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Autosomal Recessive Polycystic Kidney Disease

[*ARPKD; Polycystic Kidney Disease, Infantile*]

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Summary

Disease characteristics. The majority of individuals with autosomal recessive polycystic kidney disease (ARPKD) present in the neonatal period with enlarged echogenic kidneys. At initial presentation, approximately 45% of infants have liver abnormalities, including hepatomegaly, dilated intrahepatic biliary ducts, and increased echogenicity. Pulmonary hypoplasia resulting from oligohydramnios occurs in a number of affected infants. Approximately 30% of affected neonates die, primarily of respiratory insufficiency. More than 50% of affected children progress to end-stage renal disease (ESRD), usually in the first decade of life. With neonatal respiratory support and renal replacement therapies, the ten-year survival of those who live beyond the first year of life has improved to 82%. Fifteen-year survival is estimated to be 67%-79%. A minority of individuals present as older children, usually with hepatosplenomegaly as the presenting feature.

Diagnosis/testing. The diagnosis of ARPKD is based on clinical findings in the proband and the absence of renal cysts in the parents of the proband. Sequence analysis of *PKHD1*, the only gene known to be associated with ARPKD, is clinically available. Linkage analysis is available for families with at least one affected child.

Management. *Treatment of manifestations:* Initial management of affected neonates focuses on stabilization of respiratory function by mechanical ventilation and sometimes unilateral or bilateral nephrectomy. Neonates with oliguria or anuria may require peritoneal dialysis within the first days of life. Hypertension is treated with angiotensin-converting enzyme (ACE) or angiotensin II receptor inhibitors. Supplemental feedings via nasogastric or gastrostomy tubes are often required. Affected children with significant chronic kidney disease and growth failure may benefit from treatment with growth hormone. A porto-caval shunt may be necessary to treat progressive portal hypertension; varices may be treated with sclerotherapy or endoscopic banding. Liver transplantation may become the preferred therapy for those being considered for porto-caval shunting. *Prevention of secondary complications:* immunization against

encapsulated bacteria in those with severe portal hypertension and splenic dysfunction. *Surveillance:* annual or more frequent monitoring of blood pressure, renal function, serum electrolyte concentrations, hydration status, nutritional status, growth, and hepatic involvement. *Testing of relatives at risk:* Renal and hepatic ultrasound evaluations of older sibs of a proband allow early diagnosis and treatment. *Agents/circumstances to avoid:* sympathomimetic agents in individuals with hypertension; nephrotoxic agents (nonsteroidal anti-inflammatory drugs [NSAIDS] and aminoglycosides) 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 diagnosis of ARPKD in pregnancies at 25% risk.

Diagnosis

Clinical Diagnosis

Clinical 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:
  - Clinical/laboratory signs of hepatic fibrosis that leads to portal hypertension and may be manifested by hepato-splenomegaly and/or esophageal varices
  - Hepatic pathology demonstrating a developmental ductal plate abnormality
  - Absence of renal cysts in both parents, as demonstrated by ultrasound examination
  - Pathoanatomical proof of ARPKD in an affected sib
  - Parental consanguinity suggesting autosomal recessive inheritance

Infancy

- The presence of bilateral palpable flank masses in infants with pulmonary hypoplasia, a history of oligohydramnios, and hypertension are highly suggestive of ARPKD.
- The presence of large echogenic kidneys on prenatal ultrasound examination is also suggestive of ARPKD, although other diagnoses need to be considered.

Childhood and young adulthood

- In the atypical individual who presents later in childhood, the findings on renal imaging are less reliable.
- The hepatic abnormalities are often the prominent presenting features.

Renal Findings—Ultrasonography

- **Infancy.** Fetuses and infants have characteristic large echogenic kidneys with poor corticomedullary differentiation:

- Macrocysts are usually not present, although they may be seen with worsening disease.
- Stein-Wexler & Jain [2003] have proposed that the ultrasonographic findings of "focal rosettes," corresponding to the macroscopic appearance of radially oriented collecting tubule cysts, are specific for ARPKD.
- Although kidneys may be markedly enlarged at birth, over time the majority show stable to decreased renal size relative to body growth [Avni et al 2002]. However, with progressive disease, the ultrasonographic appearance of the kidneys may more closely resemble that seen in ADPKD [Avni et al 2002].

- **Childhood and young adulthood**
  - Kidneys are echogenic and large, but massive enlargement is generally not seen.
  - Macrocysts, more typical of ADPKD, are often seen in older children [Traubici & Daneman 2005].

Magnetic resonance imaging (MRI) has been proposed as a noninvasive alternative to renal biopsy for establishing the diagnosis of ARPKD:

- Findings on MRI include enlarged kidneys with hyperintense T2-weighted signals.
- A characteristic hyperintense, linear radial pattern in the cortex and medulla representing microcystic dilatation has been described on RARE-MR urography [Kern et al 2000].
- Cassart et al [2004] showed that MRI may be a useful additional diagnostic study in fetuses with inconclusive ultrasonography in the third trimester of pregnancy. However, its accuracy in confirming the diagnosis earlier in pregnancy has not been assessed.

Pathology reveals bilateral, symmetric kidney involvement. Microscopically, the kidneys show a pattern of fusiform dilatations ("microcysts" <4 mm in diameter) radiating from the medulla to the cortex [Dell et al 2004]. Tubular localization and microdissection studies have demonstrated that the disease is confined to the collecting tubules in all affected children, although a transient proximal tubular cystic phase occurs in fetuses [Nakanishi et al 2000].

Note: Although kidney biopsy establishes the diagnosis in many cases, it is generally not necessary when clinical criteria are met.

Hepatic Findings—Ultrasonography reveals hepatomegaly, dilated intrahepatic (and occasionally extrahepatic) biliary ducts, poor visualization of the peripheral portal veins, and increased echogenicity. These findings have been reported prenatally but may not be evident at birth.

Pathology. The histologic findings of typical ductal plate abnormality with bile duct proliferation and ectasia with hepatic fibrosis are present in all individuals with ARPKD [Kamath & Piccoli 2003].

Testing

Liver function tests and transaminases are generally normal.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *PKHD1* is the only gene known to be associated with the wide clinical spectrum of ARPKD.

Clinical testing

- **Mutation scanning.** Initial studies suggested a relatively low mutation detection rate (40%-60%) [Bergmann et al 2003, Rossetti et al 2003], but newer studies using mutation scanning by denaturing high-performance liquid chromatography (DHPLC) demonstrate an overall mutation detection rate of 82%-85% when diagnostic criteria of ARPKD are met either prenatally or postnatally [Bergmann et al 2004b, Sharp et al 2005].

  Note: The relatively low rate of mutation detection in the earlier studies has been attributed to multiple factors, including the complexity and large size of the gene, the presence of mutations throughout the gene, and the fact that most families have a unique (private) mutation [Bergmann et al 2004a].

- **Sequence analysis.** Mutation detection rates for sequence analysis of the coding region and flanking intronic regions have not been reported; they are expected to be as high or higher than those reported for mutation scanning analyses.

- **Targeted mutation analysis.** Panels of mutations specific to certain populations are available (see Table 1).

- **Linkage analysis.** 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 [Zerres et al 1998a].

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Autosomal Recessive Polycystic Kidney Disease

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method [1, 2, 3]			Test Availability
			Two Mutations	One Mutation	No Mutations	
PKHD1	Mutation scanning	Sequence variants	57%-75%	18%-39%	2%-8%	Clinical Testing
	Sequence analysis		Unknown [4]			
	Targeted mutation analysis	Panel of mutations [5]	See footnote 5			
	Linkage analysis	NA	NA			

1. In a study of 75 individuals in 59 unrelated families [Sharp et al 2005]

2. In a study of 164 neonatal survivors from 126 unrelated families [Bergmann et al 2005]

3. 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]

4. Unknown but expected to detect as many as or more mutations than mutation scanning

5. Panels of mutations specific to different population groups are offered by some laboratories listed in the GeneTests Laboratory Directory.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

To confirm 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 testing by sequence analysis or mutation scanning establishes the diagnosis in most instances.

Note: Although kidney biopsy establishes the diagnosis in many cases, it is usually not necessary when clinical criteria are met.

Carrier testing for at-risk relatives requires prior identification of the disease-causing mutations in the family or informative linkage studies in the family.

Note: Carriers are heterozygotes for this autosomal recessive disorder and are not at risk of developing the disorder.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutations in the family or informative linkage studies in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *PKHD1*.

Clinical Description

Natural History

The two organ systems primarily affected in autosomal recessive polycystic kidney disease (ARPKD) are kidney and liver; however, several other organ systems are affected secondarily as the result of the kidney and/or liver disease. Significant phenotypic variability is seen in ARPKD. Deget et al [1995] reported little intrafamilial variability in a study of 20 sibships with ARPKD, but a more recent study of mutation-confirmed ARPKD in 126 unrelated families demonstrated significant intrafamilial variability [Bergmann et al 2005].

The majority of affected individuals present in the neonatal period. With modern obstetrical ultrasonography, the diagnosis may be suspected when abnormalities are detected by prenatal ultrasound examination. A minority of affected individuals present as older children or young adults with evidence of hepatic dysfunction.

Kidney. Large bilateral flank masses are invariably present on physical examination. Urine output is usually not diminished; polyuria and polydipsia are consistent with the renal concentrating defect. However, oliguria and overt acute renal failure may be seen. 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, may improve over time, and may be normal in 20%-30% of affected individuals.

Hypertension, often severe, is usually noted within the first few weeks of life.

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

A subset of individuals with ARPKD present as older children with hepatosplenomegaly [Roy et al 1997]. In these individuals, the renal disease is often mild and may be discovered incidentally during imaging studies of the abdomen. The clinical spectrum has been further expanded: in a recent series, nearly one-third of individuals with mutations in *PKHD1* and hepatic involvement were older than age 20 years at the time of initial presentation [Adeva et al 2006].

The hepatic complications seen in ARPKD include: ascending cholangitis, progressive liver dysfunction, portal hypertension with varices, hypersplenism, and overt liver failure with cirrhosis. As advances in renal replacement methods and kidney transplantation improve long-term survival, it is likely that hepatic disease will become a factor in the natural history of ARPKD.

In a cohort of affected individuals who were born and diagnosed after 1990, evidence of portal hypertension was found in 37% of those who survived the first year of life [Guay-Woodford & Desmond 2003]. In a study of 164 neonatal survivors with identified *PKHD1* mutations, clinical evidence of congenital hepatic fibrosis, including portal hypertension, was seen in 44% and was related to age [Bergmann et al 2005].

While post-kidney transplantation allograft survival rates in individuals with ARPKD are similar to those in individuals without ARPKD, data regarding patient survival rates are conflicting. In a single-center study, 36% mortality was reported in individuals with ARPKD following renal transplantation; four of five deaths were attributed directly to hepatic complications [Khan et al 2002]. In contrast, in a study of individuals with ARPKD in the North American Pediatric Renal Transplantation Cooperative Study (NAPRTCS), Davis et al [2003] found a similar survival rate of approximately 90% at age six years in patients with ARPKD compared to those without. However, among those who died, sepsis was the cause in 64% of those with PKD versus 32% in those without PKD, a difference that the authors speculated was attributable to hepatobiliary disease/cholangitis in those with ARPKD.

Lung. Pulmonary hypoplasia resulting from oligohydramnios occurs 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.

Other abnormalities. Feeding difficulties, common in ARPKD, may result from mechanical compression of the stomach by enlarged kidneys, liver, or spleen (the latter in individuals with portal hypertension). Alternatively, individuals who have significant renal impairment may have feeding difficulties related to kidney malfunction, loss of appetite, and impaired gastric motility.

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.

Cerebral aneurysm, a common feature of autosomal dominant polycystic kidney disease (ADPKD), has been reported in an adult and a child with ARPKD [Neumann et al 1999, Lilova & Petkov 2001].

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 [Roy et al 1997, Guay-Woodford & Desmond 2003, Bergmann et al 2005]. With modern neonatal respiratory techniques, this number may be decreasing.

One-year survival is approximately 85%-87% [Guay-Woodford & Desmond 2003, Bergmann et al 2005].

Ten-year survival of those who live beyond the first year of life is estimated to be 82% [Bergmann et al 2005].

Fifteen-year survival is estimated to be 67%-79% [Roy et al 1997].

Pathophysiology. Hypertension is believed to be mediated by the renin-angiotensin II-aldosterone axis, although supporting data are limited. Plasma concentrations of renin and aldosterone have been reported to be in the low-normal range in some individuals with ARPKD. Chapman et al [1990] reported that plasma concentrations of renin and aldosterone were significantly higher in individuals with ADPKD than in individuals with essential hypertension, leading to the current hypothesis that excess renin production is a consequence of local ischemia from expanding cysts. However, in ARPKD, kidney size stabilizes over time and massive cystic enlargement is not seen. Thus, it is unknown whether the same mechanism accounts for hypertension in both ADPKD and ARPKD.

The possibility of "local" (i.e., kidney-specific) renin-angiotensin system activation is suggested by a recent histologic study that demonstrated increased expression of several renin-angiotensin axis components in two kidneys of individuals with ARPKD [Loghman-Adham et al 2005].

Genotype-Phenotype Correlations

Most *PKHD1* mutations are unique to single families, complicating the establishment of clear genotype-phenotype correlations [Bergmann et al 2004a].

Several studies have demonstrated that the truncating mutations, present in approximately 45% of kindreds studied, are associated with a more severe phenotype [Bergmann et al 2003, Bergmann et al 2005]. Amino acid substitutions were found to be more commonly associated with a non-lethal presentation at birth, whereas chain-terminating mutations were more commonly associated with neonatal demise [Furu et al 2003, Bergmann et al 2004b, Bergmann et al 2005]. However, missense changes on one or more alleles have been identified in a subset of individuals with severe disease [Bergmann et al 2003, Rossetti et al 2003, Bergmann et al 2004b].

Penetrance

Penetrance is 100%, although significant intrafamilial variation in the severity of disease may be observed [Bergmann et al 2005].

Nomenclature

In their original description of PKDs in childhood, Blyth & Ockenden [1971] categorized childhood PKD into four classes (perinatal, neonatal, infantile, and juvenile) based on clinical findings and histologic appearance of the kidneys and liver, and suggested that they represented four distinct diseases. Subsequent clinical descriptions of affected kindreds (see, e.g., Kaplan et al [1988]) provided evidence that these distinctions are not meaningful; thus, these categories are not currently used in clinical practice.

Prevalence

The incidence of ARPKD is estimated at 1:10,000 to 1:40,000. The true incidence may be underestimated because children may die in the neonatal period without a definitive diagnosis [Dell et al 2004], and previously undetected young adults are being diagnosed by molecular genetic testing [Adeva et al 2006].

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

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

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, and abdominal wall hernias).

  Although most individuals with ADPKD present in adulthood, a small percentage present in the neonatal period, often with clinical signs and symptoms indistinguishable from those of ARPKD [Guay-Woodford et al 1998].

  ADPKD may be indistinguishable from ARPKD in the newborn period; however, renal ultrasonography in ADPKD more typically demonstrates bilateral macrocysts. Early in the course of ADPKD, especially in younger children, renal involvement may be unilateral. As ADPKD progresses, however, bilateral kidney involvement occurs; cysts can become massive in size.

  Congenital hepatic fibrosis, an invariant component of ARPKD, has been reported rarely in ADPKD.

  Because ADPKD may not present until the third or fourth decade of life, a parent of a symptomatic infant or young child 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 suspected ARPKD is essential to evaluate for possible early-onset ADPKD.

  Note, however, that renal ultrasound examination may be falsely negative in up to 10% of individuals with ADPKD under age 30 years. Furthermore, approximately 5%-10% of individuals with ADPKD have a *de novo* gene mutation and thus do not have an affected parent.

- **Glomerulocystic kidney disease (GCKD)** [OMIM 137920], a rare disorder, typically presents in the neonatal period with large palpable flank masses and may be clinically indistinguishable from ARPKD. Findings on renal ultrasound examination may also resemble those seen in ARPKD, with diffusely enlarged echogenic kidneys and occasional macrocysts. Microscopic examination shows dilatation of Bowman's capsule and dysplasia with abnormal medullary differentiation. Involvement of the intrahepatic bile ducts is present in 10% of individuals and is similar to the liver lesions 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 congenital syndromes such as tuberous sclerosis complex, orofacial digital syndrome type 1, trisomy 13, brachymesomelia-renal syndrome, and short-rib-polydactyly syndrome.

- **Diffuse cystic dysplasia** is characterized by findings on ultrasound examination of large echogenic kidneys and on pathologic examination 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 [Limwongse et al 1999]. In individuals with suspected ARPKD, the presence of extrarenal or extrahepatic abnormalities suggests diffuse cystic dysplasia or possibly an autosomal recessive nonsyndromic disorder.

- **Other "polycystic kidney" diseases.** A number of studies report "polycystic kidneys" as a component of a congenital syndrome; many of these reports may, in fact, be describing syndromic forms of cystic dysplasia. Because histologic examination of the kidneys was not performed in most of the cases reported, it is difficult to determine whether the findings represent alternative forms of ARPKD.

  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, ocular hypertelorism, 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].

  A syndrome of neonatal diabetes mellitus, congenital hypothyroidism, hepatic fibrosis, PKD, and congenital glaucoma has been described in two siblings. Liver biopsy was performed and 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 tuberous sclerosis complex, malignancies such as leukemia or Wilms tumor (see Wilms Tumor Overview) [OMIM 194070], bilateral renal vein thrombosis, and contrast nephropathy [Guay-Woodford et al 1998, Dell et al 2004]. The clinical scenario usually suggests these possibilities.

Liver manifestations. Other congenital hepatorenal disorders, characterized by renal cystic changes and hepatic fibrosis, should also be considered. These include: juvenile nephronophthisis and disorders such as Meckel-Gruber syndrome, Bardet-Biedl syndrome, and Jeune asphyxiating thoracic dystrophy [Johnson et al 2003]. Syndromic disorders are usually suggested by the presence of multiple congenital anomalies that are absent in "classic" ARPKD. In individuals with juvenile nephronophthisis, an autosomal recessive disorder, the kidneys are usually small or normal in size, in contrast to the enlarged kidneys of ARPKD.

The liver lesion invariant in ARPKD is indistinguishable from that of congenital hepatic fibrosis (CHF), alternatively called Caroli's disease [Kamath & Piccoli 2003].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease 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
- Serum electrolyte concentrations to assess for electrolyte abnormalities (e.g., hyponatremia, hyperkalemia), serum creatinine concentration to assess for renal impairment, urinalysis to assess for the urine-concentrating defect as a result of collecting tubule involvement, and clinical assessment of intravascular volume status for possible volume depletion or overload
- Renal ultrasonography
- Measurement of blood pressure
- Assessment of feeding and growth
- Measurement of liver transaminases, serum bile acids, hepatic synthetic function (e.g., by assessing serum albumin concentration and coagulation studies), complete blood counts, physical examination for hepatomegaly/splenomegaly, and abdominal ultrasonography to assess the clinical extent of liver involvement

Treatment of Manifestations

Initial management of affected infants is focused on stabilization of respiratory function:

- Mechanical ventilation may be necessary to treat both pulmonary hypoplasia and respiratory compromise from massively enlarged kidneys.
- When the kidneys are severely enlarged, some authors have advocated unilateral or bilateral nephrectomy [Shukla et al 2004]. Results of these reports (involving one or two affected individuals) suggest a potential benefit for some.

Hyponatremia is common and should be treated depending on the individual's volume status.

Neonates with oliguria or anuria may require peritoneal dialysis within the first days of life.

Hypertension generally responds well to angiotensin-converting enzyme (ACE) inhibitors, which are the treatment of choice. Angiotensin II receptor inhibitors may also be useful. In many cases, hypertension may be severe enough to require several medications.

Feeding intolerance and growth failure, even in the absence of renal insufficiency, can be significant, especially in young infants.

Supplemental feedings via nasogastric or gastrostomy tubes are often required to optimize weight gain and growth [Dell et al 2004].

As with other chronic kidney disease, children with ARPKD with significant renal insufficiency and growth failure may benefit from treatment with growth hormone [Lilova et al 2003].

Leukocyturia is common and may be the result of urinary tract infection. Persons with ARPKD and fever, dysuria, or flank pain should be evaluated with a urine culture. Treatment is reserved for those with positive urine cultures.

Bacterial cholangitis is an underdiagnosed complication in those with hepatic involvement. In some affected individuals, this complication may present as recurrent bacteremia with enteric pathogens without the typical clinical features of cholangitis [Kashtan et al 1999]. Persistent fevers, particularly with right upper-quadrant pain, should be evaluated and treated appropriately.

A porto-caval shunt may be necessary to treat progressive portal hypertension. Varices may be treated with endoscopic banding or sclerotherapy. However, Tsimaratos et al [2000] reported recurrent hepatic encephalopathy and death following porto-caval shunting in two individuals with ARPKD who had ESRD. With the improved success of living-related partial liver transplantation in children, liver transplantation may become the preferred therapy for those being considered for porto-caval shunting. At present, only a small percentage 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. It has been recommended that those being evaluated for kidney transplantation undergo MR cholangiography to completely assess the extent of liver involvement to determine whether simultaneous or sequential liver transplantation is indicated [Shneider & Magid 2005].

Prevention of Secondary Complications

With severe portal hypertension and splenic dysfunction, immunization against encapsulated bacteria (pneumococcus; *H. influenza* type B; meningococcus) is indicated. Penicillin prophylaxis has also been recommended, although its effectiveness remains unproven.

Surveillance

The following should be monitored regularly:

- Blood pressure, at least yearly. In young children and/or those with significant renal impairment, blood pressure may need to be monitored more frequently.
- Renal function, at least yearly and more often if the person has evidence of renal impairment. Serum electrolytes should also be monitored. Those with evidence of renal impairment may also require additional testing to evaluate for complications such as anemia and renal osteodystrophy.
- Hydration status
- Nutritional status, with growth plotted on standard growth charts
- Hepatic involvement, yearly by physical examination and complete blood counts. If hepatomegaly is found to be present and/or splenomegaly develops, additional monitoring, including yearly ultrasonography, is indicated. It has been recommended by some authors that individuals with ARPKD undergo MR cholangiography, a more sensitive measurement for biliary ectasia, at baseline and then repeated as indicated. Endoscopy should be considered periodically in the presence of portal hypertension to detect and treat varices [Shneider & Magid 2005].

Agents/Circumstances 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

Testing of Relatives at Risk

Given the possibility of intrafamilial variability, renal and hepatic ultrasonographic evaluation of older sibs of an individual with ARPKD may be indicated in some instances to allow early diagnosis and treatment.

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

Therapies Under Investigation

Novel therapies directed at specific targets in the disease pathogenesis are currently undergoing active investigation.

Phase III clinical trials using the V2 receptor antagonist tolvaptan, which inhibits cyclic adenosine monophosphate (AMP) [Gattone et al 2003, Torres 2004], are underway in adults with ADPKD. Studies in individuals with ARPKD are not yet underway.

Phase III clinical trials using the mTOR inhibitors sirolimus and everolimus, which may slow cyst growth in ARPKD and ADPKD, are underway in adults with ADPKD. As with tolvaptan, studies in patients with ARPKD are not yet underway.

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]. Clinical studies using a specific EGFR tyrosine kinase inhibitor are expected to begin within the next several years.

Other investigational compounds including inhibitors of Src [Sweeney et al 2008] and cyclin-dependent kinase [Bukanov et al 2006] as well as somatostatin analogs have also shown promise in animal studies [Chapman 2007]. However, no clinical studies have been undertaken to date.

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

Other

Animal experiments suggest that caffeine, which may increase cyclic AMP, can worsen cystic kidney disease. However, this has not been rigorously studied in patients with ARPKD or ADPKD.

A number of other therapies have been studied in animal models of PKD, including citrate supplementation and the microtubule inhibitor, Taxol®. However, animal data have not shown a consistent benefit, and no studies in humans have been conducted [Davis et al 2001].

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

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 mutation in *PKHD1*.
- The gene 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 mutations have been identified in the family.

If the disease-causing mutations 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, Testing of Relatives at Risk for information on testing 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. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100% or testing is available by linkage only. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

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

- Prenatal testing for pregnancies at 25% risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. Both disease-causing alleles of an affected family member must be identified or linkage established in the family before prenatal testing can be performed [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 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 available for families in which the disease-causing mutations have been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Autosomal Recessive Polycystic Kidney Disease

Gene Symbol	Chromosomal Locus	Protein Name
PKHD1	6p21.1-p12	Fibrocystin

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Autosomal Recessive Polycystic Kidney Disease

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

Table C. Genomic Databases for Autosomal Recessive Polycystic Kidney Disease

Gene Symbol	Locus Specific	Entrez Gene	HGMD
PKHD1	PKHD1	606702	PKHD1

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

Despite the identification of the mutated gene and abnormal protein product, the pathogenesis of autosomal recessive polycystic kidney disease (ARPKD) remains unclear [Gunay-Aygun et al 2006, Sweeney & Avner 2006]. However, recent studies suggest that the 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]. Reduced or absent levels of normal fibrocystin function are thought to underlie the disease pathogenesis [Hiesberger et al 2004, Zhang et al 2004]. Abnormal structure and/or function of the primary cilium lead to alterations in its mechano-sensory 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 EFGR axis (reviewed in Sweeney & Avner [2006]). The molecular connection between gene defect, ciliary abnormalities, protein complex formation, and EGFR abnormalities remains highly speculative.

Additional data suggest that the protein products of *PKD1*, *PKD2*, and *PKHD1* may exist as multimeric protein complexes in 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.

Normal allelic variants: *PKHD1* contains at least 66 coding exons and multiple alternative transcripts [Onuchic et al 2002, Ward et al 2002].

Pathologic allelic variants: Multiple different mutations throughout the coding sequence have been identified in affected kindreds [Bergmann et al 2004a].

Normal gene product: The *PKHD1* gene product, polycystic kidney and hepatic disease 1 (also called fibrocystin or polyductin), 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 link to ciliary dysfunction [Ward et al 2003], or multimeric protein complex signaling. 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: Unknown. See Molecular Genetic Pathogenesis.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

ARPKD-CHF Alliance
PO Box 70
Kirkwood PA 17536
Phone: 800-708-8892; 717-529-5555
Fax: 800-807-9110
Email: info@arpkdchf.org
www.arpkdchf.org

National Library of Medicine Genetics Home Reference
Polycystic kidney disease

PKD Foundation
9221 Ward Parkway Suite 400
Kansas City MO 64114-3367
Phone: 800-PKD-CURE; 816-931-2600
Fax: 816-931-8655
Email: pkdcure@pkdcure.org
www.pkdcure.org

The Kidney Foundation of Canada
700-15 Gervais Drive
Toronto ON M3C 1Y8
Canada
Phone: 800-387-4474; 416-445-0373
Fax: 416-445-7440
Email: kidney@kidney.on.ca
www.kidney.on.ca

National Kidney Foundation
30 East 33rd Street Suite 1100
New York NY 10016
Phone: 800-622-9010; 212-889-2210
Fax: 212-689-9261
Email: info@kidney.org
www.kidney.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

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]

Avner ED, Sweeney WE. Renal cystic disease: new insights for the clinician. *Pediatr Clin North Am* 2006;53:889–909. [PubMed: 17027616]

Avni FE, Guissard G, Hall M, Janssen F, DeMaertelaer V, Rypens F. Hereditary polycystic kidney diseases in children: changing sonographic patterns through childhood. *Pediatr Radiol* 2002;32:169–74. [PubMed: 12164348]

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]

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]

Bergmann C, Senderek J, Sedlacek B, Pegiazoglou I, Puglia P, Eggermann T, Rudnik-Schneborn S, Furu L, Onuchic LF, De Baca M, Germino GG, Guay-Woodford L, Somlo S, Moser M, Buttner R, Zerres K. Spectrum of Mutations in the Gene for Autosomal Recessive Polycystic Kidney Disease (ARPKD/PKHD1). *J Am Soc Nephrol* 2003;14:76–89. [PubMed: 12506140]

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]

Blyth H, Ockenden BG. Polycystic disease of kidney and liver presenting in childhood. *J Med Genet* 1971;8:257–84. [PubMed: 5097134]

Bukanov NO, Smith LA, Klinger KW, Ledbetter SR, Ibraghimov-Beskrovnaya O. Long-lasting arrest of murine polycystic kidney disease with CDK inhibitor roscovitine. *Nature* 2006;14:949–52.

Cassart M, Massez A, Metens T, Rypens F, Lambot MA, Hall M, Avni FE. Complementary role of MRI after sonography in assessing bilateral urinary tract anomalies in the fetus. *AJR Am J Roentgenol* 2004;182:689–95. [PubMed: 14975971]

Chapman AB, Johnson A, Gabow PA, Schrier RW. The renin-angiotensin-aldosterone system and autosomal dominant polycystic kidney disease. *N Engl J Med* 1990;323:1091–6. [PubMed: 2215576]

Chapman AB. Autosomal dominant polycystic kidney disease: time for a change? *J Am Soc Nephrol* 2007;18:1399–407. [PubMed: 17429048]

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]

Davis ID, MacRae Dell K, Sweeney WE, Avner ED. Can progression of autosomal dominant or autosomal recessive polycystic kidney disease be prevented? *Semin Nephrol* 2001;21:430–40. [PubMed: 11559884]

Deget F, Rudnik-Schoneborn S, Zerres K. Course of autosomal recessive polycystic kidney disease (ARPKD) in siblings: a clinical comparison of 20 sibships. *Clin Genet* 1995;47:248–53. [PubMed: 7554350]

Dell KM, McDonald R, Watkins SL, Avner ED (2004) Polycystic kidney disease. In: Avner ED, Harmon W, Niadet P (eds) Pediatric Nephrology, 5th ed. Lippincott Williams & Wilkins, Philadelphia

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]

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]

Furu L, Onuchic LF, Gharavi A, Hou X, Esquivel EL, Nagasawa Y, Bergmann C, Senderek J, Avner E, Zerres K, Germino GG, Guay-Woodford LM, Somlo S. Milder presentation of recessive polycystic kidney disease requires presence of amino Acid substitution mutations. *J Am Soc Nephrol* 2003;14:2004–14. [PubMed: 12874454]

Gattone VH, Wang X, Harris PC, Torres VE. Inhibition of renal cystic disease development and progression by a vasopressin V2 receptor antagonist. *Nat Med* 2003;9:1323–6. [PubMed: 14502283]

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]

Guay-Woodford LM, Desmond RA. Autosomal recessive polycystic kidney disease: the clinical experience in North America. *Pediatrics* 2003;111:1072–80. [PubMed: 12728091]

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]

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. [PubMed: 16887426]

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]

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. [PubMed: 15067314]

Johnson CA, Gissen P, Sergi C. Molecular pathology and genetics of congenital hepatorenal fibrocystic syndromes. *J Med Genet* 2003;40:311–9. [PubMed: 12746391]

Kamath BM, Piccoli DA. Heritable disorders of the bile ducts. *Gastroenterol Clin North Am* 2003;32:857–75. [PubMed: 14562578]

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]

Kashtan CE, Primack WA, Kainer G, Rosenberg AR, McDonald RA, Warady BA. Recurrent bacteremia with enteric pathogens in recessive polycystic kidney disease. *Pediatr Nephrol* 1999;13:678–82. [PubMed: 10502126]

Kern S, Zimmerhackl LB, Hildebrandt F, Ermisch-Omran B, Uhl M. Appearance of autosomal recessive polycystic kidney disease in magnetic resonance imaging and RARE-MR-urography. *Pediatr Radiol* 2000;30:156–60. [PubMed: 10755752]

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]

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]

Lilova MI, Petkov DL. Intracranial aneurysms in a child with autosomal recessive polycystic kidney disease. *Pediatr Nephrol* 2001;16:1030–2. [PubMed: 11793094]

Limwongse C, Clarren SK, Cassidy SB (1999) Syndromes and malformations of the urinary tract. In: Barratt TM, Avner ED, Harmon WE (eds) Pediatric Nephrology. Lippincott Williams & Wilkins, Baltimore, pp 427-52

Lin F, Satlin LM. Polycystic kidney disease: the cilium as a common pathway in cystogenesis. *Curr Opin Pediatr* 2004;16:171–6. [PubMed: 15021197]

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]

Nakanishi K, Sweeney WE, Zerres K, Guay-Woodford LM, Avner ED. Proximal tubular cysts in fetal human autosomal recessive polycystic kidney disease. *J Am Soc Nephrol* 2000;11:760–3. [PubMed: 10752536]

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]

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]

Ong AC, Wheatley DN. Polycystic kidney disease--the ciliary connection. *Lancet* 2003;361:774–6. [PubMed: 12620752]

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. [PubMed: 11898128]

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]

Rossetti S, Torra R, Coto E, Consugar M, Kubly V, Malaga S, Navarro M, El-Youssef M, Torres VE, Harris PC. A complete mutation screen of PKHD1 in autosomal-recessive polycystic kidney disease (ARPKD) pedigrees. *Kidney Int* 2003;64:391–403. [PubMed: 12846734]

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]

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. [PubMed: 15805161]

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]

Shneider BL, Magid MS. Liver disease in autosomal recessive polycystic kidney disease. *Pediatr Transplant* 2005;9:634–9. [PubMed: 16176423]

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]

Stein-Wexler R, Jain K. Sonography of macrocysts in infantile polycystic kidney disease. *J Ultrasound Med* 2003;22:105–7. [PubMed: 12523616]

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]

Sweeney WE, Avner ED. Molecular and cellular pathophysiology of autosomal recessive polycystic kidney disease (ARPKD). *Cell Tissue Res* 2006;326:671–85. [PubMed: 16767405]

Sweeney WE, 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]

Sweeney WE, von Vigier RO, Frost P, Avner ED. Src Inhibition ameliorates polycystic kidney disease. *J Am Soc Nephrol* 2008;19:1331–41. [PubMed: 18385429]

Torres VE. Therapies to slow polycystic kidney disease. Nephron *Exp Nephrol* 2004;98:1–7.

Traubici J, Daneman A. High-resolution renal sonography in children with autosomal recessive polycystic kidney disease. *AJR* 2005;184:1630–3. [PubMed: 15855129]

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]

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]

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]

Watkins SL, McDonald RA, Avner ED (1999) Renal dysplasia, hypoplasia and miscellaneous cystic disorders. In: Barratt TM, Avner ED, Harmon WE (eds) Pediatric Nephrology. Lippincott Williams & Wilkins, Baltimore, pp 415-25

Wilson PD. Polycystic kidney disease. *N Engl J Med* 2004;350:151–64. [PubMed: 14711914]

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]

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]

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]

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. [PubMed: 14983006]

Suggested Reading

Harris PC, Rossetti S. Molecular genetics of autosomal recessive polycystic kidney disease. Mol Genet Metab 2004;81:75–85. [PubMed: 14741187]

Chapter Notes

Author Notes

Dr. Dell's Web site: www.rainbowbabies.org

Dr. Avner's Web site: www.chw.org/research

Revision History

- 7 August 2008 (cg) Comprehensive update posted live
- 21 March 2006 (me) Comprehensive update posted to live Web site
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- 13 January 2003 (kmd) Revision: gene identified
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- April 2001 (kmd) Original submission