

Congenital hepatic fibrosis with polycystic kidney disease

Two case reports

Chang Jiang, MB^a, Qiang Zhou, MM^a, Meishan Jin, MD^b, Junqi Niu, MD^a, Yanhang Gao, MD^{a,*}

Abstract

Introduction: Congenital hepatic fibrosis (CHF) is a rare autosomal recessive disease derived from biliary dysgenesis secondary to ductal plate malformation and is often accompanied by renal cysts or increased renal echogenicity.

Patient concerns: A 25-year-old woman was admitted to our hospital with splenomegaly and hepatic cirrhosis of a 3-month duration and fever accompanied by abdominal pain for 3 days. The second patient was a 25-year-old male referred to our hospital with hepatomegaly and splenomegaly of 6-year duration who had experienced fever for 3 months and abdominal distension for 1 week. Both 25-year-old patients were found to have CHF with polycystic kidney disease.

Diagnosis: Radiological imaging, including computed tomography (CT), magnetic resonance imaging (MRI), and sonography, revealed hepatic fibrosis, portal hypertension, splenomegaly, ascites, bile duct malformation, polycystic kidneys, and CHF. For the first patient, a liver biopsy confirmed the pathological features of CHF, and genetic testing revealed three heterozygous missense mutations, which were classified as “undetermined” in the public Wilson’s disease/ATP7B and ADPKD/PKD1 databases.

Interventions: The first patient had undergone a splenectomy for anemia 2 months previously. Because there is no radical cure for CHF, and due to economic reasons, neither patient received liver transplantation. Therefore, we administered only anti-fibrotic supportive treatment for symptoms.

Outcomes: Both patients were discharged after their symptoms improved, and both survived for 2 years of follow-up.

Conclusion: These cases highlight the value of radiological imaging, pathological examination, and genetic evaluation for the diagnosis of CHF. When an individual with unexplained cirrhosis presents with bile duct dilation and malformation as well as polycystic kidneys, the possibility of CHF should be considered. For individuals found to have polycystic kidneys at a young age, the results of liver function tests and imaging examinations including Fibroscan imaging should be continuously and dynamically monitored to enable early diagnosis of CHF.

Abbreviations: ADPK = autosomal dominant polycystic kidney disease, ANA = antinuclear antibodies, ARPKD = autosomal recessive polycystic kidney disease, CHF = congenital hepatic fibrosis, CT = computed tomography, IVC = inferior vena cava, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, MRI = magnetic resonance imaging, PKD = polycystic kidney disease, PT = prothrombin time, PTA = plasma thromboplastin antecedent.

Keywords: congenital hepatic fibrosis, diagnosis, polycystic kidney, therapy

Editor: N/A.

Funding: This work was sponsored by the National Science and Technology Major Project (2017ZX10202202, 2018ZX10302206); National key research plan “precision medicine research” key project (2017YFC0908103); The National Natural Science Foundation of Jilin Province (20160101097JC); Program for JLU Science and Technology Innovative Research Team (2017TD-08) and the Fundamental Research Funds for the Central Universities.

The authors report no conflicts of interest.

^a Department of Hepatology, ^b Department of Pathology, The First Hospital of Jilin University, Changchun, Jilin, China.

* Correspondence: Yanhang Gao, Department of Hepatology, The First Hospital of Jilin University, Changchun, Jilin 130021, China (e-mail: yanhang@mail.jlu.edu.cn).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2019) 98:20(e15600)

Received: 30 November 2018 / Received in final form: 4 April 2019 / Accepted: 16 April 2019

<http://dx.doi.org/10.1097/MD.00000000000015600>

1. Introduction

Congenital hepatic fibrosis (CHF) is a rare autosomal recessive disease derived from biliary dysgenesis secondary to ductal plate malformation^[1]; it often coexists with Caroli’s disease, von Meyenburg complexes, autosomal dominant polycystic kidney disease (ADPKD), and autosomal recessive polycystic kidney disease (ARPKD).^[2] Although CHF was first named and described in detail by Kerr et al in 1961,^[3] its pathogenesis still remains unclear. The exact incidence and prevalence are not known, and only a few hundred patients with CHF have been reported in the literature to date. However, with the development of noninvasive diagnostic techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), CHF may now be more frequently detected.^[4] Patients with CHF exhibit variable clinical presentations, ranging from no symptoms to severe symptoms such as acute hepatic decompensation and even cirrhosis. The most common presentations in these patients are splenomegaly, esophageal varices, and gastrointestinal bleeding due to portal hypertension.^[5] In addition, in younger children, CHF often is accompanied by

renal cysts or increased renal echogenicity. Great variability exists among the signs and symptoms of the disease from early childhood to the 5th or 6th decade of life, and in most patients the disorder is diagnosed during adolescence or young adulthood.^[6]

Here, we present two cases of 25-year-old patients found to have CHF with polycystic kidney disease (PKD) according to the results of medical imaging (CT or MRI), a liver biopsy, and genetic testing.

2. Case presentation

2.1. Case 1

A 25-year-old woman was admitted to our hospital with splenomegaly and hepatic cirrhosis of a 3-month duration and fever accompanied by abdominal pain for 3 days.

At the age of 19, she suffered from increasingly severe anemia with progressive thrombocytopenia despite the prescription of iron formulations. At the age of 25, a bone marrow biopsy ruled out hematological disease. Three months before admission, she underwent splenectomy in our hospital as treatment for splenomegaly with thrombocytopenia. Pathologic findings from a liver biopsy obtained during that surgery showed hepatic cirrhosis and congestive splenomegaly. Her platelet count gradually increased postoperatively to $625 \times 10^9/L$ by day 7. She had no personal history of hepatitis, smoking or drinking and no family history of liver disease. On physical examination, her chest was clear and no heart murmur was detected. An abdominal examination revealed tenderness in the upper right quadrant.

Laboratory findings at admission showed a prothrombin time (PT) of 15.7 s, plasma thromboplastin antecedent (PTA) of 60%, hemoglobin (Hb) level of 8.2 g/L, mean corpuscular volume (MCV) of 70.9 fl, mean corpuscular hemoglobin (MCH) of 20.8 pg, mean corpuscular hemoglobin concentration (MCHC) of 293 g/L, and platelet count of $497 \times 10^9/L$. Her liver function test results were almost normal. A viral hepatitis panel was negative. Her serum copper level was also in the normal range. Autoimmune antibody and immunoglobulin tests were negative.

Her chest CT scan findings were normal, but MRI of her abdomen showed hepatic fibrosis, a small volume of ascites, portal hypertension, and collateral circulation around the portal

vein. In addition, bile duct dilation and malformation along with cholecystitis were observed, and a thrombus was located in the portal vein trunk, including its left and right branches. Two cysts were seen in the right lobe of the liver, and multiple cysts were seen in the kidneys. Sonography of her abdomen along with Doppler imaging of the inferior vena cava (IVC) showed thrombi in the portal vein trunk including its left and right branches, which were at acute and subacute stages. Abdominal sonography was undertaken to further characterize the disorders in the patient. The images showed a poorly developed biliary system and hepatic fibrosis, a thrombus in the portal vein, portal hypertension with collateral circulation, obviously dilated and intertwined splenic veins, and polycystic kidneys.

A liver biopsy showed irregularly shaped lobular parenchyma that appeared to be separated and surrounded by fibrous bands, with visible nodules that indicated cirrhosis, thick fibrous bands containing bile ductular proliferation along with duct dilation (Figs. 1–4). Bile duct dilation and malformation were observed, and the number of interlobular veins was increased. Histopathology of her liver confirmed CHF.

We extracted genomic DNA from the peripheral blood of the patient and performed genetic analysis for nine genes related to CHF or PKD (*PKHD1*, *PKD1*, *PKD2*, *ATP7B*, *ATP8B1*, *ABCB11*, *ABCB4*, *SERPINA1*, and *NPHP3*). The results showed that our patient carried three heterozygous missense mutations that are currently classified as “undetermined” in the public Wilson’s disease/ATP7B and ADPKD/PKD1 databases (Table 1). A heterozygous missense mutation in exon 15 (c.3316G>A, p.Val106Ile) of *ATP7B* was identified in the patient in addition to a second heterozygous missense mutation in exon 19 (c.7670A>G, p.Asp2557Gly) of *PKD1* and a third heterozygous missense mutation in exon 15 (c.5494G>A, p.Gly1832Ser) of *PKD1*.

The patient had undergone splenectomy 2 months previously, and the symptoms of anemia were improved. However, portal vein thrombosis occurred, for which she was given anticoagulant therapy. We recommend that patients undergo liver transplantation, but the patient and her family refused for economic reasons. Therefore, we provided anti-fibrosis treatment for liver protection and symptomatic supportive treatment. The patient was discharged when her symptoms improved. She remained alive and developed recurrent ascites during 2 years of follow-up. Her

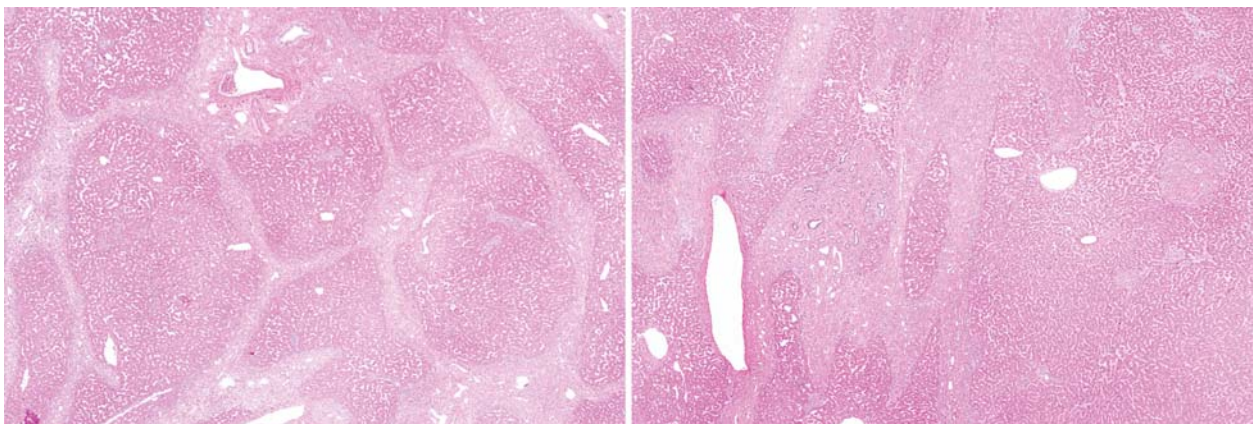


Figure 1 and 2. Hematoxylin and eosin staining of liver tissue (40× magnification). Irregular bridging fibrosis with bile ductular proliferation and nodules indicative of cirrhosis. Fibrosis was closely connected without significant inflammation.

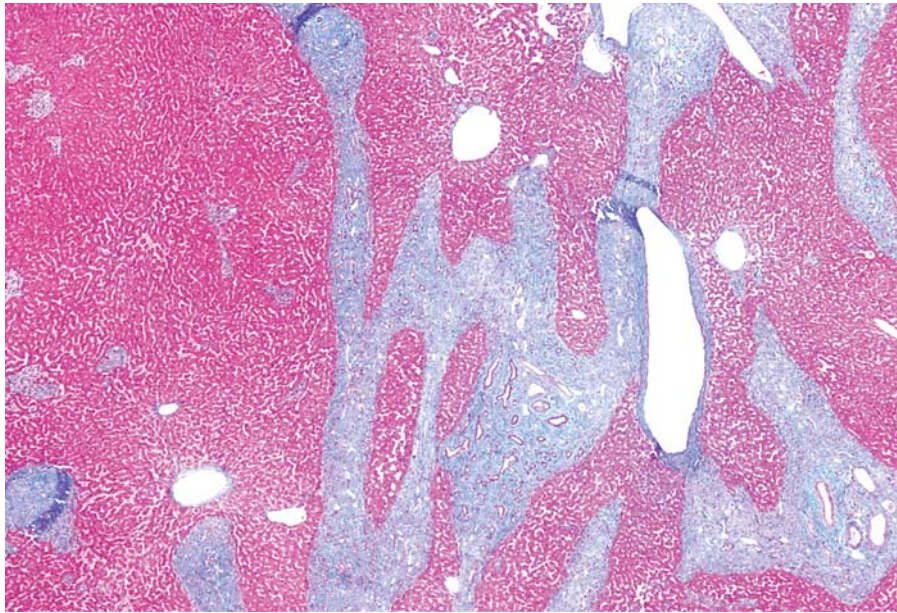


Figure 3. Masson's trichrome staining of liver tissue (40× magnification). Irregular bridging fibrosis was seen with the appearance of a jigsaw puzzle.

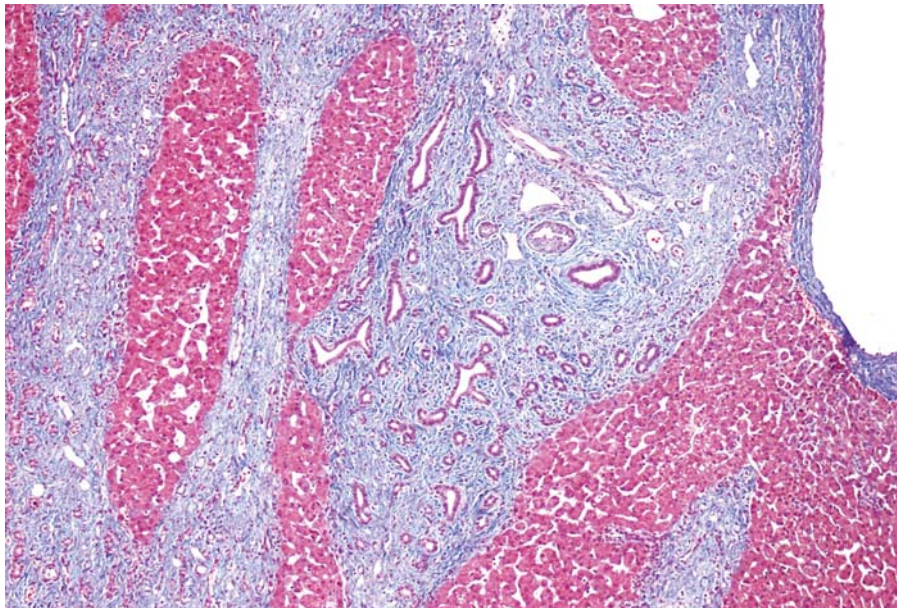


Figure 4. Masson's trichrome staining of liver tissue (100× magnification). A portion of the bile duct that exhibited dilation and malformation is shown. The number of interlobular veins was increased.

condition improved with symptomatic treatment of ascites drainage and intermittent infusion of albumin.

2.2. Case 2

The second patient was a 25-year-old male referred to our hospital with hepatomegaly and splenomegaly of 6 year-duration as well as fever lasting for 3 months and abdominal distension for 1 week. Physical examination showed an obviously distended abdomen, which was positive for shifting dullness. The patient

had a family history of hepatitis B-associated cirrhosis, but a virology test of his liver was negative. He had no personal history of drinking, and no obvious abnormalities of the heart and lung were observed.

The laboratory findings showed a gamma-glutamyl transferase (γ -GT) level of 262.7 U/L, alkaline phosphatase level of 287.2 U/L, albumin concentration of 30.6 g/L, PT of 15.3 s, PTA of 65%, Hb of 9.8 g/L, MCV of 78.8 fl, MCH of 23.6 pg, MCHC of 300 g/L, and platelet count of 113×10^9 /L. Like the first patient, the results for serum ceruloplasmin, tumor markers, and antinuclear

Table 1**Three heterozygous missense mutations identified in the first patient.**

Gene	Reference sequence	Intra-nucleotide base change	Amino acid change	Gene subregion	Chromosomal location
<i>ATP7B</i>	NM-000053	c.3316G>A	p.Val106Ile	Ex15/CDS15	Chr13: 52516618
<i>PKD1</i>	NM-001009944	c.7670A>G	p.Asp2557Gly	Ex19/CDS19	Chr16: 2156125
<i>PKD1</i>	NM-001009944	c.5494G>A	p.Gly1832Ser	Ex15/CDS15	Chr16: 2159674

antibodies (ANA) were all within normal limits, and the T spot test was negative. He did not undergo a liver biopsy or genetic testing; however, abdominal CT scans showed hepatic cirrhosis, splenomegaly, ascites, portal hypertension with collateral circulation, hepatomegaly, splenomegaly, non-homogeneous intrahepatic bile duct expansion and malformation, polycystic kidneys, and pulmonary fibrosis in both lungs, all suggestive of CHF.

The second patient also did elect to undergo liver transplantation. Like the first patient, he was discharged after his symptoms improved with supportive treatment, and he remained alive over 2 years of follow-up.

3. Discussion

CHF is an autosomal recessive inherited malformation defined pathologically by a variable degree of periportal fibrosis and irregularly shaped proliferating bile ducts, which also can occur in hereditary PKD. Therefore, hereditary PKD is one of the causes of unexplained liver fibrosis and liver cirrhosis.^[7] CHF is characterized by hepatic fibrosis, portal hypertension, and renal cystic disease. Typical presentation of CHF is in the form of portal hypertension in adolescents and young adults.^[8] Four clinical forms have been defined^[9]:

1. Portal hypertension (most common; more severe in the presence of portal vein abnormality);
2. Cholangitic cholestasis and recurrent cholangitis;
3. Mixed;
4. Latent-presentation at a late age.

Portal hypertension is most commonly observed in China. In particular, CHF lacks typical clinical presentation, and misdiagnosis is not uncommon.

In the two cases described herein, the initial presentation of CHF was splenomegaly, and the age at onset was similar (~25 years). Neither patient had a history of hepatitis, smoking or drinking, access to a schistosomiasis-affected area, long-term toxicant exposure, or drug abuse, and hematopoietic disease was eliminated for each patient. Noninvasive diagnostic procedures such as ultrasound, CT, or MRI showed hepatic fibrosis, portal hypertension, splenomegaly, ascites, bile duct malformation, and polycystic kidneys. Serum levels of ceruloplasmin, tumor markers, and ANA were within normal limits. No obvious abnormalities of the heart and lung observed. All of these findings together indicated CHF, and the imaging examinations were most helpful for the precise identification and diagnosis of CHF.

Although noninvasive imaging technologies, including ultrasound, CT, and MRI, are very useful for the diagnosis of CHF in patients who are likely at risk, genetic testing and liver biopsy are the gold standards for CHF diagnosis. CHF is characterized by a ductal plate malformation of the interlobular bile ducts, and in humans, often coexists with Caroli's disease, von Meyenburg complexes, ARPKD, and ADPKD.^[10–12] The first case presented showed hepatocytes in lobules without significant inflammation

or necrosis, surrounding portal fibrosis and bridging fibrosis, with a marked increase in small or irregular bile duct profiles. Histopathological examination of the liver in the first case confirmed CHF. The patient also underwent genetic testing while hospitalized, and although the results could not directly confirm CHF, the identified mutations provided some insight into the patient's condition.

Concurrent renal cystic disease has been observed in some CHF patients, and this clinical presentation has been mainly associated with ARPKD. Mutations at a single locus, *PKHD1* (polycystic kidney and hepatic disease 1), are responsible for all typical forms of ARPKD.^[13] Although ADPKD is rare in humans, it is the most common inherited renal cystic disease. Thus far, two main genes have been identified (*PKD1* [chromosome region 16p13.3] and *PKD2* [chromosome region 4q21]).^[14] In the first case, we evaluated several genes (*PKHD1*, *PKD1*, *PKD2*, *ATP7B*, *ATP8B1*, *ABCB11*, *ABCB4*, *SERPINA1*, *NPHP3*) and detected three heterozygous missense mutations: one in exon 15 (c.3316G>A, p.Val106Ile) of *ATP7B*, which is related to Wilson's disease, another in exon 19 (c.7670A>G, p.Asp2557Gly) of *PKD1*, and a third in exon 15 (c.5494G>A, p.Gly1832Ser) of *PKD1*, which has been recorded in the public ADPKD database. The pathogenicity of these mutations is currently classified as "undetermined" in the database due to an insufficient number of reported cases. We can define the mutation as a polymorphism at present, and perhaps, its pathogenicity will be confirmed in the future.

Medical or surgical treatment may be useful for CHF. Medications including anti-fibrotic drugs, such as colchicine, interferon gamma, angiotensin II receptor blockers, pirfenidone, and ursodeoxycholic acid, have been evaluated in clinical trials, but without marked benefit. Portosystemic shunt surgery can be a good option for CHF patients, because the risk of postoperative hepatic encephalopathy is low. Endoscopic treatment, such as endoscopic variceal ligation (EVL), is used either for acute bleeding or for primary and secondary prophylaxis. There is no radical cure for CHF, and liver transplantation may be the best long-term treatment. In general, treatment for these patients is aimed at alleviating symptoms, including complications of CHF such as variceal bleeding, hypersplenism, cholangitis, etc.^[15]

4. Conclusions

In summary, we report two cases of CHF associated with PKD. This case report highlights the value of radiological imaging, pathological examination, and genetic evaluation in the diagnosis of CHF. Differential diagnosis of CHF should be considered if liver and kidney cysts are present concurrently. Moreover, for any individual with unexplained cirrhosis with bile duct dilation and malformation along with polycystic kidneys on CT, MRI or other noninvasive tests, the possibility of CHF should be considered and then confirmed by genetic testing and liver biopsy. For patients who present with polycystic kidneys at a

young age, the results of liver function tests and imaging examinations, including Fibroscan imaging, should be continuously and dynamically monitored to enable early diagnosis of CHF.

Note: Each patient provided informed consent for publication of his/her case.

Author contributions

Formal analysis: Qiang Zhou.

Investigation: Qiang Zhou.

Methodology: Qiang Zhou, Meishan Jin, Yanhang Gao.

Project administration: Qiang Zhou, Junqi Niu, Yanhang Gao.

Resources: Meishan Jin, Yanhang Gao.

Supervision: Junqi Niu.

Validation: Junqi Niu.

Writing – original draft: Chang Jiang.

Writing – review & editing: Chang Jiang, Yanhang Gao.

References

- [1] Ward CJ, Hogan MC, Rossetti S, et al. The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein. *Nat Genet* 2002;30:259–69.
- [2] Desmet VJ. Congenital diseases of intrahepatic bile ducts: variations on the theme “ductal plate malformation”. *Hepatology* 1992;16:106–83.
- [3] Caine Y, Deckelbaum RJ, Weizman Z, et al. Congenital hepatic fibrosis—unusual presentations. *Arch Dis Child* 1984;59:1094–6.
- [4] Gunay-Aygun M, Font-Montgomery E, Lukose L, et al. Characteristics of congenital hepatic fibrosis in a large cohort of patients with autosomal recessive polycystic kidney disease. *Gastroenterology* 2013;144:112–21.
- [5] Yonem O, Ozkayar N, Balkanci F, et al. Is congenital hepatic fibrosis a pure liver disease? *Am J Gastroenterol* 2006;101:1253–9.
- [6] Zeitoun D, Brancatelli G, Colombat M, et al. Congenital hepatic fibrosis: CT findings in 18 adults. *Radiology* 2004;231:109–16.
- [7] Wu YJ, Ding HG. Hereditary polycystic kidney disease: a neglected etiology of liver cirrhosis. *Zhonghua Gan Zang Bing Za Zhi* 2016;24:728–31.
- [8] Bharani V, Venkatesh GV, Saikia UN, et al. Congenital hepatic fibrosis with polycystic kidney disease: an unusual cause of neonatal cholestasis. *Indian Pediatr* 2017;54:589–92.
- [9] Shorbagi A, Bayraktar Y. Experience of a single center with congenital hepatic fibrosis: a review of the literature. *World J Gastroenterol* 2010;16:683–90.
- [10] Roskams TA, Theise ND, Balabaud C, et al. Nomenclature of the finer branches of the biliary tree: canals, ductules, and ductular reactions in human livers. *Hepatology* 2004;39:1739–45.
- [11] Awasthi A, Das A, Srinivasan R, et al. Morphological and immunohistochemical analysis of ductal plate malformation: correlation with fetal liver. *Histopathology* 2004;45:260–7.
- [12] Libbrecht L, Cassiman D, Desmet V, et al. The correlation between portal myofibroblasts and development of intrahepatic bile ducts and arterial branches in human liver. *Liver* 2002;22:252–8.
- [13] 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;70:1305–17.
- [14] Pedrolli C, Cereda E. Autosomal dominant polycystic disease. *Hepatology* 2009;50:1671–2.
- [15] Meral Gunay-Aygun M, Gahl WA, Heller T. Congenital Hepatic Fibrosis Overview. *GeneReviews*®. Seattle, WA: University of Washington; 2008. Updated April 24, 2014.