHD1* mutations.(Zhu et al., 2020) Its occurrence in adults with ADPKD represents a diagnostic dilemma due to overlapping features and the absence of typical *PKHD1* involvement.(O'Brien et al., 2012, Liu et al., 2024) Although sporadic cases of CHF in patients with ADPKD phenotypes were reported in the pre-genomic era,(Tazelaar et al., 1984, Kerr et al., 1961) the molecular basis remained elusive. We present a case of adult CHF and ADPKD characterized by a unique genetic profile involving heterozygous variants in both *PKD1* and *PAX2*.

Clinically, this case illustrates the "portal hypertension-predominant" phenotype of adult CHF, which often leads to misdiagnosis. Unlike typical ADPKD patients who progress to renal failure, our patient presented with severe portal hypertension complications (splenorenal shunts, varices) while maintaining preserved hepatic synthetic function. This pattern aligns with observations by O'Brien et al.,(O'Brien et al., 2012) who described ADPKD patients with CHF exhibiting disproportionately severe portal hypertension relative to their renal disease. Furthermore, as noted by Loeb et al.,(Loeb et al., 2024) thrombocytopenia —as observed in our patient—is often the first indicator of latent portal hypertension, serving as a critical signal for clinicians to investigate beyond hepatic cysts.

Histopathologically, diagnosis was confirmed by identifying DPM. According to Desmet,(Desmet, 1998) DPM results from failure of embryonic bile ducts to remodel, leading to persistent biliary structures and progressive periportal fibrosis. In this case, liver biopsy was essential to distinguish CHF from cryptogenic cirrhosis, as the characteristic "jigsaw" fibrosis pattern without regenerative nodules explained the preserved synthetic function despite advanced fibrosis. The discrepancy between "cirrhotic" imaging appearance and preserved hepatic function is a hallmark of CHF described by Alsomali et al.(Alsomali et al., 2020), reinforcing the necessity of histological confirmation in atypical cases.

Genetically, the coexistence of *PKD1* and *PAX2* variants offers a compelling hypothesis for this rare phenotype. While *PKD1* mutations typically cause renal and hepatic cysts, they rarely induce fibrosis.

(Brancatelli et al., 2005) The identified *PKD1* c.2534T > C variant likely drives the renal cystic phenotype, whereas hepatic fibrosis suggests involvement of a genetic modifier. *PAX2* is a transcription factor essential for urogenital development. Although classically associated with Renal-Coloboma Syndrome, Fu et al.(Fu et al., 2025) demonstrated that ocular anomalies are not obligate features—consistent with our patient's presentation.

We hypothesize a synergistic interaction between *PKD1* and *PAX2* as the driver of this severe hepatorenal phenotype. This hypothesis is supported by experimental evidence from murine models: Stayner et al.(Stayner et al., 2006) demonstrated that *Pax2* haploinsufficiency in *Pkd1*-mutant mice significantly alters cystogenesis, providing direct evidence of epistatic interaction between these two genes. Mechanistically, Qin et al.(Qin et al., 2012) showed that *Pax2* overexpression is a downstream consequence of aberrant c-Met/Wnt signaling in *Pkd1*-deficient cells, directly promoting cystogenesis. Additionally, Saifudeen et al.(Saifudeen et al., 2012) highlighted the p53-Pax2 pathway's role in nephrogenesis. Extrapolating from these findings, the combined effect of the *PKD1* variant and *PAX2* mutation in our patient may have disrupted ciliary signaling pathways essential for biliary remodeling, shifting the phenotype from simple cyst formation (PLD) to malformation and fibrosis (CHF). This interpretation aligns with the "oligogenic" model proposed in ciliopathies, where phenotypic severity depends on mutational burden across interacting genes.(Bergmann et al., 2005) However, functional validation of this specific variant combination remains necessary to confirm causality.

In conclusion, this report expands the phenotypic spectrum of ADPKD to include CHF and implicates *PAX2* as a potential genetic modifier. It underscores the necessity of considering CHF in adult patients with unexplained liver fibrosis and renal cysts.(Sila et al., 2023) Furthermore, our findings support the utility of comprehensive genetic profiling in atypical cases to elucidate the complex molecular underpinnings of hepatorenal fibrocystic diseases and facilitate personalized long-term monitoring. Ultimately, this case highlights that proactive genetic counseling based on meticulous pedigree analysis is essential for implementing precision medicine and early screening strategies in families affected by rare hereditary disorders.

Declarations

Conflict of Interest:

The authors declare no conflicts of interest for this article.

Ethics Approval and Consent to Participate:

The protocol for this research project has been approved by the Institutional Review Board of Severance Hospital (Approval No. 4-2025-1675). The requirement for informed consent was waived by the Institutional Review Board due to the retrospective nature of the study and the use of de-identified clinical data.

Consent for Publication

The requirement for informed consent for publication was waived by the Institutional Review Board due to the retrospective nature of the study and the use of de-identified clinical data.

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Author Contribution

Jung Pyo Hong and Da Bin Lee wrote the original draft. Jun Yong Park reviewed and edited the manuscript. Da Bin Lee, Dong Yun Kim, and Taek Chung performed data curation. All authors read and approved the final manuscript.

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none.

Data Availability

The datasets presented in this article are not readily available because of ethical/privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

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Figures

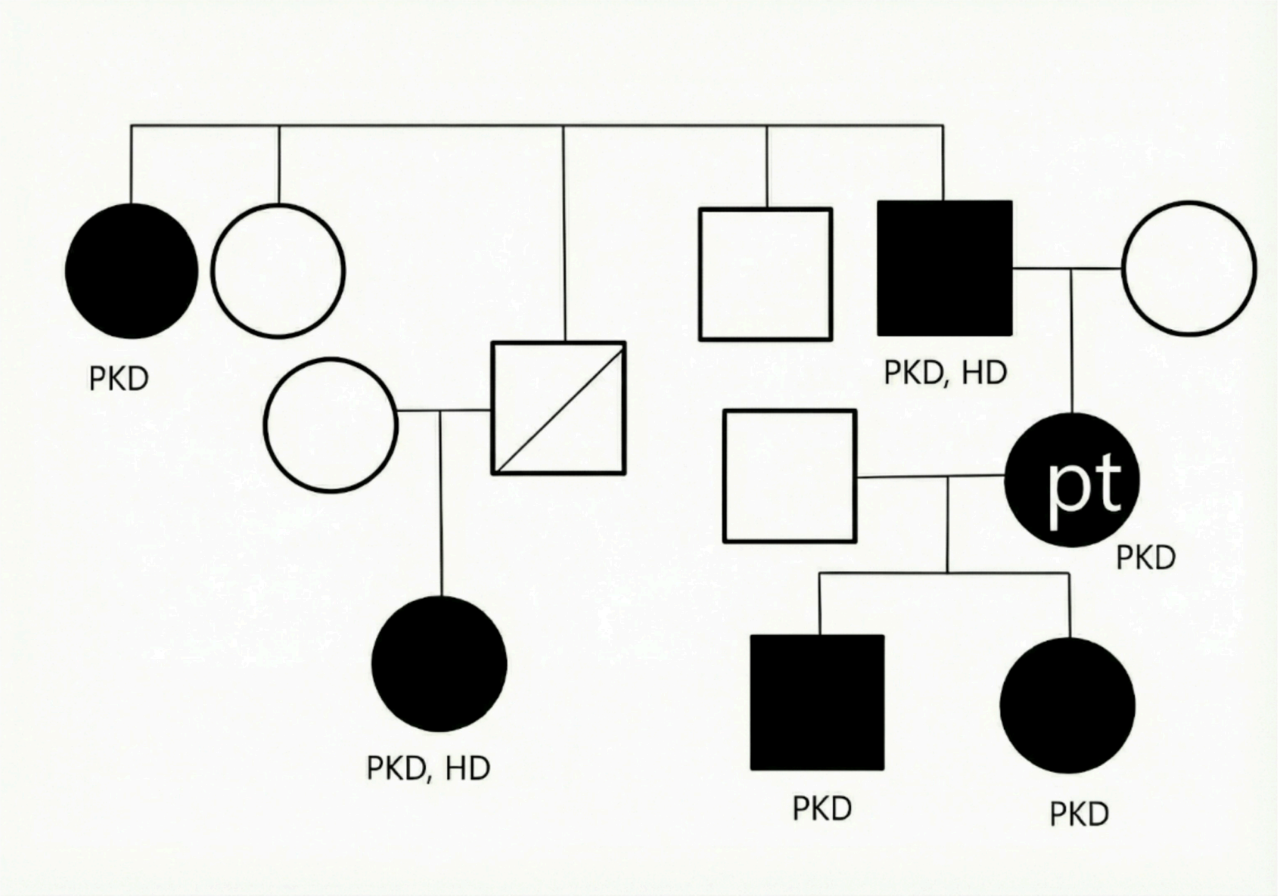


Figure 1

Pedigree of the patient's family. The pedigree illustrates an autosomal dominant inheritance pattern of hepatorenal fibrocystic disease. The proband (**arrow**) presented with both *PKD1* and *PAX2*variants. Squares represent males, and circles represent females. A diagonal line indicates deceased status, and filled symbols represent affected individuals.

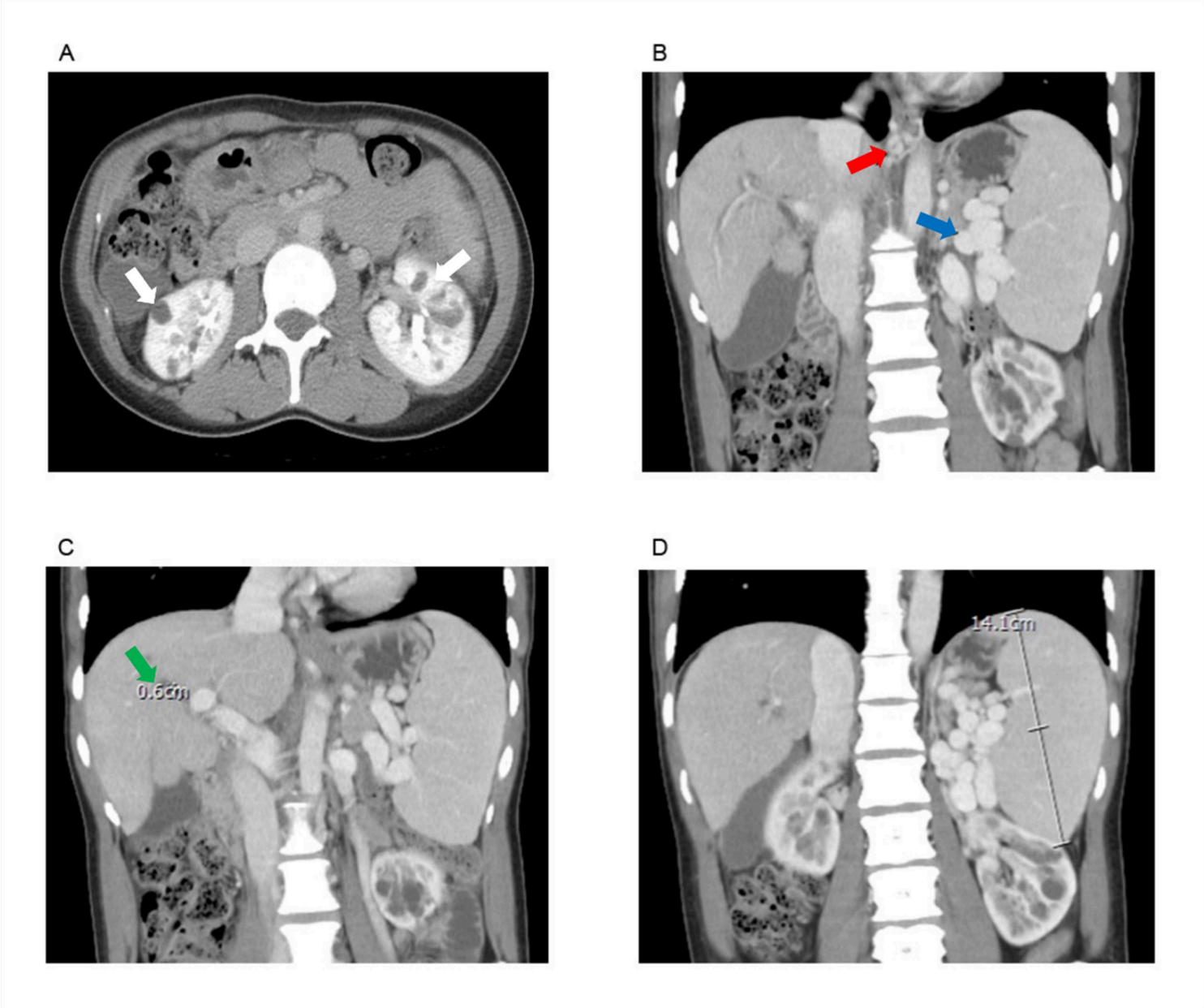


Figure 2

Abdominal computed tomography (CT) findings. (A) Axial CT scan showing multiple bilateral renal cysts (**white arrows**), consistent with autosomal dominant polycystic kidney disease (ADPKD). **(B)**Coronal scan revealing extensive collateral circulation: paraesophageal varices (**red arrow**) and a prominent splenorenal shunt (**blue arrow**). **(C)**Coronal scan demonstrating intrahepatic bile duct dilatation (**green arrow**) measuring 0.6 cm in the absence of mechanical obstruction. **(D)** Coronal scan showing significant splenomegaly with a maximal diameter of 14.1 cm.

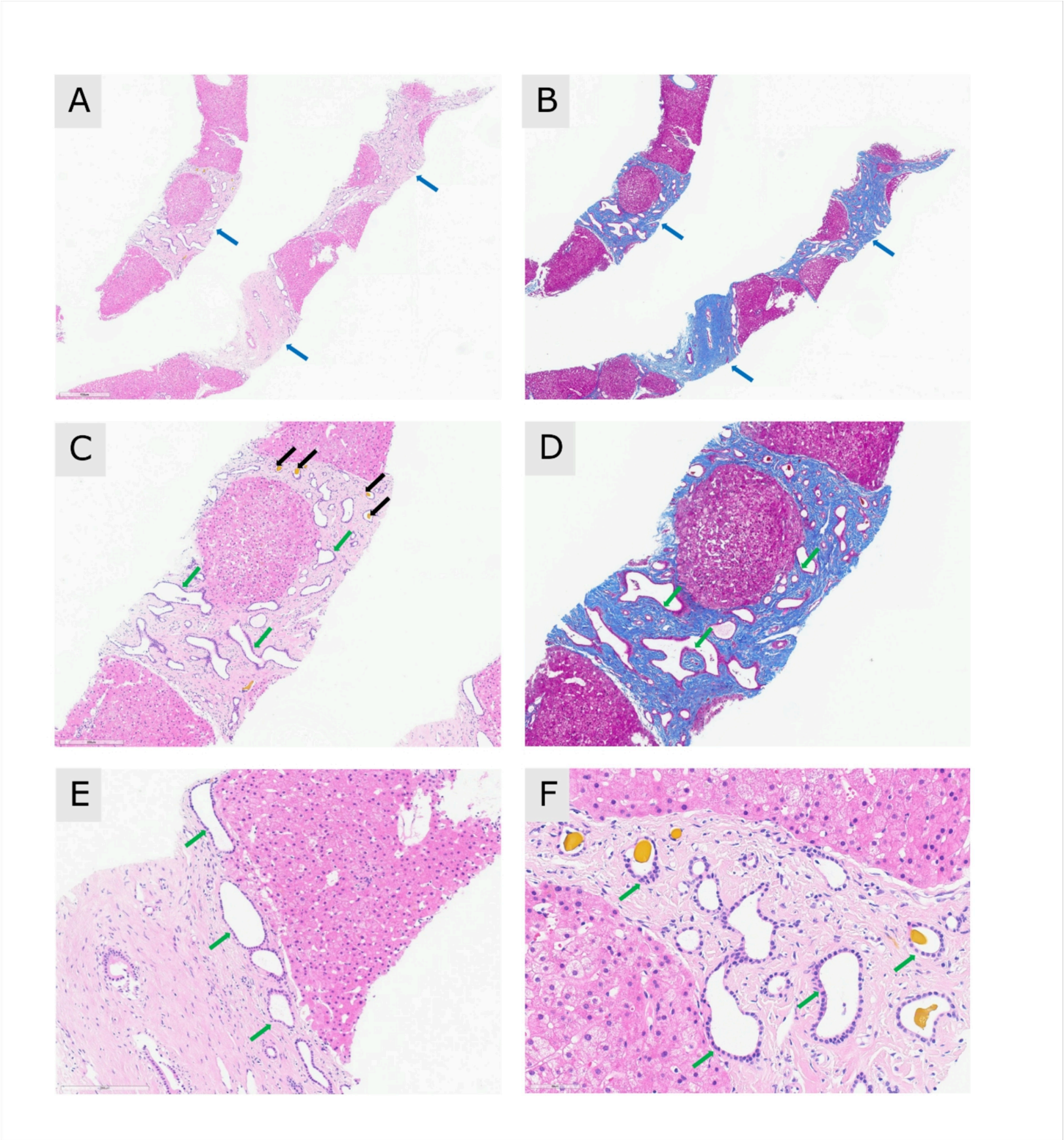


Figure 3

Histopathological evaluation of the liver biopsy specimen. (A, B) Low-magnification views (hematoxylin and eosin [H&E] and Masson's trichrome [MT], ×40) revealing a characteristic "jigsaw" pattern of fibrosis, with dense fibrous septa (**blue arrows**) partitioning the parenchyma into irregularly shaped islands without regenerative nodules. **(C, D)** Intermediate-magnification views (H&E and MT, ×100) demonstrating ductal plate malformation (DPM) with irregularly dilated and branched bile ducts (**green**

arrows) forming complex networks. Note the presence of inspissated bile plugs within the lumens (**black arrows in C**). **(E)** High-magnification view (H&E, ×200) illustrating an interrupted linear arrangement of malformed ducts (**green arrows**) at the fibro-lobular interface. **(F)** Ultra-high magnification view (H&E, ×400) confirming that the malformed biliary structures are lined by a single layer of well-differentiated cuboidal epithelium (**green arrows**).