American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2023; 24: e938507
DOI: 10.12659/AJCR.938507

Received: 2022.09.27
Accepted: 2022.12.28
Available online: 2023.01.04
Published: 2023.01.24

Predominant Liver Cystic Disease in a New Heterozygotic PKHD1 Variant: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ACDEF 1 Jacob D. Van Buren
BD 2 Jeremy T. Neuman
ABCDE 3 Richard Sidlow

1 Medical School for International Health, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer Sheva, Israel
2 Radiology Associates of Main Street, New York-Presbyterian Queens, Flushing, NY, USA
3 Department of Medical Genetics and Metabolism, Valley Children's Hospital, Madera, CA, USA

Corresponding Author: Jacob D. Van Buren, e-mail: vanburen@post.bgu.ac.il
Financial support: None declared
Conflict of interest: None declared

Patient: Male, 3-year-old
Final Diagnosis: Autosomal recessive polycystic kidney disease • polycystic liver disease
Symptoms: Enlarged cystic kidneys • hyperbilirubinemia
Medication: —
Clinical Procedure: Kasai procedure
Specialty: Genetics • Pediatrics and Neonatology

Objective: Rare disease

Background: The polycystic kidney and hepatic disease 1 (PKHD1) gene codes for fibrocystin-polyductin, a protein that takes part in cell-signaling for cell differentiation, especially in kidney tubules and bile ducts. A homozygous or compound heterozygous defect in this gene can cause autosomal recessive polycystic kidney disease (ARPKD). Polycystic liver disease (PCLD) can also be caused by single heterozygous variants in the PKHD1 gene. ARPKD presents with renal insufficiency and cystic dilatation of bile ducts, although disease is not expected with a single heterozygous mutation. PCLD presents with multiple cysts in the liver and dilated bile ducts as well, but with less of an impact on the kidneys than with ARPKD. Our purpose in publishing this report is to introduce an as-yet unknown variant to the body of genetic defects associated with ARPKD and PCLD, as well as to argue for the likely pathogenicity of the variant according to the prevailing criteria used for classifying gene variants.

Case Report: We present a patient with a de novo PKHD1 variant currently classified as a variant of unknown significance manifesting with bilaterally enlarged cystic kidneys and echogenic cystic structures in the hepatic portal system, indicative of cystic disease.

Conclusions: Given this patient's liver and kidney presentation that does not fully align with either ARPKD or PCLD, the authors believe that the single heterozygous variant in this patient's PKHD1 gene is worthy of reporting. This new single heterozygous variant in PKHD1 gene causing cystic kidney and cystic hepatic disease in the patient should be considered 'likely pathogenic' according to the criteria set by the American College of Medical Genetics.

Keywords: PKHD1 Protein, Human • Polycystic Kidney Disease 1 Protein • Polycystic Kidney, Autosomal Dominant • Polycystic Kidney, Autosomal Recessive • Polycystic Liver Disease

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/938507

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

Background

Autosomal recessive polycystic kidney disease (ARPKD) is a genetic ciliopathy caused by mutations in the polycystic kidney and hepatic disease 1 (PKHD1) gene. It is estimated to affect 1 out of every 20 000 live births [1]. It is invariably accompanied by congenital hepatic fibrosis (CHF), although clinical symptoms of CHF are present in only 50% of newborns. Phenotypes of ARPKD/CHF vary widely in presentation and severity. Renal symptoms are caused by non-obstructive dilatation of renal collecting ducts; they include hypertension, nephromegaly, and renal insufficiency [2]. Symptomatic CHF becomes more prevalent as long-term survival improves and patients enter their second and third decades of life. These symptoms can manifest as portal hypertension, causing esophageal and gastric varices, gastrointestinal bleeding, and recurrent cholangitis [3]. Cystic dilation of the common or intrahepatic bile ducts can also occur, known as Caroli syndrome. Caroli syndrome may present with jaundice, biliary cirrhosis, and recurrent bacterial cholangitis [2,4,5].

More than half of ARPKD patients are diagnosed in the perinatal period. Diagnosis of ARPKD is confirmed by the identification of biallelic pathogenic variants of PKHD1 through molecular genetic testing, the presence of CHF, and renal enlargement [4]. Enlarged kidneys with high echogenicity are observable on fetal ultrasound, of which a potential consequence is oligohydramnios and even pulmonary hypoplasia, the leading cause of mortality in neonates with this disease [6]. Patients that survive the first year of life have a 10-year survival rate of 82% [7]. Most of the patients undiagnosed in this stage will present in childhood with any combination of the previously described liver or kidney symptoms, and a small minority present as adults with hepatic dysfunction as the primary issue [2,4].

The PKHD1 gene responsible for ARPKD/CHF is located on the short arm of chromosome 6 (6p12.2). The gene contains at least 470 kb comprised of 86 axons, which can be alternatively spliced, and 67 of these exons make up its largest open reading frame (ORF), encoding the protein product fibrocystin/polyductin (FCPD) [6]. FCPD is a receptor-like protein with extracellular, transmembrane, and intracellular domains, found in the primary cilia and basal bodies of the epithelial cells of both the liver and the kidneys, although its actual function remains unclear [2,5]. Although about 20% of all PKHD1 mutations can be traced to a specific missense mutation (p.Thr36Met), most mutations are rare variants spread throughout the gene, many of which are exclusive to a single family. The majority of ARPKD/CHF patients are compound heterozygous for these alleles [2,6]. The great heterogeneity of allelic variants in the PKHD1 gene is likely the primary contributor to the large differences in the phenotype and severity of the disease in affected individuals.

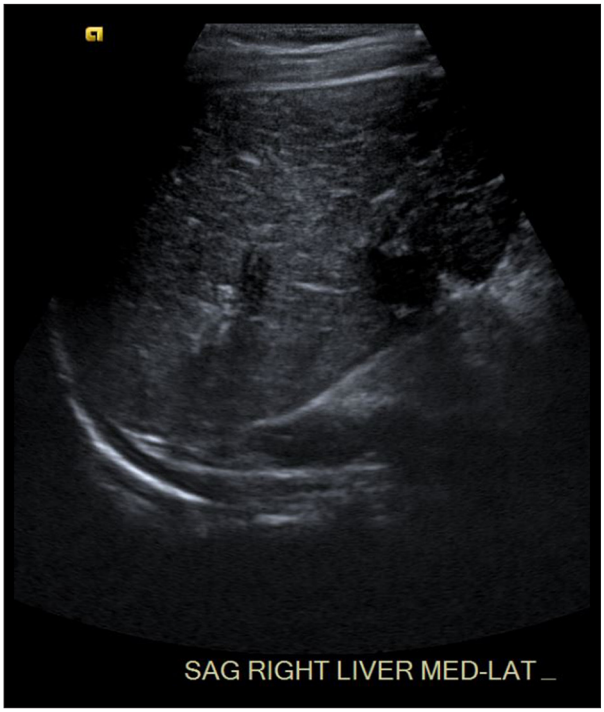

Figure 1. Transverse sonographic image of the liver demonstrates diffusely heterogeneous/coarsened architecture suggesting underlying hepatocellular disease.

We report a case in which a child heterozygous for a unique variant of the PKHD1 gene presented with important liver involvement accompanied by mild cystic kidney disease. Although mutations in the PKHD1 gene are usually associated with ARPKD, its heterozygous de novo nature, as well as its clinical presentation, do not align with typical ARPKD, which we consider worthy of publishing.

Case Report

A 3-month-old boy with unremarkable birth, past medical/surgical history, and social history presented with unresolved jaundice after initial diagnosis of hyperbilirubinemia as a newborn, at which time he was treated with intravenous fluids (IVF) and phototherapy. His mother's pregnancy was uncomplicated. The patient showed no other issues besides very light-yellow stools. Blood chemistry showed elevated bilirubin and liver enzymes (total bilirubin 11.1 mg/dl; direct bilirubin 6.3 mg/dl; aspartate aminotransferase (AST) 262 U/L; alanine aminotransferase (ALT) 105 U/L; alkaline phosphatase (AP) 1653 U/L; total protein 5.1; g/dl albumin 3.5 g/dl). Hepatic sonography did not show dilated ductal structures, and the gallbladder appeared unusually small (**Figure 1**).

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

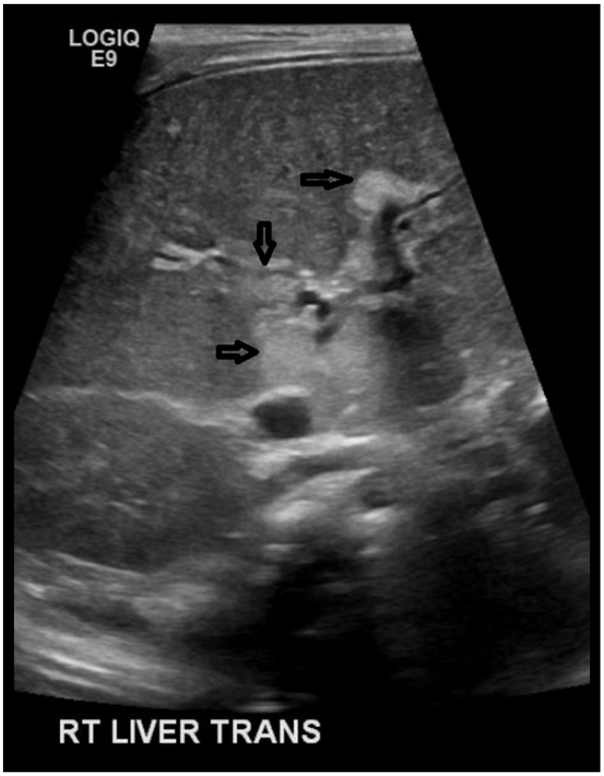

Figure 2. Transverse sonographic image of the liver in the periportal region shows ill-defined hyper-echoic regions adjacent to the portal vessels (arrows) which can reflect periportal fibrosis.

The boy was subsequently diagnosed with biliary atresia, and a cholangiogram with the intent of Kasai procedure was recommended and performed shortly thereafter.

At age 3 months, the patient was referred for genetic testing for newly detected bilaterally enlarged cystic kidneys and echogenic cystic structures in the porta hepatis region and inferior right hepatic lobe (**Figures 2-4**).

A Polycystic Kidney Disease Panel performed by GeneDx determined that the patient had a heterozygous variant of unknown significance in exon 62 of the PKHD1 gene (c.11207T>A/p.I3736K; NM_138694.3; chr 6: 51513986). Upon further query, his family history included 3 maternal family members with renal disease, and a paternal grandfather that required a liver transplantation in his 40's. An attempt was made to establish hereditability of the patient's phenotype, so familial variant analysis was performed. The mutation was determined to be a de novo mutation when analysis revealed that neither parents' genomes contained the variant.

At follow-up, the boy appeared well and was asymptomatic while being continuously monitored by hepatology and nephrology services. Magnetic resonance cholangiopancreatography

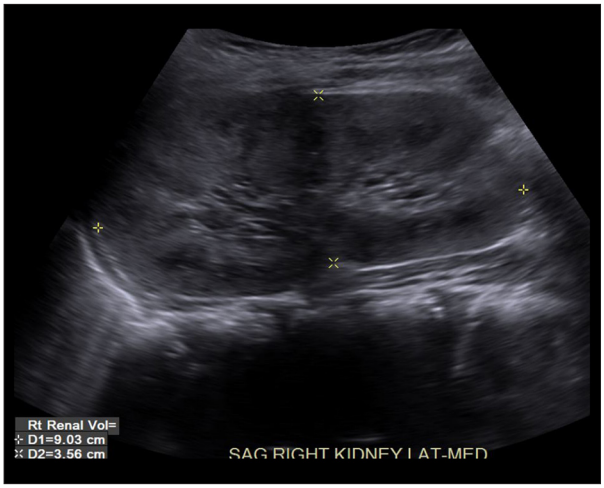

Figure 3. Longitudinal sonographic image of the right kidney depicting large-for-age but otherwise normal-appearing kidney.

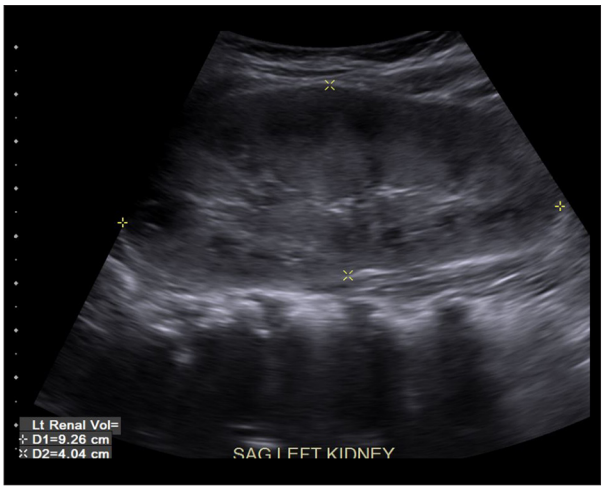

Figure 4. Longitudinal sonographic image of the left kidney depicting a large-for-age but otherwise normal-appearing kidney.

(MRCP) performed then showed 2 porta hepatis cysts and thickening/prominence of numerous portal triads.

Discussion

The FCPD protein product of PKHD1 is a very large protein, thousands of amino acids in size, with numerous alternatively spliced products that interact with many other gene products, making precise genotype/phenotype correlations difficult to establish when altered in any way. Its interactions with the protein products of polycystin 1 and 2 (PC1 and PC2), alterations of which cause autosomal dominant polycystic kidney disease (ADPKD), and the genes protein kinase C substrate 80K-H (PRKCSH) and Sec63, alterations of which cause polycystic

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

liver disease (PCLD), are useful in beginning to understand its role in cyst formation.

ADPKD has similar symptoms to ARPKD, but manifests later in life with a genotype-dependent progression to end-stage renal disease. The polycystic kidney disease 1 and 2 genes (PKD1 and PKD2) are responsible for cellular sensory signaling on the apical surface of the primary cilia of both kidney tubules and biliary epithelia [8].

The liver cysts of PCLD are identical to those of ADPKD; however, PCLD does not involve the kidney. In a cohort of PCLD patients, 35% of the cases were explained by loss-of-function mutations in glucosidase II-beta (GIIbeta), encoded by the PRKCSH gene, and Sec63, encoded by the Sec63 gene, both of which are responsible for post-translational modification of PC1 and PC2 in the endoplasmic reticulum. Alterations in PRKCSH and Sec63 lead to the occurrence of ADPKD and PCLD in a polycystin dose-dependent manner [9]. Significant to our case is that heterozygous carriers of PKHD1 variants were found in at least 10% of PCLD cases unexplained by variants in GIIbeta and Sec63. Uniquely, this population displayed numerous small liver cysts on computed tomography imaging, whereas PCLD cysts from other gene variants tended to be larger and fewer. The prevalence of heterozygous PKHD1 mutations in the PCLD cohort relative to the same mutations in the general population was enough to be statistically significant, supporting the hypothesis that heterozygous PKHD1 variants have pathogenic potential [10].

Although the same study demonstrated that PKHD1 was not directly related to PC1 and PC2 function, its prevalence in patients with cystic kidney disease may point to an as-yet unknown interaction between FCPD and polycystin [8]. Such a possibility is supported by a study in which mice with a homozygous PKHD1 mutation had a much more severe presentation of both kidney and liver cystic disease when combined with a heterozygous mutation in PKD1 [10]. In researching the interrelationships between the 5 genes mentioned (PKD1, PKD2, GIIbeta, Sec63, and PKHD1), PC1 expression demonstrated a significant influence over cyst formation, acting as the rate-limiting component in cyst development for PCLD, ADPKD, and ARPKD [9]. However, PC1 overexpression in PKHD1del4/del4 mice did not reduce liver cysts, suggesting that PKHD1 does have some function in bile ducts independent of PC1 activity.

Located 11 amino acids downstream from an N-glycosylation site, variants at this locus can adversely affect cell adhesion and communication, thereby hindering terminal differentiation of the epithelial cells that make up renal canaliculi and biliary duct cell adhesion in tandem with other proteins (including PC1) [11,12]. Additionally, its proximity to the splice acceptor site of exon 62 could cause aberrant splicing [13].

According to the criteria described by the American College of Medical Genetics, we attest that the mutation found in this patient should be considered 'likely pathogenic', with the following supporting evidence: The mutation fulfills 1 criterion in the 'strong' category (PS2), given that it is a de novo mutation in the child where the absence of the variant was confirmed in both parents. Additionally, it also fulfills 1 criterion in the 'moderate' category (PM2); the variant found in this patient has not been recorded in any existing exome databases. Lastly, other 'supporting' level criteria met by this mutation include PP3 and PP4. The variant present in our patient is unattested in ClinVar and Leiden Open Variation Database (LOVD), with a Provean score of -2.63 (≤-2.5 arguing a deleterious effect on protein structure/function), fulfilling PP3, and because the patient presented with symptoms not dissimilar to those of PCLD, which has been shown to result from PKHD1 gene mutations, PP4 is also fulfilled [14,15]. 'Likely pathogenic' classification demands fulfillment of 1 'strong' and 1-2 'moderate' criteria to be satisfied. We believe the evidence provided adequately supports the 'likely pathogenic' classification and obviates a need to search for an alternative cause for our patient's phenotype [16].

Although all the previous data was used to support ideas of how aberrancy in the interactions between the products of these genes may be causing disease in this case, a limitation of this study is that the research surrounding the minutia of these interactions is ambiguous at best, and much is still left to conjecture. Another limitation is that RNA transcriptomic studies of our patient's variant were not performed, but they could be definitive in not only determining its deleterious nature, but also being able to quantify the extent to which it affects functional mRNA production.

We hope that the unique location and properties of this variant can help contribute to what is known about the genes responsible. A recent study has shown the importance of cilia in organoid differentiation using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) [17]. Further research into this technology, as well as additional patients with this same variant manifesting similar findings, could elucidate the ways PKHD1 affects tubule development and lead to novel therapeutic discoveries.

Conclusions

In summary, we present a patient harboring a de novo variant of PKHD1 who presented with liver and kidney cystic disease that does not perfectly align with either ARPKD or PCLD, the diseases typically associated with this gene. Based on the previously mentioned ACMG criteria, we hypothesize that the location and type of this variant is very likely causing this patient's

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]

presentation in the absence of any other causative mutation or disease. We thus recommend that the classification of this mutation be considered 'likely pathogenic'.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Zerres K, Rudnik-Schoneborn S, Steinkamm C, et al. Autosomal recessive polycystic kidney disease. J Mol Med. 1998;76:303-9
2. Gunay-Aygun M, Tuchman M, Font-Montgomery E, et al. PKHD1 sequence variations in 78 children and adults with autosomal recessive polycystic kidney disease and congenital hepatic fibrosis. Mol Genet Metab. 2010;99(2):160-73
3. Sanyal, AJ, Boyer TD, Terrault N, Lindor KD, editors. Zakim and Boyer's Hepatology: A Textbook of Liver Disease. Seventh edition. Pennsylvania: Elsevier; 2018
4. Sweeney WE, Avner ED. Polycystic kidney disease, autosomal recessive. 2001 Jul 19 [Updated 2019 Feb 14]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1326/
5. Hao X, Liu S, Dong Q, et al. Whole exome sequencing identifies recessive PKHD1 mutations in a Chinese twin family with Caroli disease. PLoS One. 2014;9(4):e92661
6. Melchionda S, Palladino T, Castellana S, et al. Expanding the mutation spectrum in 130 probands with ARPKD: Identification of 62 novel PKHD1 mutations by sanger sequencing and MLPA analysis. J Hum Genet. 2016;61(9):811-21
7. Hoyer PF. Clinical manifestations of autosomal recessive polycystic kidney disease. Curr Opin Pediatr. 2015;27:186-92
8. Besse W, Dong K, Choi J, et al. Isolated polycystic liver disease genes define effectors of polycystin-1 function. J Clin Invest. 2017;127(5):1772-85 [Erratum in: J Clin Invest. 2017;127(9):3558]
9. Fedeles SV, Tian X, Gallagher AR, et al. A genetic interaction network of five genes for human polycystic kidney and liver diseases defines polycystin-1 as the central determinant of cyst formation. Nat Genet. 2011;43(7):639-47
10. Garcia-Gonzalez MA, Menezes LF, Piontek KB, et al. Genetic interaction studies link autosomal dominant and recessive polycystic kidney disease in a common pathway. Hum Mol Genet. 2007;16(16):1940-50
11. Kopanos C, Tsiolkas V, Kouris A, et al. VarSome: The human genomic variant search engine. Bioinformatics. 2019;35(11):1978-80
12. Onuchic LF, Furu L, Nagasawa Y, et al. PKHD1, the polycystic kidney and hepatic disease 1 gene, encodes a novel large protein containing multiple immunoglobulin-like plexin-transcription-factor domains and parallel beta-helix 1 repeats. Am J Hum Genet. 2002;70(5):1305-17
13. Crotti LB, Horowitz DS. Exon sequences at the splice junctions affect splicing fidelity and alternative splicing. Proc Natl Acad Sci USA. 2009;106:18954-59
14. Fokkema IF, Taschner PE, Schaafsma GC, et al. LOVD v.2.0: The next generation in gene variant databases. 2011. Hum Mutat. 2011;32(5):557-63
15. Landrum MJ, Lee JM, Benson M, et al. ClinVar: Improving access to variant interpretations and supporting evidence. Nucleic Acids Res. 2018;46(D1):D1062-67
16. Richards S, Aziz N, Bale S, et al. ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-24
17. Cruz NM, Reddy R, McFaline-Figueroa JL, et al. Modelling ciliopathy phenotypes in human tissues derived from pluripotent stem cells with genetically ablated cilia. Nat Biomed Eng. 2022;6(4):463-75

Indexed in: [PMC] [PubMed] [Emerging Sources Citation Index (ESCI)] [Web of Science by Clarivate]