NCBI Bookshelf. A service of the National Library of Medicine, National Institutes of Health.

Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2015.

Polycystic Kidney Disease, Autosomal Recessive

Synonyms: ARPKD; Polycystic Kidney Disease, Infantile; ARPKD/CHF

William E Sweeney, MS
Assistant Professor of Pediatrics
Operations Manager, Children's Research Institute
Co-Director, Multidisciplinary Program for Childhood PKD
Medical College and Children's Health System of Wisconsin
Milwaukee, Wisconsin
bsweeney@mcw.edu

Ellis D Avner, MD
Professor of Pediatrics and Physiology
Director, Multidisciplinary Program for Childhood PKD
Founding Associate Dean for Pediatric Research and Director of Children's Research Institute
Medical College and Children's Health System of Wisconsin
Milwaukee, Wisconsin
eavner@mcw.edu

Initial Posting: July 19, 2001; Last Update: March 6, 2014.

Summary

Disease characteristics. Autosomal recessive polycystic kidney disease (ARPKD) belongs to a group of congenital hepatorenal fibrocystic syndromes and is a cause of significant renal and liver-related morbidity and mortality in children. The majority of individuals with ARPKD classically present in the neonatal period with enlarged echogenic kidneys. Renal disease is characterized by nephromegaly, hypertension, and varying degrees of renal dysfunction. More than 50% of children with ARPKD who have a classic presentation progress to end-stage renal disease (ESRD) within the first decade of life; ESRD may require kidney transplantation.

Pulmonary hypoplasia resulting from oligohydramnios occurs in a number of affected infants. Approximately 30% of these infants die in the neonatal period or within the first year of life from respiratory insufficiency or superimposed pulmonary infections. With neonatal respiratory support and renal replacement therapies, the long-term survival of these infants has improved to greater than 80%.

Hepatobiliary disease is characterized by hepatomegaly, splenomegaly, a risk of ascending cholangitis and progressive portal hypertension. At initial presentation, approximately 40%-60% of infants have biliary abnormalities leading to hepatomegaly due to dilated intrahepatic (and occasionally extrahepatic) biliary ducts. Up to 70% of affected individuals, including long-term survivors with classic presentations and those who present with predominantly hepatobiliary disease, develop portal hypertension due to progressive periportal fibrosis; bleeding from esophageal varices contributes significantly to the morbidity and mortality of the disease. A subset of affected individuals will develop recurrent or persistent bacterial ascending cholangitis due to dilated bile ducts and stagnant bile flow. An increasing number of affected individuals surviving the neonatal period will eventually require portosystemic shunting or liver transplantation for complications of portal hypertension or cholangitis.

The classic neonatal presentation of ARPKD notwithstanding, there is significant variability in age and presenting clinical symptoms related to the relative degree of renal and biliary abnormalities.

Diagnosis/testing. The diagnosis of ARPKD is based on clinical findings in the proband and the absence of renal disease in the proband's biological parents. *PKHD1* is the only gene in which mutation is known to be associated with ARPKD.

Management. *Treatment of manifestations:* Management of affected neonates centers on stabilization of respiratory function by mechanical ventilation and (rarely) unilateral or bilateral nephrectomy if massive kidney enlargement impairs diaphragmatic excursion. Neonates with oliguria or anuria may require peritoneal dialysis within the first days of life. Early recognition and treatment of dehydration is critical. Supplemental feedings or fluid therapy via

nasogastric or gastrostomy tubes may be required. Hypertension is treated with angiotensin-converting enzyme (ACE) or angiotensin II receptor inhibitors (ARBs). Affected children with significant chronic kidney disease should be treated with all modalities of modern pediatric ESRD therapy. Treatment of biliary dysfunction focuses on: (a) malabsorption of nutrients and fat-soluble vitamins; and (b) the risk for ascending cholangitis. Treatment includes administration of synthetic bile acids and early recognition and treatment of ascending cholangitis. In those with progressive portal hypertension, endoscopy with sclerotherapy or banding of varices may be required. Portosystemic shunting and/or consideration of liver transplantation may be required. Those with ESRD and severe portal hypertension may be candidates for dual renal/liver transplantation. Feeding intolerance and growth failure may require supplemental feedings via nasogastric or gastrostomy tubes; some children may be candidates for growth hormone therapy.

Prevention of secondary complications: Ursodiol treatment may increase the amount of bile acid and/or reduce the development of gallstones. Immunization against encapsulated bacteria in those with severe portal hypertension and splenic dysfunction is recommended. Palivizumab (Synagis®) for children younger than age 24 months with chronic lung disease and/or prematurity is recommended. Prophylaxis with antibiotics is recommended for those at high risk of developing ascending cholangitis.

Surveillance: Regular monitoring of blood pressure, renal function, serum electrolyte concentrations, hydration status, nutritional status, and growth. Hepatobiliary dysfunction leading to portal hypertension is monitored by physical examination evaluating for hepatosplenomagly; regular examination of platelet count, in addition to serum albumin levels, PT/PTT, and 25-OH vitamin D, vitamin E levels, and fat soluble vitamin levels. Periodic ultrasonography and referral to a hepatologist if hepatomegaly and/or splenomegaly develops; periodic monitoring by esophagogastroduodenoscopy (EGD) to detect and treat esophageal varices by esophageal band ligation and/or sclerotherapy. Consideration of MR cholangiography, a more sensitive measurement for biliary ectasia, at baseline and then as indicated

Evaluation of relatives at risk: Given significant intrafamilial variation and progression of ARPKD, high-resolution renal and hepatic ultrasonographic evaluation and monitoring of systemic blood pressure may identify disease in sibs of a proband.

Agents/circumstances to avoid: Sympathomimetic agents in individuals with hypertension; nephrotoxic agents (NSAIDS and aminoglycosides) unless clinically indicated. Potentially hepatotoxic agents (e.g., acetaminophen doses of >30mg/kg/day, herbal supplements, and alcohol) should be minimized. Preclinical data suggest that caffeine, theophylline-like medications, and calcium channel blockers should be avoided unless clinically necessary.

Genetic counseling. ARPKD is inherited in an autosomal recessive manner. Each sib of a proband has a 25% chance of inheriting both disease-causing alleles and being affected, a 50% chance of inheriting a disease-causing allele and being a carrier, and a 25% chance of inheriting neither disease-causing allele and not being a carrier. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible if both disease-causing alleles have been identified in the family or if linkage studies are informative. No systematic data are available on the sensitivity and specificity of prenatal ultrasound examination in establishing the diagnosis of ARPKD in at-risk pregnancies.

Diagnosis

Clinical Diagnosis

The diagnosis of classic autosomal recessive polycystic kidney disease (ARPKD) should be considered in individuals who have bilaterally enlarged, diffusely echogenic kidneys. Diagnosis is typically made based on clinical presentation and radiographic findings [Dell et al 2009, Sweeney & Avner 2011, Telega et al 2013, Sweeney & Avner 2014]. Specific diagnostic criteria of autosomal recessive polycystic kidney disease (ARPKD) modified from Zerres et al [1996]:

- Typical findings on renal imaging

  AND

- One or more of the following:
  - Imaging findings consistent with biliary ductal ectasia (see **Ultrasonography**)
  - Clinical/laboratory signs of congenital hepatic fibrosis that leads to portal hypertension and may be indicated by hepatosplenomegaly and/or esophageal varices
  - Hepatobiliary pathology demonstrating a characteristic developmental biliary ductal plate abnormality and resultant congenital hepatic fibrosis (see **Childhood and young adulthood**)
  - Absence of renal enlargement and/or characteristic imaging findings in both parents, as demonstrated by high-resolution ultrasonography (HRUS) examination
  - Pathologic (biopsy or autopsy) or genetic diagnosis of ARPKD in an affected sib

Typical Findings on Imaging

Ultrasonography (US)

US is the diagnostic method of choice for assessing fetal and pediatric ARPKD because it is cost effective, painless, widely available, and does not require radiation or sedation. It is predominantly useful in identifying renal abnormalities but abdominal US may also indicate biliary ductal involvement or splenic enlargement in those with ARPKD. However renal US alone is never diagnostic (see Polycystic Kidney Disease, Autosomal Dominant).

The renal diagnostic criteria for ARPKD detected by ultrasonography are:

- Increased renal size (in relation to normative size based on age and size of the affected individual
- Increased echogenicity, and
- Poor corticomedullary differentiation (CMD)

Prenatal. Sonography may demonstrate echogenic, enlarged, reniform kidneys, oligohydramnios, or an empty urinary bladder in severe cases of ARPKD.

- Severely affected fetuses with oligohydramnios may have pulmonary hypoplasia and high mortality due to pulmonary insufficiency; or multiple intrauterine compression anomalies of lethal Potter sequence.
- The presence of large reniform echogenic kidneys with poor corticomedullary differentiation and oligohydramnios on prenatal ultrasound examination suggests ARPKD, although other diagnoses are possible.

Infancy

- The presence of bilateral palpable flank masses in infants with poorly characterized chronic pulmonary disease, a history of oligohydramnios or spontaneous pneumothorax as a newborn, and hypertension are highly suggestive of ARPKD but not diagnostic.
- Biliary findings as noted above, as well as signs of portal hypertension such as hepatosplenomegaly, make a diagnosis of ARPKD more likely.

Childhood and young adulthood

- The findings on renal imaging are noted as above and renal size may actually decrease with age as fibrosis progresses.

- The hepatobiliary abnormalities with progressive portal hypertension are often the prominent presenting features (see Congenital Hepatic Fibrosis Overview).

Microscopic cystic lesions may be present in the early stages with later development of macroscopic cysts.

Recent studies suggest that HRUS may significantly improve the diagnosis of mild disease as well as provide noninvasive, detailed definition of kidney manifestations without extensive use of ionizing radiation or contrast agents [Turkbey et al 2009, Gunay-Aygun et al 2010b].

Magnetic resonance imaging (MRI) offers no advantage over HRUS or genetic testing in the diagnosis of ARPKD.

Magnetic Resonance Cholangiopancreatography (MRCP)

Imaging findings consistent with biliary ductal ectasia are based on magnetic resonance cholangiopancreatography (MRCP) which provides a clear depiction of the biliary ductal system. The findings on MRCP are a sensitive measure of biliary ductal anatomy. Combined with the imaging findings of the kidney, the biliary ductal abnormalities are diagnostic of ARPKD and have largely replaced the more invasive analysis of ductal anatomy by liver biopsy [Turkbey et al 2009, Gunay-Aygun et al 2010a, Gunay-Aygun et al 2013].

Note: Renal biopsies are not used to diagnose ARPKD.

Pathology

The histologic findings of developmental ductal plate abnormalities, including bile duct proliferation, biliary ectasia and periportal fibrosis, are present in all individuals with ARPKD [Kamath & Piccoli 2003].

- The hepatobiliary disease in ARPKD is the result of a developmental defect where a failure of ductal plate remodeling results in persistence of embryologic bile duct structures; these eventually can become massively dilated.
- The dilated bile ducts may evolve into macroscopic cysts that are in connection with the intrahepatic bile ducts and can be detected by imaging modalities, particularly MRCP.
- Associated portal veins are often abnormal, demonstrating an increased number of smaller portal vein branches.
- There is often a significant amount of fibrosis in the portal tract even at birth, and as these affected children age, the amount of peri-portal fibrosis increases, frequently resulting in hepatomegaly and progressive portal hypertension.
- Interestingly and for unclear reasons, ARPKD-affected livers often demonstrate proportionally larger left lobes compared to the right lobes [Gunay-Aygun et al 2013].

Molecular Genetic Testing

Gene. Mutation of *PKHD1* is responsible for all features of the disease.

Clinical testing

Table 1.

Summary of Molecular Genetic Testing Used in Autosomal Recessive Polycystic Kidney Disease

Gene [1]	Test Method	Mutations Detected [2]	Mutation Detection Frequency by Test Method [3]
PKHD1	Sequence analysis	Sequence variants [4]	83% [5, 6] 77% [5, 7] 85% [5, 8] 79% [9]

	Targeted mutation analysis	Panel of mutations	See footnote 10
	Deletion/duplication analysis [11]	Partial- and whole-gene deletions	See footnote 12
	Linkage analysis	NA	See footnote 13

1. See Table A. Genes and Databases for chromosome locus and protein name.
2. See Molecular Genetics for information on allelic variants.
3. The ability of the test method used to detect a mutation that is present in the indicated gene
4. Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site mutations; typically, exonic or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Mutation detection frequency using whole-genome deep sequencing is expected to detect as many as or more mutations than standard mutation scanning.
6. In a study of 75 individuals in 59 unrelated families [Sharp et al 2005]
7. In a study of 164 neonatal survivors from 126 unrelated families [Bergmann et al 2005]
8. In a study of 48 fetuses from 40 unrelated families with at least one child affected by severe ARPKD (defined as perinatal/neonatal mortality) [Bergmann et al 2004b]
9. In 78 individuals from 68 unrelated families in which affected individuals survived beyond age 6 months, traveled to NIH for evaluation, and had clinical confirmation of the diagnosis of arPKD (i.e., typical kidney and liver involvement on imaging and/or biopsy; absence of congenital malformations; autosomal recessive inheritance) [Gunay-Aygun et al 2010a]
10. Mutation panels may vary by laboratory.
11. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.
12. In three of 16 persons with ARPKD in whom only one mutation was detected by sequence analysis, three different *PKHD1* deletions were identified using MLPA [Zvereff et al 2010].
13. Linkage studies are based on the accurate clinical diagnosis of ARPKD in the affected family member and accurate delineation of the genetic relationships in the family. Linkage analysis is dependent on the availability and willingness of family members to be tested. The markers used for ARPKD linkage are highly informative and tightly linked to the 6p21 locus [Lau et al 2010].

Testing Strategy

To confirm/establish the diagnosis in a proband

- When clinical diagnostic criteria for ARPKD are met, molecular genetic testing is usually not necessary to confirm the diagnosis.
- When clinical diagnostic criteria for ARPKD are not met, molecular genetic testing can establish the diagnosis in most instances.
    - Some laboratories provide sequence analysis of the entire coding region; others offer sequence analysis of select exons followed by analysis of the remaining exons if two mutations are not identified.
    - If such testing does not identify two mutations, deletion/duplication analysis may be considered.

Note: Although kidney biopsy or liver biopsy can establish the diagnosis in many cases, such invasive tests are not usually necessary since ARPKD can be diagnosed through noninvasive clinical evaluations and/or genetic testing.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *PKHD1*.

Clinical Description

Natural History

Autosomal recessive polycystic kidney disease (ARPKD) belongs to a group of congenital hepatorenal fibrocystic syndromes and is a cause of significant renal and liver-related morbidity and mortality in children. The two organ systems primarily affected are kidney and liver; however, secondary effects are seen in several other organ systems.

The majority of affected individuals present in the neonatal period. With modern obstetric ultrasonography, the diagnosis may be suspected when abnormalities are detected by prenatal ultrasound examination. Severely affected fetuses detected during prenatal ultrasound display a "Potter-like" oligohydramnios phenotype with lethal pulmonary hypoplasia and massively enlarged echogenic kidneys, which can compromise normal delivery.

Due to its wide clinical variation, the diagnosis may be made during any stage of childhood, and in rare cases does not present until adolescence or adulthood [Gunay-Aygun et al 2010b]. A minority of affected individuals present as older children or young adults with evidence of hepatic dysfunction as the prominent presenting feature (see **Liver**).

Kidney. Large bilateral flank masses (nephromegaly) are invariably present on physical examination.

- Urine output is usually not diminished; polyuria and polydipsia are consistent with a renal concentrating defect. However, oliguria and overt acute renal failure may be seen in the first week of life.
- Hyponatremia is often present in the neonatal period but usually resolves unless renal failure is present.
- Renal function (as reflected in serum concentrations of creatinine and blood urea nitrogen [BUN]) is often impaired. Apparent improvement in renal function over time occurs with progression of normal kidney development over the first three years of life.
- Hypertension, often severe, is usually noted within the first few weeks of life but may improve over time with developmental maturation.

End-stage renal disease (ESRD). More than 50% of affected individuals progress to end-stage renal disease (ESRD), usually in the first decade of life [Roy et al 1997, Guay-Woodford & Desmond 2003]. ESRD may require kidney transplantation (see Management).

- Perinatal presentation and corticomedullary involvement demonstrated by high-resolution ultrasound examination are associated with more rapid progression of renal disease [Gunay-Aygun et al 2010b].
- In a large cohort of neonatal survivors, actuarial kidney survival rates were 86% at age five years, 71% at age ten years, and 42% at age 20 years [Bergmann et al 2005].

Liver. As advances in renal replacement therapy and kidney transplantation improve long-term survival, it is likely that clinical hepatobiliary disease will become a major feature of the natural history of ARPKD [Dell et al 2009, Sweeney & Avner 2011, Sweeney & Avner 2014].

Congenital hepatic fibrosis (CHF). The invariant liver lesion of ARPKD (also known as congenital hepatic fibrosis) is a developmental abnormality of biliary ductal plate remodeling.

- Individuals with congenital hepatic fibrosis develop progressive portal hypertension with resulting esophageal or gastric varices, enlarged hemorrhoids, splenomegaly, hypersplenism, protein-losing enteropathy, and gastrointestinal bleeding [Dell et al 2009, Telega et al 2013].
    - Up to 70% of affected individuals (including long-term survivors with classic presentations and those who present with predominantly hepatobiliary disease) develop portal hypertension due to progressive

periportal fibrosis; bleeding from esophageal varices contributes significantly to the morbidity and mortality of the disease [Gunay-Aygun et al 2013, Sweeney & Avner 2014].

- In a cohort of individuals with ARPKD born after 1990, 37% of those who survived the first year of life had evidence of portal hypertension [Guay-Woodford & Desmond 2003].
- Bergmann et al [2005] reported age-related clinical evidence of congenital hepatic fibrosis, including portal hypertension, in 44% (72/164) of individuals with confirmed *PKHD1* mutations who were diagnosed in the neonatal period and survived beyond the first month of life.

- Although histologic hepatic fibrosis is invariably present at birth, clinical, radiographic, or laboratory evidence of liver disease may be absent in newborns [Shneider & Magid 2005]. In 115 children with ARPKD with a mean age of diagnosis at 29 days, Zerres et al [1996] found that 45% had clinical evidence of liver involvement at presentation.

Caroli syndrome. In addition to congenital hepatic fibrosis, nonobstructed dilatation of the intrahepatic bile ducts (Caroli syndrome) and dilatation of the common bile duct occur in more than 60% of individuals with ARPKD.

- The resultant abnormal hepatobiliary drainage contributes to a significant risk of recurrent or persistent bacterial ascending cholangitis with sepsis.
- Cholestasis may also lead to malabsorption of fat-soluble vitamins (A, D, E, and K).
- The overall abnormal proliferation of biliary cells has reportedly led to benign or malignant tumors in older individuals. Cholangiocarcinoma has been reported in individuals with ARPKD in adulthood [Fonck et al 2001].

Caroli syndrome is most commonly associated with ARPKD [Wen 2011].

Hepatosplenomegaly. A subset of individuals with ARPKD are identified with hepatosplenomegaly [Roy et al 1997]; the renal disease is often mild and may be discovered incidentally during imaging studies of the abdomen.

- In a well-studied National Institute of Health (NIH) cohort of 73 individuals who had confirmed ARPKD, splenomegaly was found to be an early indicator of biliary dysfunction [Gunay Aygun et al 2013].
- Splenomegaly was found in 60% of the affected children under age five years; platelet count was the best predictor of spleen volume:
  - Spleen volume was inversely correlated with platelet count.
  - Spleen length corrected for height correlated inversely with platelet count.
  - Spleen volume did not correlate with renal function, the type of *PKHD1* mutation, or severity of renal disease [Gunay Aygun et al 2013].
- In a study that challenged many assumptions about the timing of liver involvement in ARPKD, Adeva et al [2006] reported that nearly one third of individuals with mutations in *PKHD1* and hepatic involvement were older than age 20 years at the time of initial presentation.
- This wide variability in age was confirmed in a cohort of 78 affected individuals enrolled in an NIH natural history study where affected individuals ranged in age from one to 56 years [Gunay-Aygun et al 2010a, Gunay-Aygun et al 2010b]. This data demonstrates that the clinical spectrum of ARPKD/CHF is much broader than previously assumed.

Lung. Pulmonary hypoplasia resulting from oligohydramnios occurs to varying degrees in a number of affected infants, and is a major cause of morbidity and mortality in the newborn period. Massively enlarged kidneys may also lead to hypoventilation and respiratory distress as a result of limitation of diaphragmatic excursion.

- Potter's facies and other components of the oligohydramnios sequence, including low-set ears, micrognathia, flattened nose, limb positioning defects, and growth deficiency, may be present.
- In contrast to neonates with other disorders complicated by oligohydramnios, a small proportion of newborns with ARPKD and oligo- or anhydramnios in the third trimester may have relatively minor lung disease [Sweeney & Avner 2011]. The reason for this is unclear, but the authors speculate that intrauterine renal overproduction of growth factors critical for lung development (including members of the epidermal growth factor axis) may have an as-yet unexplained positive effect on lung development.

Other

- Recent data suggest that with aggressive nutritional support, growth may be normal in a significant number of children [Dell et al 2009, Sweeney & Avner 2011]. Aggressive nutritional support in the first two years of life has dramatically improved growth rates even in children with significant renal impairment and portal hypertension [Telega et al 2013].
- Feeding difficulties may result from mechanical compression of the stomach by enlarged kidneys, liver, or spleen, the latter a complication of portal hypertension. Alternatively, significant renal impairment may result in feeding difficulties, loss of appetite, and/or impaired gastric motility.
- Cerebral aneurysm, a potentially severe complication of autosomal dominant polycystic kidney disease (ADPKD), has been reported in two adults and a child with ARPKD [Neumann et al 1999, Lilova & Petkov 2001, Chalhoub et al 2013]. In the most recent case report, a man age 21 years with ARPKD presented with subarachnoid hemorrhage secondary to a ruptured intracranial aneurysm. Given the newly discovered interactions between the ARPKD and ADPKD proteins, these may actually represent more than just coincidental occurrences (see Molecular Genetic Pathogenesis), although further study is needed.

Mortality. Although the short- and long-term mortality rates of ARPKD are significant, the survival of children with ARPKD has improved significantly with modern neonatal respiratory support and renal replacement therapies.

- Approximately 23%-30% of affected infants die in the neonatal period or within the first year of life, primarily of respiratory insufficiency or superimposed pulmonary infections [Roy et al 1997, Guay-Woodford & Desmond 2003, Bergmann et al 2005].
- Of those who survive beyond the first year of life (with the use of dialysis and kidney and/or liver transplantation as indicated), one-year survival is approximately 85%-87% [Guay-Woodford & Desmond 2003, Bergmann et al 2005] and ten-year survival is 82% [Bergmann et al 2005].
- Despite improved survival, morbidity of this dual organ disease is significant due to the following:
  - Renal collecting duct ectatic cysts and marked renal enlargement, leading to systemic hypertension and progressive renal failure;
  - Biliary dysgenesis, leading to abnormal bile duct formation with progressive periportal congenital hepatic fibrosis.

Kidney and liver transplantation. For individuals with ARPKD who undergo kidney transplantation, allograft survival rates are comparable to those in individuals without ARPKD; however, data on survival rates are conflicting.

- In a single-center study, mortality following renal transplantation for ARPKD was 36%; four of five deaths were attributed directly to hepatic complications [Khan et al 2002].
- In the North American Pediatric Renal Transplantation Cooperative Study (NAPRTCS), the survival rate at age six years in children with ARPKD was approximately 90% that in the corresponding group of those without PKD [Davis et al 2003]. Sepsis was the cause of death in 64% of those with PKD versus 32% in those with other renal diseases.

- Of those affected individuals who succumb after kidney transplant, 64%-80% of the time mortality is directly attributable to cholangitis/sepsis, a consequence of hepatobiliary disease [Telega et al 2013].
    - A significant number of individuals with ARPKD who require a renal transplant also suffer from significant hepatobiliary disease and progressive portal hypertension that will most likely require portosystemic shunting or a liver transplant in the future [Gunay-Aygun et al 2013].
        - It is estimated that approximately 10% of affected children surviving the neonatal period will require liver transplantation [Wen 2011].
    - Risk benefit analysis suggests that individuals who have severe renal and severe hepatobiliary disease will have less morbidity and mortality if they undergo a liver transplant at the same time as their renal transplant (a dual organ transplant).
    - An algorithm for management and evaluating the risk benefit of dual organ transplant in individuals with ARPKD who have both severe kidney and liver disease has been proposed to assist clinicians in the decision making process [Telega et al 2013] (see Management).

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been established to date; sequence analyses of families with multiple affected probands suggest that most *PKHD1* mutations are "private" or unique to single families [Bergmann et al 2004a].

In a recent study of 73 persons with ARPKD of varying ages, mutation type did not correlate with kidney size or function [Gunay-Aygun et al 2010a].

Modifying genes, epigenetic changes, and variations in other non-coding regions of the genome are believed to be responsible for the wide clinical variability [Dell et al 2009, Sweeney & Avner 2014].

Penetrance

Penetrance is 100%; significant intrafamilial variation in disease severity is observed [Bergmann et al 2005, Dell et al 2009, Sweeney & Avner 2011, Sweeney & Avner 2014].

Nomenclature

In their original description of polycystic kidney disease in childhood, Blyth & Ockenden [1971] used clinical and histologic findings in the kidneys and liver to categorize childhood PKD as perinatal, neonatal, infantile, and juvenile, suggesting four distinct diseases or "stages of disease." Subsequently, families with multiple affected sibs (see, e.g., Kaplan et al [1988], Guay-Woodford & Desmond [2003]) provided evidence that these distinctions were not meaningful.

The most recent trend it to refer to this condition as ARPKD/CHF; at least one patient advocacy group, the ARPKD/CHF Alliance, has adopted this terminology (see Resources).

Prevalence

The incidence of ARPKD is estimated at 1:10,000 to 1:40,000. The true incidence may be underestimated because of the failure to correctly diagnose persons of all ages, ranging from newborns [Dell et al 2009] to young adults [Adeva et al 2006, Gunay-Aygun et al 2010a].

The carrier frequency for a *PKHD1* mutation in the general population is estimated to be 1:70 [Zerres et al 1998b].

Differential Diagnosis

Renal manifestations. Disorders with cystic renal disease include the following:

- Autosomal dominant polycystic kidney disease **(ADPKD)** is characterized by progressive cyst development and bilaterally enlarged polycystic kidneys. ADPKD is a systemic disease with cysts in other organs (e.g., the liver, seminal vesicles, pancreas, and arachnoid membrane) and non-cystic abnormalities (e.g., intracranial aneurysms and dolichoectasias, dilatation of the aortic root and dissection of the thoracic aorta, mitral valve prolapse, colonic diverticulae, abdominal wall hernias).

  Although most ADPKD presents in adulthood, 1%-2% present as newborns, often with signs and symptoms indistinguishable from those of ARPKD [Guay-Woodford et al 1998, Sweeney & Avner 2011, Sweeney & Avner 2014]. Renal ultrasonography may distinguish between the two: bilateral macrocysts are typical of ADPKD. Early in the course of ADPKD, especially in younger children, renal involvement may be unilateral. As ADPKD progresses involvement becomes bilateral; cysts can become massive.

  Congenital hepatic fibrosis, an invariable finding in ARPKD, is rarely observed in ADPKD [O'Brien et al 2012].

  Because ADPKD may not present until the third or fourth decade of life, an asymptomatic parent may not be identified as having ADPKD until after the birth of an affected child [Fick et al 1993]. Renal ultrasound examination of the parents of any individual with atypical ARPKD or suspected ADPKD is needed to evaluate for possible previously undiagnosed ADPKD. Of note, (a) Pei et al [2009] observed that it may not be possible to exclude the diagnosis of ADPKD in a small subset of persons (i.e., those with *PKD2* mutations) until age 40 years and (b) approximately 5%-10% of individuals with ADPKD have *de novo* mutation, and thus do not have an affected parent.

- **Glomerulocystic kidney disease (GCKD)** (OMIM 137920), a rare disorder that typically presents in the neonatal period with large palpable flank masses, may be clinically indistinguishable from ARPKD. Findings on renal ultrasound examination may also resemble those seen in ARPKD: diffusely enlarged echogenic kidneys and occasional macrocysts. Histologic examination shows dilatation of Bowman's capsule and dysplasia with abnormal medullary differentiation. Ten percent have involvement of the intrahepatic bile ducts, similar to the biliary ductal plate abnormality of ARPKD.

  GCKD can be a subtype of ADPKD; however, in at least one large kindred, linkage to both ADPKD loci was excluded [Sharp et al 1997]. GCKD also occurs as part of genetic disorders including the tuberous sclerosis complex, orofacial digital syndrome type 1, trisomy 13, brachymesomelia-renal syndrome, and short-rib-polydactyly syndrome.

- **Diffuse cystic dysplasia** is characterized by ultrasonographic findings of large echogenic kidneys and histologic findings of disorganized, poorly differentiated nephron segments with primitive elements such as cartilage [Watkins et al 1999]. Diffuse cystic dysplasia can occur sporadically or more commonly as a component of numerous syndromes (e.g., Joubert syndrome, Meckel-Gruber syndrome, Jeune asphyxiating thoracic dystrophy) [Limwongse et al 1999]. In these syndromes, the extrarenal or extrahepatic abnormalities clinically predominate; the diffuse cystic dysplasia remains a more minor feature.

- **Other "polycystic kidney" diseases.** A number of studies report "polycystic kidneys" as a component of numerous congenital syndromes. In fact, many of these reports may be describing syndromic forms of cystic dysplasia.

  Hallermann et al [2000] reported a family with typical features of ARPKD in association with multiple congenital anomalies including brachymelia, vertebral abnormalities, Potter's facies, widely spaced eyes, and low-set ears. Linkage to the 6p21 locus was excluded. Three families with similar features were also reported by Gillessen-Kaesbach et al [1993].

  There are a number of diseases where renal cysts are a pathologic finding. These differ from ARPKD in that the

renal cysts represent only one component of multiple developmental abnormalities that characterize the syndrome [Limwongse 2009]. A syndrome of neonatal diabetes mellitus, congenital hypothyroidism, hepatic fibrosis, PKD, and congenital glaucoma has been described in two siblings. Liver biopsy confirmed the classic findings of congenital hepatic fibrosis; histologic evaluation of the kidneys was not performed (OMIM 601331).

Disorders with renal involvement that may mimic ARPKD in the neonatal period include malignancies such as leukemia or Wilms tumor (see Wilms Tumor Overview), bilateral renal vein thrombosis, and radiocontrast nephropathy [Guay-Woodford et al 1998, Dell et al 2009, Sweeney & Avner 2011].

Liver manifestations. Other hepatorenal disorders characterized by renal cystic changes and hepatic fibrosis to consider include a number of disorders already mentioned: juvenile nephronophthisis and multisystem disorders such as Meckel-Gruber syndrome, Bardet-Biedl syndrome, Joubert syndrome, and Jeune asphyxiating thoracic dystrophy [Johnson et al 2003]. In these autosomal recessive disorders the kidneys are usually small or normal in size, in contrast to the enlarged kidneys of ARPKD (see Hepatic Fibrosis Overview).

Note to clinicians: For a patient-specific 'simultaneous consult' related to this disorder, go to SimulConsult®, an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with autosomal recessive polycystic kidney disease (ARPKD), the following evaluations are recommended:

- Evaluation of respiratory status, including physical examination, pulse oximetry, and chest radiographs (as indicated)
- Tests of renal function, including serum concentrations of BUN, creatinine, and cystatin C, which allows a more accurate estimation of glomerular filtration rate (GFR) [Gunay-Aygun et al 2010a]
- Serum electrolyte concentrations to identify electrolyte abnormalities (e.g., hyponatremia, hyperkalemia)
- Urinalysis to assess for the urinary concentration and proteinuria. Clinical assessment of intravascular volume status for possible volume depletion or overload.

  Note: White blood cells are commonly present in the urine of children with ARPKD and may not represent infection. If there is a clinical suspicion of urinary tract infection, a urine culture should be obtained before initiating treatment.
- Renal ultrasonography (consider high-resolution technology when available)
- Measurement of blood pressure. If elevated, home blood pressure monitoring can be helpful in distinguishing fixed hypertension from "white coat" hypertension (i.e., high blood pressure that occurs during medical examinations).
- Assessment of feeding, weight gain, and linear growth with formal nutrition consultation as appropriate
- Measurement of liver transaminases, serum bile acids, hepatic synthetic function (e.g., by assessing serum albumin concentration, 25-OH vitamin D levels, vitamin E levels and coagulation studies), fat-soluble vitamin levels, complete blood counts, physical examination for hepatomegaly/splenomegaly, and abdominal ultrasonography to assess the clinical extent of liver involvement
- Medical genetics consultation

Treatment of Manifestations

(See recent comprehensive reviews including Dell et al [2009], Sweeney & Avner [2011], Sweeney & Avner [2014] for detailed management strategies.)

Initial management of affected infants centers on stabilization of respiratory function.

Respiratory

- Mechanical ventilation may be necessary to treat pulmonary hypoplasia (characterized by inability to oxygenate despite jet or oscillating ventilation with 100% oxygen) or hypoventilation from massively enlarged kidneys (characterized by increased pCO_2 despite adequate oxygenation). It may also be required in the first 48-72 hours postnatally to determine whether pulmonary hypoplasia or reversible pulmonary disease is present.
- When massively enlarged kidneys prevent diaphragmatic excursion and/or cause severe feeding intolerance, some have advocated unilateral or bilateral nephrectomy [Shukla et al 2004].
    - Experience suggests that unilateral nephrectomy may be of limited value, since the contralateral kidney often shows marked enlargement following unilateral nephrectomy [unpublished observations]
    - Bilateral nephrectomy with placement of a peritoneal dialysis catheter followed by a short period of hemodialysis often allows the peritoneum to heal in preparation for chronic peritoneal dialysis [Sweeney & Avner 2011]. The timing of these procedures, as well as potential coordination with a preemptive living donor transplantation, will be dictated by factors such as the age, size, and clinical status of the patient as well as living donor availability.

Renal

- Neonates with oliguria or anuria may require peritoneal dialysis within the first days of life.
- Hyponatremia is common and should be treated depending on the individual's volume status.
- Early recognition and treatment of dehydration is critical. Supplemental feedings or fluid therapy via nasogastric or gastrostomy tubes may be required.
- Hypertension generally responds well to angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor inhibitors (ARBs), which are the treatments of choice. In many cases, hypertension may be severe enough to require multiple antihypertensive medications.
- Affected children with significant chronic kidney disease should be treated with all modalities of modern pediatric end-stage renal disease (ESRD) therapy, including dialysis and kidney transplantation.
- Anemia in children with Stage III or higher chronic kidney disease may require treatment with iron supplementation and erythropoietin-stimulating agents (ESAs).

Liver. Treatment of biliary dysfunction focuses on: (a) malabsorption of nutrients and fat soluble vitamins; and (b) the risk for ascending cholangitis.

- Administration of synthetic bile acids
    - The presence of poor serum levels of fat soluble vitamins (K, D, E, A) or poor weight gain despite adequate caloric supplementation may indicate the need for bile acid supplementation.
    - Clinical suspicion of bile acid deficiency may be verified by measurement of serum bile acids.
    - Administration of synthetic bile acids is indicated if there is evidence of significant intrahepatic ductal dilation (Caroli syndrome), which can be appreciated by MRCP.
- Bacterial cholangitis, often an underdiagnosed complication in those with hepatic involvement, may present as recurrent bacteremia with enteric pathogens without typical clinical features of cholangitis. Persistent fevers, particularly with right upper-quadrant pain, should be evaluated and treated aggressively.

- Alkaline phosphatase and γGTP may be elevated during episodes of acute ascending cholangitis and may be helpful in establishing a diagnosis [Dell et al 2009, Telega et al 2013].

- Esophageal varices should be treated with endoscopic banding or sclerotherapy as indicated.
- Portosystemic shunting may be necessary to treat progressive portal hypertension; however, Tsimaratos et al [2000] reported recurrent hepatic encephalopathy and death following portocaval shunting in two individuals with ARPKD who had ESRD.
- In severe instances of intractable portal hypertension, or severe dual renal and hepatobiliary disease, hepatic or dual renal–hepatic transplantation has become a viable option [Telega et al 2013].

Dual-organ transplantation. Successful simultaneous liver-kidney transplantation in individuals with ARPKD has been reported in a small case series [Harps et al 2011].

- Previously, only a small percent of individuals with ARPKD, particularly those diagnosed later in life, have required liver transplantation. However, with improved survival and advances in renal replacement therapy, it is likely that the number of individuals with ARPKD requiring liver transplantation may increase.
- An algorithm for evaluating the risk benefit of dual organ transplant in individuals with ARPKD who have both severe kidney and liver disease has been proposed to assist clinicians in the decision making process [Telega et al 2013] (see Table 2 and Figure 1).

Feeding and growth

- Feeding intolerance and growth failure, even in the absence of renal insufficiency, can be significant, especially in young infants. Aggressive nutritional support, which may include supplemental feedings via nasogastric or gastrostomy tubes, is often required to optimize weight gain and growth [Dell et al 2009, Sweeney & Avner 2011, Sweeney & Avner 2014].
- Children with growth failure may benefit from treatment with growth hormone [Lilova et al 2003]. The optimal age for starting growth hormone therapy depends on the growth velocity of the child; recent studies suggest that treatment is beneficial in children with chronic kidney disease who are age two years or younger [Seikaly et al 2007].

Prevention of Secondary Complications

Ursodeoxycholic acid (ursodiol or Actigall) is a bile acid that can be used to increase the amount and flow of bile and/or to reduce the development of gallstones in individuals with ARPKD who have significant hepatobiliary disease.

With severe portal hypertension and splenic dysfunction, immunization against encapsulated bacteria (pneumococcus; *H. influenza* type B; meningococcus) is indicated.

Updated guidelines advise that palivizumab (Synagis®) be administered to at-risk children younger than age 24 months who have chronic lung disease and/or a history of prematurity [Committee on Infectious Diseases 2009].

Although the role of chronic antibiotic prophylaxis in all children with ARPKD remains controversial, prophylaxis with antibiotics is recommended for persons with ARPKD who are at high risk of developing ascending cholangitis, including persons who have experienced an episode of ascending cholangitis in the past.

Surveillance

The following should be monitored regularly, depending on disease course and complications:

- Blood pressure monitored at periodic physician's visits as well as home blood pressure monitoring if indicated (see Evaluations Following Initial Diagnosis)

- Renal function in those with chronic kidney disease Stage III or less; close monitoring for the complications of CKD should be undertaken by the treating nephrologist according to standard practices outlined in the KDOQI Guidelines.
- Electrolyte balance, monitored by obtaining serum concentrations of sodium, potassium, and chloride. Mineral balance, monitored by assessing calcium and phosphorous. If the calcium level is low, magnesium concentration should be evaluated [Dell et al 2009, Sweeney & Avner 2011, Sweeney & Avner 2014].
- Hydration status
- Nutritional status, with growth plotted on standard growth charts and nutrition consultation as indicated
- Hepatoportal duct involvement, by physical examination and complete blood counts, in addition to serum albumin levels, PT/PTT, and 25-OH vitamin D, vitamin E levels, and fat soluble vitamin levels
- If hepatomegaly is present and/or splenomegaly develops, additional monitoring, including periodic ultrasonography or MRI. With hepatosplenomegaly, referral to a pediatric hepatologist is suggested for evaluation and periodic monitoring by esophagogastroduodenoscopy (EGD) to detect and treat esophageal varices by esophageal band ligation and/or sclerotherapy [Telega et al 2013].
- Consideration of MR cholangiography, a more sensitive measurement for biliary ectasia, at baseline and then as indicated [Shneider & Magid 2005]

Agents to Avoid

The following should be avoided:

- For affected individuals with hypertension, sympathomimetic agents
- In general, unless the clinical situation warrants their use, known nephrotoxic agents including nonsteroidal anti-inflammatory drugs (NSAIDs) and aminoglycosides

Potentially hepatotoxic agents (e.g., acetaminophen doses >30 mg/kg/day, herbal supplements, and alcohol) should be minimized.

Work in cell and animal models suggests that caffeine, theophylline-like agents, and calcium channel blockers may exacerbate cyst formation and growth. However, this has not been rigorously studied in individuals with ARPKD or ADPKD.

Evaluation of Relatives at Risk

Given the possibility of intrafamilial variability, high-resolution renal and hepatic ultrasonographic evaluation and monitoring of systemic blood pressure of sibs of an individual with ARPKD may be indicated in some instances to permit early diagnosis and treatment and to allay significant parental anxiety, provided that imaging limitations are understood.

Molecular genetic testing may be possible if the pathogenic variants have been identified in an affected family member.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

No specific recommendations exist regarding pregnancy management.

When the pregnancy is complicated by oligohydramnios and/or massively enlarged kidneys, delivery at a tertiary care center is strongly recommended.

Therapies Under Investigation

Novel therapies directed at specific targets in the disease pathogenesis are currently under active investigation. Of note, all studies currently underway or completed have been conducted in adults with ADPKD. Studies in ARPKD are not yet underway but are planned in some instances. For detailed reviews of therapies that have been effective in animal genetic models of ARPKD, see Dell et al [2009], Torres et al [2010], Sweeney & Avner [2011], and Sweeney & Avner [2014].

Click here for additional therapies under investigation.

Preclinical studies of agents directed against the epidermal growth factor receptor (EGFR)-related growth factor axis demonstrated efficacy in orthologous and non-orthologous ARPKD animal models [Sweeney et al 2000, Dell et al 2001, Sweeney et al 2003, Gunay-Aygun et al 2006, Sweeney & Avner 2006]. Sweeney & Avner [2014] (Table 1) list the therapies that are currently under consideration for clinical trials based on success in both in vitro and in vivo pre-clinical trials in orthologous and non-orthologous animal models.

Based on systemic toxicities and preclinical studies to date, it appears that no single drug alone would be adequate in slowing or preventing the progressive renal cyst growth and decreased renal function that occur in ARPKD and ADPKD, nor the hepatobiliary abnormalities that lead to congenital hepatic fibrosis in ARPKD. Future clinical trials will most likely consider the use of the following:

- Multiple, complementary agents;
- Agents that inhibit key intersecting points of abnormally active pathways (i.e., cSrc); or
- Compounds that inhibit multiple pathways with agents such as multikinase inhibitors

It is also probable that effective therapies will need to be designed to target specific stages of disease progression requiring further delineation of disease mechanisms and pathways.

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Autosomal recessive polycystic kidney disease (ARPKD) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one mutant allele).
- Heterozygotes are asymptomatic.
- It is important to perform renal ultrasonography on parents of children with suspected ARPKD to exclude the possibility of ADPKD (see Clinical Diagnosis).

Sibs of a proband

- At conception, each sib of a proband has a 25% chance of inheriting both disease-causing alleles and being affected, a 50% chance of inheriting a disease-causing allele and being a carrier, and a 25% risk of inheriting neither disease-causing allele and not being a carrier.

- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband

- The offspring of an individual with ARPKD are obligate heterozygotes (carriers) for a disease-causing allelic variant in *PKHD1*.
- The carrier frequency in the general population is estimated to be 1:70 [Zerres et al 1998b]. Therefore, the risk of disease in offspring of a proband is approximately 0.7%.

Other family members of a proband. Each sib of the proband's parents is at a 50% risk of being a carrier.

Carrier Detection

Carrier testing is possible once the family-specific pathogenic variants have been identified.

If the pathogenic variants in *PKHD1* cannot be identified, carrier detection using linkage analysis may be possible in families with at least one affected child and in which informative linked markers have been identified.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing

High-risk pregnancies (i.e., those at 25% risk based on family history)

- If both pathogenic variants have been identified in an affected family member (or linkage has been established in the family), prenatal testing for pregnancies at 25% risk may be available from a clinical laboratory that offers either testing for this disease/gene or custom prenatal testing [Zerres et al 1998a].
- No systematic data are available on the sensitivity and specificity of prenatal ultrasound examination in diagnosis of ARPKD in pregnancies at 25% risk.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Low-risk pregnancies (i.e., those not known to be at increased risk but in which routine prenatal ultrasound examination reveals enlarged cystic kidneys)

- Karyotype or array GH and detailed fetal ultrasonography should be performed to evaluate for the presence of a chromosomal abnormality and/or other congenital anomalies in a fetus not known to be at increased risk for ARPKD.

- Molecular genetic testing of *PKHD1* may be appropriate. Failure to detect two mutations, however, does not exclude the diagnosis of ARPKD.
- Renal ultrasound examinations of both parents should be considered in all fetuses with suspected ARPKD to evaluate for the possibility of ADPKD.

Preimplantation genetic diagnosis (PGD) may be an option for some families in which the pathogenic variants have been identified. Note: A preimplantation genetic diagnosis protocol for couples who both carry a *PKHD1* mutation and wish to conceive children unaffected by ARPKD has been developed. Whole-genome amplification of single blastomeres by multiple displacement amplification (MDA), and haplotype analysis with novel short tandem repeat (STR) markers from *PKHD1* and flanking sequences are used [Lau et al 2010]. All new intragenic STR markers developed as well as the unique method of whole-genome amplification is available free of charge from Children's Hospital of Wisconsin (see contact information).

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **ARPKD/CHF Alliance**
  PO Box 70
  Kirkwood PA 17536
  Phone: 800-708-8892 (toll-free); 717-529-5555
  Fax: 800-807-9110 (toll-free)
  Email: info@arpkdchf.org
  www.arpkdchf.org
- **National Library of Medicine Genetics Home Reference**
  Polycystic kidney disease
- **PKD Foundation**
  8330 Ward Parkway
  Suite 510
  Kansas City MO 64114-2000
  Phone: 800-753-2873 (toll-free); 816-931-2600
  Fax: 816-931-8655
  Email: pkdcure@pkdcure.org
  www.pkdcure.org
- **Kidney Foundation of Canada**
  310-5160 Decarie Blvd.
  Montreal Ontario H3X 2H9
  Canada
  Phone: 800-361-7494 (toll-free); 514-369-4806
  Fax: 514-369-2472
  Email: info@kidney.ca
  www.kidney.ca
- **National Kidney Foundation (NKF)**
  30 East 33rd Street
  New York NY 10016
  Phone: 800-622-9010 (toll-free); 212-889-2210
  Email: info@kidney.org

www.kidney.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A.

Polycystic Kidney Disease, Autosomal Recessive: Genes and Databases

Gene Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
PKHD1	6p12.3-p12.2	Fibrocystin	Autosomal Recessive Polycystic Kidney Disease Mutation Database PKHD1 database	PKHD1

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) to which links are provided, click here.

Table B.

OMIM Entries for Polycystic Kidney Disease, Autosomal Recessive (View All in OMIM)

263200	POLYCYSTIC KIDNEY DISEASE, AUTOSOMAL RECESSIVE; ARPKD
606702	PKHD1 GENE; PKHD1

Molecular Genetic Pathogenesis

Notwithstanding the identification of *PKHD1* and its protein product, fibrocystin, the pathogenesis of autosomal recessive polycystic kidney disease (ARPKD) remains unclear [Gunay-Aygun et al 2006, Sweeney & Avner 2006, Sweeney & Avner 2011, Sweeney & Avner 2014]. Reduced or absent function of fibrocystin is thought to underlie the disease pathogenesis [Hiesberger et al 2004, Zhang et al 2004].

Recent studies suggest that many PKD-related proteins are involved with function of the primary cilia, an organelle located on the apical surface of most epithelial cells including kidney tubule and biliary cells [Lin & Satlin 2004, Pazour 2004]. Abnormal structure and/or function of the primary cilium lead to alterations in its mechanosensory properties, which may result in activation of downstream second messenger pathways, notably the cyclic AMP system [Nauli et al 2003, Pazour 2004]. These pathways are thought to activate known cystogenic processes such as cell proliferation and fluid secretion. A consistent feature of all proliferative cystic epithelia is the expression of qualitative and quantitative abnormalities of the EGFR-axis (reviewed in Sweeney & Avner [2011], Sweeney & Avner [2014]). The molecular connection between gene defect, ciliary abnormalities, protein complex formation, and EGFR abnormalities remains speculative.

Fibrocystin, along with polycystin-1 and polycystin-2 (involved in Polycystic Kidney Disease, Autosomal Dominant) have been shown to interact at a molecular level in addition to direct interactions of the protein products. These cystoproteins exist as multimeric protein complexes at multiple sites in addition to cilia. These polycystin complexes are located on the apical cell surface, the lateral cell surface adjacent to the adherens junction, and the basal cell membrane in association with the focal adhesion kinase [Wilson 2004, Avner & Sweeney 2006]. The integration of signaling downstream from multimeric protein complexes may link the molecular and cellular pathophysiology of ARPKD. Recently, c-Src has been identified as a key intermediate in the abnormal signaling of fibrocystin [Sweeney et al 2008].

Hypertension in ADPKD is believed to be mediated by the renin-angiotensin system (RAS); however, supporting data in ARPKD are limited. Studies in the last decade have highlighted the importance of "local" (e.g., kidney-specific) RAS activation that may not be reflected in systemic measurements. The potential role of local kidney RAS in the pathogenesis of hypertension in ARPKD is supported by a histologic study that demonstrated increased expression of several renin-angiotensin axis components in two kidneys of individuals with ARPKD [Loghman-Adham et al 2005]. More recent data in an ARPKD animal model demonstrated RAS activation in the kidneys of affected animals and also in the liver [Goto et al 2010a, Goto et al 2010b]. This raises the question of whether RAS activation may be a more fundamental feature of ARPKD pathogenesis rather than a nonspecific manifestation of chronic kidney disease.

Gene structure. *PKHD1* is an extremely large gene that comprises 86 coding exons [Onuchic et al 2002, Ward et al 2002, Bergmann et al 2004a]. The largest reading frame encompasses 67 exons (NM_138694.3), but multiple alternatively spliced transcripts have been described [Bergmann et al 2004a]. For a detailed summary of gene and protein information, see Table A, **Gene Symbol**.

Pathogenic allelic variants. Different types of mutations are distributed across the gene. See LSDB and HGMD Databases in Table A.

Normal gene product. The *PKHD1* product is a large protein with receptor-like properties [Onuchic et al 2002, Ward et al 2002]. It is localized to kidney, bile ducts, and pancreas. In addition, fibrocystin has been shown to localize to primary cilia as well as other discrete locations in renal tubular epithelial cells, suggesting a possible link of multiple pathways to ciliary dysfunction in some instances [Ward et al 2003], or multimeric protein complex signaling in cystic epithelium and endothelium. Abnormalities in ciliary structure and function may participate in the pathogenesis of many different types of cystic kidney diseases [Ong & Wheatley 2003] (see Molecular Genetic Pathogenesis).

Abnormal gene product. Reduced or absent function of fibrocystin is thought to underlie the disease pathogenesis [Hiesberger et al 2004, Zhang et al 2004]. See Molecular Genetic Pathogenesis.

References

Literature Cited

1. Adeva M, El-Youssef M, Rossetti S, Kamath PS, Kubly V, Consugar MB, Milliner DM, King BF, Torres VE, Harris PC. Clinical and molecular characterization defines a broadened spectrum of autosomal recessive polycystic kidney disease (ARPKD). Medicine (Baltimore) 2006;85:1–21. [PubMed: 16523049]
2. Avner ED, Sweeney WE. Renal cystic disease: new insights for the clinician. Pediatr Clin North Am. 2006;53:889–909. [PubMed: 17027616]
3. Bergmann C, Senderek J, Kupper F, Schneider F, Dornia C, Windelen E, Eggermann T, Rudnik-Schoneborn S, Kirfel J, Furu L, Onuchic LF, Rossetti S, Harris PC, Somlo S, Guay-Woodford L, Germino GG, Moser M, Buttner R, Zerres K. PKHD1 mutations in autosomal recessive polycystic kidney disease (ARPKD). Hum Mutat. 2004a;23:453–63. [PubMed: 15108277]
4. Bergmann C, Senderek J, Schneider F, Dornia C, Kupper F, Eggermann T, Rudnik-Schoneborn S, Kirfel J, Moser M, Buttner R, Zerres K. PKHD1 mutations in families requesting prenatal diagnosis for autosomal recessive polycystic kidney disease (ARPKD). Hum Mutat. 2004b;23:487–95. [PubMed: 15108281]
5. Bergmann C, Senderek J, Windelen E, Kupper F, Middeldorf I, Schneider F, Dornia C, Rudnik-Schoneborn S, Konrad M, Schmitt CP, Seeman T, Neuhaus TJ, Vester U, Kirfel J, Buttner R, Zerres K. Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). Kidney Int. 2005;67:829–48. [PubMed: 15698423]
6. Blyth H, Ockenden BG. Polycystic disease of kidney and liver presenting in childhood. J Med Genet. 1971;8:257–84. [PMC free article: PMC1469189] [PubMed: 5097134]
7. Chalhoub V, Abi-Rafeh L, Hachem K, Ayoub E, Yazbeck P. Intracranial aneurysm and recessive polycystic kidney disease: the third reported case. JAMA Neurol. 2013;70:114–6. [PubMed: 23318517]

8. Committee on Infectious Diseases; From the American Academy of Pediatrics: Policy statements--Modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. Pediatrics. 2009;124:1694–701. [PubMed: 19736258]
9. Davis ID, Ho M, Hupertz V, Avner ED. Survival of childhood polycystic kidney disease following renal transplantation: the impact of advanced hepatobiliary disease. Pediatr Transplant. 2003;7:364–9. [PubMed: 14738296]
10. Dell KM, Sweeney WE, Avner ED. Polycystic kidney disease. In: Avner ED, Harmon W, Niadet P,Yoshikawa N, eds. *Pediatric Nephrology*. 6 ed. Heidelberg, Germany: Springer-Verlag; 2009:849-88.
11. Dell KM, Nemo R, Sweeney WE, Levin JI, Frost P, Avner ED. A novel inhibitor of tumor necrosis factor-alpha converting enzyme ameliorates polycystic kidney disease. Kidney Int. 2001;60:1240–8. [PubMed: 11576338]
12. Fick GM, Johnson AM, Strain JD, Kimberling WJ, Kumar S, Manco-Johnson ML, Duley IT, Gabow PA. Characteristics of very early onset autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1993;3:1863–70. [PubMed: 8338917]
13. Fonck C, Chauveau D, Gagnadoux MF, Pirson Y, Grünfeld JP. Autosomal recessive polycystic kidney disease in adulthood. Nephrol Dial Transplant. 2001;16:1648–52. [PubMed: 11477168]
14. Gillessen-Kaesbach G, Meinecke P, Garrett C, Padberg BC, Rehder H, Passarge E. New autosomal recessive lethal disorder with polycystic kidneys type Potter I, characteristic face, microcephaly, brachymelia, and congenital heart defects. Am J Med Genet. 1993;45:511–8. [PubMed: 8465860]
15. Goto M, Hoxha N, Osman R, Dell KM. The renin-angiotensin system and hypertension in autosomal recessive polycystic kidney disease. Pediatr Nephrol. 2010a;25:2449–57. [PubMed: 20798958]
16. Goto M, Hoxha N, Osman R, Wen J, Wells R, Dell KM. Renin-Angiotensin System (RAS) Activation in Congenital Hepatic Fibrosis in the PCK Rat Model of Autosomal Recessive Polycystic Kidney Disease (ARPKD). J Pediatr Gastroenterol Nutr. 2010b;50:639–44. [PMC free article: PMC4241057] [PubMed: 20400910]
17. Guay-Woodford LM, Desmond RA. Autosomal recessive polycystic kidney disease: the clinical experience in North America. Pediatrics. 2003;111:1072–80. [PubMed: 12728091]
18. Guay-Woodford LM, Galliani CA, Musulman-Mroczek E, Spear GS, Guillot AP, Bernstein J. Diffuse renal cystic disease in children: morphologic and genetic correlations. Pediatr Nephrol. 1998;12:173–82. [PubMed: 9630032]
19. Gunay-Aygun M, Avner ED, Bacallao RL, Choyke PL, Flynn JT, Germino GG, Guay-Woodford L, Harris P, Heller T, Ingelfinger J, Kaskel F, Kleta R, LaRusso NF, Mohan P, Pazour GJ, Schneider BL, Torres VE, Wilson P, Zak C, Zhou J, Gahl WA. Autosomal recessive polycystic kidney disease and congenital hepatic fibrosis: summary statement of a first National Institutes of Health/ Office of Rare Diseases conference. J Pediatr. 2006;149:159–64. [PMC free article: PMC2918414] [PubMed: 16887426]
20. Gunay-Aygun M, Tuchman M, Font-Montgomery E, Lukose L, Edwards H, Garcia A, Ausavarat S, Ziegler SG, Piwnica-Worms K, Bryant J, Bernardini I, Fischer R, Huizing M, Guay-Woodford L, Gahl WA. PKHD1 sequence variations in 78 children and adults with autosomal recessive polycystic kidney disease and congenital hepatic fibrosis. Mol Genet Metab. 2010a;99:160–73. [PMC free article: PMC2818513] [PubMed: 19914852]
21. Gunay-Aygun M, Font-Montgomery E, Lukose L, Tuchman M, Graf J, Bryant JC, Kleta R, Garcia A, Edwards H, Piwnica-Worms K, Adams D, Bernardini I, Fischer RE, Krasnewich D, Oden N, Ling A, Quezado Z, Zak C, Daryanani KT, Turkbey B, Choyke P, Guay-Woodford LM, Gahl WA. Correlation of kidney function, volume and imaging findings, and PKHD1 mutations in 73 patients with autosomal recessive polycystic kidney disease. Clin J Am Soc Nephrol. 2010b;5:972–84. [PMC free article: PMC2879301] [PubMed: 20413436]
22. Gunay-Aygun M, Font-Montgomery E, Lukose L, Tuchman Gerstein M, Piwnica-Worms K, Choyke P, Daryanani KT, Turkbey B, Fischer RE, Bernardini I, Sincan M, Zhou X, Sandler NG, Roque A, Douek DC, Graf J, Huizing M, Bryant JC, Mohan P, Gahl WA, Heller T. Characteristics of congenital hepatic fibrosis in a large cohort of patients with autosomal recessive polycystic kidney disease. Gasteroenterology. 2013;144:112–21. [PMC free article: PMC4162098] [PubMed: 23041322]
23. Hallermann C, Mucher G, Kohlschmidt N, Wellek B, Schumacher R, Bahlmann F, Shahidi-Asl P, Theile U, Rudnik-Schoneborn S, Muntefering H, Zerres K. Syndrome of autosomal recessive polycystic kidneys with

skeletal and facial anomalies is not linked to the ARPKD gene locus on chromosome 6p. Am J Med Genet. 2000;90:115–9. [PubMed: 10607948]

24. Harps E, Brinkert F, Ganschow R, Briem-Richter A, van Husen M, Schmidtke S, Herden U, Nashan B, Fischer L, Kemper MJ. Immediate postoperative intensive care treatment of pediatric combined liver-kidney transplantation: outcome and prognostic factors. Transplantation. 2011;91:1127–31. [PubMed: 21544033]
25. Hiesberger T, Bai Y, Shao X, McNally BT, Sinclair AM, Tian X, Somlo S, Igarashi P. Mutation of hepatocyte nuclear factor-1beta inhibits Pkhd1 gene expression and produces renal cysts in mice. J Clin Invest. 2004;113:814–25. [PMC free article: PMC362119] [PubMed: 15067314]
26. Johnson CA, Gissen P, Sergi C. Molecular pathology and genetics of congenital hepatorenal fibrocystic syndromes. J Med Genet. 2003;40:311–9. [PMC free article: PMC1735460] [PubMed: 12746391]
27. Kamath BM, Piccoli DA. Heritable disorders of the bile ducts. Gastroenterol Clin North Am. 2003;32:857–75. [PubMed: 14562578]
28. Kaplan BS, Kaplan P, de Chadarevian JP, Jequier S, O'Regan S, Russo P. Variable expression of autosomal recessive polycystic kidney disease and congenital hepatic fibrosis within a family. Am J Med Genet. 1988;29:639–47. [PubMed: 3377007]
29. Khan K, Schwarzenberg SJ, Sharp HL, Matas AJ, Chavers BM. Morbidity from congenital hepatic fibrosis after renal transplantation for autosomal recessive polycystic kidney disease. Am J Transplant. 2002;2:360–5. [PubMed: 12118859]
30. Lau EC, Janson MM, Roesler MR, Avner ED, Strawn EY, Bick DP. Birth of a healthy infant following preimplantation PKHD1 haplotyping for autosomal recessive polycystic kidney disease using multiple displacement amplification. J Assist Reprod Genet. 2010;27:397–407. [PMC free article: PMC2922704] [PubMed: 20490649]
31. Lilova M, Kaplan BS, Meyers KE. Recombinant human growth hormone therapy in autosomal recessive polycystic kidney disease. Pediatr Nephrol. 2003;18:57–61. [PubMed: 12488992]
32. Lilova MI, Petkov DL. Intracranial aneurysms in a child with autosomal recessive polycystic kidney disease. Pediatr Nephrol. 2001;16:1030–2. [PubMed: 11793094]
33. Limwongse C, Syndromes and malformations of the urinary tract. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa N, eds. *Pediatric Nephrology*. 6 ed. Berlin, Germany: Springer-Verlag; 2009:121-55.
34. Limwongse C, Clarren SK, Cassidy SB. Syndromes and malformations of the urinary tract. In: Barratt TM, Avner ED, Harmon WE, eds. *Pediatric Nephrology*. 4 ed. Baltimore, MD: Lippincott Williams & Wilkins; 1999:427-52.
35. Lin F, Satlin LM. Polycystic kidney disease: the cilium as a common pathway in cystogenesis. Curr Opin Pediatr. 2004;16:171–6. [PubMed: 15021197]
36. Loghman-Adham M, Soto CE, Inagami T, Sotelo-Avila C. Expression of components of the renin-angiotensin system in autosomal recessive polycystic kidney disease. J Histochem Cytochem. 2005;53:979–88. [PubMed: 15879580]
37. Nauli SM, Alenghat FJ, Luo Y, Williams E, Vassilev P, Li X, Elia AE, Lu W, Brown EM, Quinn SJ, Ingber DE, Zhou J. Polycystins 1 and 2 mediate mechanosensation in the primary cilium of kidney cells. Nat Genet. 2003;33:129–37. [PubMed: 12514735]
38. Neumann HP, Krumme B, van Velthoven V, Orszagh M, Zerres K. Multiple intracranial aneurysms in a patient with autosomal recessive polycystic kidney disease. Nephrol Dial Transplant. 1999;14:936–9. [PubMed: 10328473]
39. O'Brien K, Font-Montgomery E, Lukose L, Bryant J, Piwnica-Worms K, Edwards H, Riney L, Garcia A, Daryanani K, Choyke P, Mohan P, Heller T, Gahl WA, Gunay-Aygun M. Congenital hepatic fibrosis and portal hypertension in autosomal dominant polycystic kidney disease. J Pediatr Gastroenterol Nutr. 2012;54:83–9. [PubMed: 21694639]
40. Ong AC, Wheatley DN. Polycystic kidney disease--the ciliary connection. Lancet. 2003;361:774–6. [PubMed: 12620752]
41. Onuchic LF, Furu L, Nagasawa Y, Hou X, Eggermann T, Ren Z, Bergmann C, Senderek J, Esquivel E, Zeltner R, Rudnik-Schoneborn S, Mrug M, Sweeney W, Avner ED, Zerres K, Guay-Woodford LM, Somlo S, Germino

GG. 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. [PMC free article: PMC447605] [PubMed: 11898128]

42. Pazour GJ. Intraflagellar transport and cilia-dependent renal disease: the ciliary hypothesis of polycystic kidney disease. J Am Soc Nephrol. 2004;15:2528–36. [PubMed: 15466257]
43. Pei Y, Obaji J, Dupuis A, Paterson AD, Magistroni R, Dicks E, Parfrey P, Cramer B, Coto E, Torra R, San Millan JL, Gibson R, Breuning M, Peters D. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol. 2009;20:205–12. [PMC free article: PMC2615723] [PubMed: 18945943]
44. Roy S, Dillon MJ, Trompeter RS, Barratt TM. Autosomal recessive polycystic kidney disease: long-term outcome of neonatal survivors. Pediatr Nephrol. 1997;11:302–6. [PubMed: 9203177]
45. Seikaly MG, Salhab N, Warady BA, Stablein D. Use of rhGH in children with chronic kidney disease: lessons from NAPRTCS. Pediatr Nephrol. 2007;22:1195–204. [PubMed: 17530299]
46. Sharp AM, Messiaen LM, Page G, Antignac C, Gubler MC, Onuchic LF, Somlo S, Germino GG, Guay-Woodford LM. Comprehensive genomic analysis of PKHD1 mutations in ARPKD cohorts. J Med Genet. 2005;42:336–49. [PMC free article: PMC1736033] [PubMed: 15805161]
47. Sharp CK, Bergman SM, Stockwin JM, Robbin ML, Galliani C, Guay-Woodford LM. Dominantly transmitted glomerulocystic kidney disease: a distinct genetic entity. J Am Soc Nephrol. 1997;8:77–84. [PubMed: 9013451]
48. Shneider BL, Magid MS. Liver disease in autosomal recessive polycystic kidney disease. Pediatr Transplant. 2005;9:634–9. [PubMed: 16176423]
49. Shukla AR, Kiddoo DA, Canning DA. Unilateral nephrectomy as palliative therapy in an infant with autosomal recessive polycystic kidney disease. J Urol. 2004;172:2000–1. [PubMed: 15540776]
50. Sweeney WE Jr, Avner ED. Molecular and cellular pathophysiology of autosomal recessive polycystic kidney disease (ARPKD). Cell Tissue Res. 2006;326:671–85. [PubMed: 16767405]
51. Sweeney WE Jr, Avner ED. Diagnosis and management of childhood polycystic kidney disease. Pediatr Nephrol. 2011;26:675–92. [PubMed: 21046169]
52. Sweeney WE Jr, Avner ED. Pathophysiology of childhood polycystic kidney diseases: new insights into disease -specific therapy. Pediatr Res. 2014;75:148–57. [PMC free article: PMC3953890] [PubMed: 24336431]
53. Sweeney WE, Chen Y, Nakanishi K, Frost P, Avner ED. Treatment of polycystic kidney disease with a novel tyrosine kinase inhibitor. Kidney Int. 2000;57:33–40. [PubMed: 10620185]
54. Sweeney WE Jr, Hamahira K, Sweeney J, Garcia-Gatrell M, Frost P, Avner ED. Combination treatment of PKD utilizing dual inhibition of EGF-receptor activity and ligand bioavailability. Kidney Int. 2003;64:1310–9. [PubMed: 12969149]
55. Sweeney WE Jr, von Vigier RO, Frost P, Avner ED. Src Inhibition ameliorates polycystic kidney disease. J Am Soc Nephrol. 2008;19:1331–41. [PMC free article: PMC2440293] [PubMed: 18385429]
56. Telega G, Cronin D, Avner ED. New approaches to the autosomal recessive polycystic kidney disease patient with dual kidney-liver complications. Pediatr Transplant. 2013;17:328–35. [PMC free article: PMC3663883] [PubMed: 23593929]
57. Torres VE, Boletta A, Chapman A, Gattone V, Pei Y, Qian Q, Wallace DP, Weimbs T, Wüthrich RP. Prospects for mTOR inhibitor use in patients with polycystic kidney disease and hamartomatous diseases. Clin J Am Soc Nephrol. 2010;5:1312–29. [PubMed: 20498248]
58. Tsimaratos M, Cloarec S, Roquelaure B, Retornaz K, Picon G, Chabrol B, Guys JM, Sarles J, Nivet H. Chronic renal failure and portal hypertension--is portosystemic shunt indicated? Pediatr Nephrol. 2000;14:856–8. [PubMed: 10955945]
59. Turkbey B, Ocak I, Daryanani K, Font-Montgomery E, Lukose L, Bryant J, Tuchman M, Mohan P, Heller T, Gahl WA, Choyke PL, Gunay-Aygun M. Autosomal recessive polycystic kidney disease and congenital hepatic fibrosis (ARPKD/CHF). Pediatr Radiol. 2009;39:100–11. [PMC free article: PMC2918426] [PubMed: 19089418]
60. Ward CJ, Hogan MC, Rossetti S, Walker D, Sneddon T, Wang X, Kubly V, Cunningham JM, Bacallao R, Ishibashi M, Milliner DS, Torres VE, Harris PC. The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein. Nat Genet. 2002;30:259–69. [PubMed: 11919560]

61. Ward CJ, Yuan D, Masyuk TV, Wang X, Punyashthiti R, Whelan S, Bacallao R, Torra R, LaRusso NF, Torres VE, Harris PC. Cellular and subcellular localization of the ARPKD protein; fibrocystin is expressed on primary cilia. Hum Mol Genet. 2003;12:2703–10. [PubMed: 12925574]
62. Watkins SL, McDonald RA, Avner ED. Renal dysplasia, hypoplasia and miscellaneous cystic disorders. In: Barratt TM, Avner ED, Harmon WE, eds. *Pediatric Nephrology*. 4 ed. Baltimore, MD: Lippincott Williams & Wilkins; 1999:415-25.
63. Wen J. Congenital hepatic fibrosis in autosomal recessive polycystic kidney disease. Clin Transl Sci. 2011;4 (6):460–5. [PMC free article: PMC3252199] [PubMed: 22212229]
64. Wilson PD. Polycystic kidney disease. N Engl J Med. 2004;350:151–64. [PubMed: 14711914]
65. Zerres K, Mucher G, Becker J, Steinkamm C, Rudnik-Schoneborn S, Heikkila P, Rapola J, Salonen R, Germino GG, Onuchic L, Somlo S, Avner ED, Harman LA, Stockwin JM, Guay-Woodford LM. Prenatal diagnosis of autosomal recessive polycystic kidney disease (ARPKD): molecular genetics, clinical experience, and fetal morphology. Am J Med Genet. 1998a;76:137–44. [PubMed: 9511976]
66. Zerres K, Rudnik-Schoneborn S, Deget F, Holtkamp U, Brodehl J, Geisert J, Scharer K. Autosomal recessive polycystic kidney disease in 115 children: clinical presentation, course and influence of gender. Arbeitsgemeinschaft fur Padiatrische, Nephrologie. Acta Paediatr. 1996;85:437–45. [PubMed: 8740301]
67. Zerres K, Rudnik-Schoneborn S, Steinkamm C, Becker J, Mucher G. Autosomal recessive polycystic kidney disease. J Mol Med. 1998b;76:303–9. [PubMed: 9587064]
68. Zhang MZ, Mai W, Li C, Cho SY, Hao C, Moeckel G, Zhao R, Kim I, Wang J, Xiong H, Wang H, Sato Y, Wu Y, Nakanuma Y, Lilova M, Pei Y, Harris RC, Li S, Coffey RJ, Sun L, Wu D, Chen XZ, Breyer MD, Zhao ZJ, McKanna JA, Wu G. PKHD1 protein encoded by the gene for autosomal recessive polycystic kidney disease associates with basal bodies and primary cilia in renal epithelial cells. Proc Natl Acad Sci U S A. 2004;101:2311–6. [PMC free article: PMC356947] [PubMed: 14983006]
69. Zvereff V, Yao S, Ramsey J, Mikhail FM, Vijzelaar R, Messiaen L. Identification of PKHD1 multiexon deletions using multiplex ligation-dependent probe amplification and quantitative polymerase chain reaction. Genet Test Mol Biomarkers. 2010;14:505–10. [PubMed: 20575693]

Suggested Reading

1. Harris PC. 2008 Homer W. Smith Award: insights into the pathogenesis of polycystic kidney disease from gene discovery. J Am Soc Nephrol. 2009;20:1188–98. [PubMed: 19423684]

Chapter Notes

Author Notes

Children's Research Institute Web site: www.chw.org/research

Contact information for Children's Hospital of Wisconsin (preimplantation genetic diagnosis protocol)

David Bick, MD
Section Chief, Department of Pediatrics, Obstetrics and Gynecology
Children's Hospital of Wisconsin
PO Box 1997
Milwaukee Wi 53201-1997
(414) 266-2979
dbick@mcw.edu

Author History

Ellis Avner, MD (2001-present)
Katherine MacRae Dell, MD; Case Western Reserve University School of Medicine (2001-2014)
William E Sweeney, MS (2014-present)

Revision History

- 6 March 2014 (me) Comprehensive update posted live
- 22 September 2011 (me) Comprehensive update posted live
- 14 July 2009 (cd) Revision: deletion/duplication analysis available clinically
- 7 August 2008 (me) Comprehensive update posted live
- 21 March 2006 (me) Comprehensive update posted to live Web site
- 23 October 2003 (me) Comprehensive update posted to live Web site
- 13 January 2003 (kmd) Revision: gene identified
- 19 July 2001 (me) Review posted to live Web site
- April 2001 (kmd) Original submission

Figures

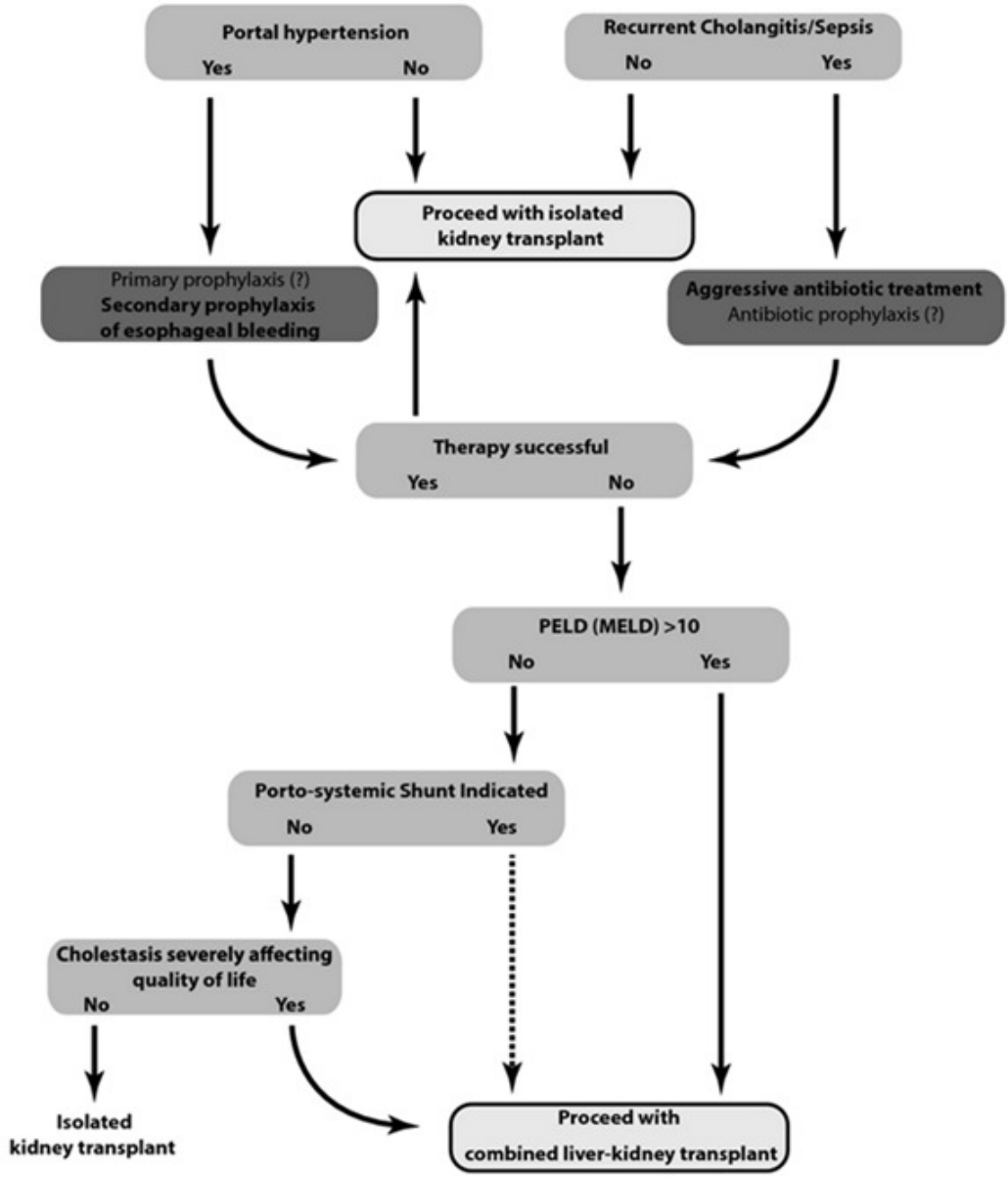

Figure 1.

New approaches to the individual with autosomal recessive polycystic kidney disease who has dual kidney–liver complications.

Bookshelf ID: NBK1326 PMID: 20301501