Renal cystic diseases encompass a broad group of disorders with variable phenotypic expression. Cystic disorders can present during infancy, childhood, or adulthood. Often, but not always, they can be distinguished by the clinical features including age at presentation, renal imaging characteristics, including cyst distribution, and the presence/distribution of extrarenal manifestations. It is important to take the clinical context into consideration when assessing renal cystic disease in children and adults. For example, solitary kidney cysts may be completely benign when they develop during adulthood but may represent early polycystic kidney disease when observed during childhood. In this review, we have categorized renal cystic disease according to inherited single-gene disorders, for example, autosomal recessive polycystic kidney disease; syndromic disorders associated with kidney cysts, for example, tuberous sclerosis complex; and nongenetic forms of renal cystic disease, for example, simple kidney cysts. We present an overview of the clinical characteristics, genetics (when appropriate), and molecular pathogenesis and the diagnostic evaluation and management of each renal cystic disease. We also provide an algorithm that distinguishes kidney cysts based on their clinical features and may serve as a helpful diagnostic tool for practitioners. A review of Autosomal Dominant Polycystic Disease was excluded as this disorder was reviewed in this journal in March 2010, volume 17, issue 2.

Key Words: Polycystic kidney, Nephronophthisis, Glomerulocystic, Tuberous sclerosis, Bardet-Biedl

RENA L CYSTIC DISEASES ASSOCIATED WITH SINGLE-GENE DEFECTS

Autosomal Recessive Polycystic Kidney Disease

Disease Characteristics. Autosomal recessive polycystic kidney disease (ARPKD, MIM 173900) is a severe hepatorenal fibrocystic disorder characterized by nonobstructive dilatation of the kidney collecting ducts and malformation of the portal biliary system. It occurs with an estimated frequency of 1 in 20,000 live births. ARPKD is typically diagnosed in utero or at birth and manifests as progressive renal insufficiency and portal hypertension. The typical kidney phenotype consists of enlarged echogenic kidneys with loss of corticomedullary differentiation because of fusiform dilatation of the collecting ducts. Affected fetuses often have oligohydramnios leading to fetal constraint and the “Potter sequence” that consists of characteristic dysmorphic facies, pulmonary hypoplasia, and limb defects. The estimated perinatal mortality rate is 30% because of respiratory insufficiency. In patients who survive the first month of life, 1-year survival rates of 92% to 95% have been reported.

The clinical course of infants who survive the neonatal period is characterized by severe systemic hypertension, progressive renal insufficiency, and portal hypertension. Although the pathophysiology of underlying hypertension is unclear, at least 1 study demonstrates intrarenal Renin-angiotensin-aldosterone system activation. Infants often have hyponatremia, presumably because of defects in free water excretion. Most ARPKD patients progress to ESRD, although the age of onset is variable. The kidney survival rate of 1 large cohort of neonatal survivors was 86% at 5 years and decreased to 42% at 20 years. Age of ESRD onset is somewhat correlated with age at ARPKD diagnosis.

Histologic liver involvement is invariably present in all ARPKD patients and is characterized by defective remodeling of the ductal plate with intrahepatic duct dilatation and progressive portal tract fibrosis. Portal hypertension is the predominant clinical manifestation and may cause gastrointestinal varices and hypersplenism. Splenomegaly may further result in thrombocytopenia, leukopenia, and anemia with the potential for splenic dysfunction and predisposition to bacterial infections. ARPKD patients with extensive dilatations of intrahepatic and extrahepatic bile ducts are at increased risk of ascending bacterial cholangitis. Because hepatocytes are not involved, hepatocellular dysfunction is rare and liver enzymes are characteristically not increased.

Genetics and Molecular Pathogenesis. ARPKD is caused by mutations in the polycystic and hepatic disease gene 1 (PKHD1) that encodes fibrocystin-polyductin complex (FPC), a protein expressed in primary cilia of kidney and bile duct epithelial cells. PKHD1 is an exceptionally large gene that spans approximately 470 kb of genomic DNA and consists of 86 exons, with 67 exons included in the longest open-reading frame transcript. A number of alternatively spliced transcripts have been identified; however, the exact function and clinical significance of these isoforms have not been elucidated. Almost 750 pathogenic PKHD1 mutations have been identified to date (http://www.humgen.rwth-aachen.de/), with approximately 44% classified as missense mutations. A small number of relatively common mutations (eg, p.T36 M) account for ~10% of all PKHD1 pathogenic variants. Most affected patients are compound heterozygotes, carrying 2 different mutant alleles.
Phenotype-genotype studies suggest that patients carrying a truncating mutation on both parental alleles have a more severe phenotype leading to perinatal demise. However, there are notable exceptions, for example, a child homozygous for a large PKHD1 deletion who survived well past the neonatal period. Although most missense mutations are associated with milder disease, a number of missense mutations result in severe phenotypes when present with a truncating mutation or in the homozygous form.

FPC is a 4074-amino acid transmembrane protein predominantly expressed in kidney cortical and medullary collecting ducts and thick ascending loops of Henle and ductal structures in the liver and pancreas. FPC has been identified as a structural component of primary cilia in kidney tubular epithelial cells and cholangiocytes of bile ducts. The specific functions of FPC remain to be fully characterized. However, numerous other proteins associated with other hepatorenal fibrocystic diseases (eg, autosomal dominant polycystic kidney disease [ADPKD], nephronophthisis [NPHP], Meckel-Gruber, Joubert, Bardet-Biedl, and other ciliary chondrodysplasias) also localize to the primary cilia/basal body (Fig 1), suggesting a role for primary cilia in the development and maintenance of kidney tubular architecture.

**Diagnosis and Management.** Sonographic features of ARPKD include enlarged, echogenic kidneys with poor corticomedullary differentiation. Dilated cortical collecting ducts just under the kidney capsule may be visible with high-resolution ultrasound (US). The cortex is often compressed to the periphery by the dilated medullary collecting ducts, forming a hyperechoic halo.

Macrocysts are not routinely present at birth. Furthermore, kidney size in ARPKD stabilizes or may decrease over time and does not show progressive macrocystic enlargement as in ADPKD.

It can be difficult to differentiate ARPKD from ADPKD, in that a subset of ADPKD patients may present in infancy or early childhood with enlarged echogenic kidneys. Likewise, ARPKD can present in older children, who may demonstrate kidney macrocysts that can mimic the kidney cysts of ADPKD.

**Renal cystic diseases encompass a broad range of disorders that manifest in both children and adults with variable clinic features.**

**The identification of disease-causing genes has expanded our understanding of cystic disease pathogenesis and enhanced diagnostic accuracy.**

**Nephronophthisis**

**Disease Characteristics.** NPHP (MIM 256100) is an autosomal recessive tubulointerstitial disorder and one of the most common causes of inherited end-stage kidney disease in children and young adults.

The initial features typically present between 4 and 6 years of age and include polydipsia and polyuria. Decreased urinary concentration is invariably present. Slowly progressive decline in kidney function is typical of NPHP. One-third of patients develop normocytic anemia before the onset of renal insufficiency.

This early anemia may be secondary to impaired function or...
regulation of erythropoietin-producing cells. Growth retardation, out of proportion to the degree of renal impairment, is a common finding. An exception to this clinical presentation is the infantile variant, resulting primarily from mutations in the \textit{NPHP2} or \textit{NPHP3} genes, in which patients present in the first few months of life with kidney insufficiency and hypertension with rapid progression to ESRD.

Extrarenal manifestations have been described in 10% to 20% of NPHP patients. The most frequently associated anomaly is retinal dystrophy because of tapetoretinal degeneration (Senior-Loken syndrome). Congenital hepatic fibrosis occurs in some NPHP patients, but the associated bile duct proliferation is mild and qualitatively different from that found in ARPKD.

Genetics and Molecular Pathogenesis. To date, 19 causative genes have been identified (\textit{NPHP1-19}). Homozygous deletions in the \textit{NPHP1} gene account for 21% of all NPHP cases; however, causative genes are still unknown in approximately 70% of affected individuals. Disease expression seems to be exacerbated by oligogenic inheritance, that is, patients carrying 2 mutations in a single NPHP gene and a third mutation in an additional NPHP gene. Most of the protein products of the NPHP-associated genes, denoted “nephrocystins,” are expressed in primary cilia or the associated centrosome and play important roles in ciliogenesis and regulation of ciliary signaling.

Diagnosis and Management. Kidneys appear to be normal in size or hypoplastic, except in the infantile form, where nephromegaly is present. Cysts can be observed at the corticomедullary junction. Genetic testing may be helpful in establishing the diagnosis; however, it must be noted that defects in these genes only account for 30% to 40% of NPHP patients. Given the large number of NPHP-related genes, single-gene analysis is cost prohibitive. Newer strategies using next-generation sequencing technologies in the context of commercially available gene panels currently allows high-throughput mutation detection for 9 to 12 of the known \textit{NPHP} genes. Current treatment of NPHP is entirely supportive.

Glomerulocystic Kidney Disease

\textbf{Disease Characteristics.} Glomerulocystic kidney disease (GCKD) is not a single disorder but a histologic...
designation that involves cystic dilatation of Bowman’s space in the context of multiple clinical disorders. GCKD has both sporadic and familial occurrence. The clinical presentation of GCKD can be variable, and the appearance of the kidneys on US may be similar to other renal cystic diseases. Kidneys are echogenic and may be small, normal sized, or enlarged. Small renal volumes have typically been reported in cases of hereditary GCKD. Kidney cysts are not always evident on US. Hyperuricemia and an autosomal dominant inheritance pattern may be present in patients with UMOD mutations.

**Genetics and Molecular Pathogenesis.** Glomerulocystic disease can be divided into 5 major categories: (1) an early manifestation of ADPKD (PKD1 mutations); (2) hereditary GCKD associated with other single-gene defects (eg, hepcytocoe nuclear factor-1 beta [HNF1B] and UMOD); (3) GCKD associated with syndromic disorders (eg, Bardet-Biedl syndrome, orofacial digital syndrome, and tuberous sclerosis complex [TSC]); (4) obstructive GCKD with or without kidney dysplasia; and (5) isolated, sporadic cases. Genetic testing should be performed as an autosomal dominant trait. The diagnosis of GCKD is typically transmitted in a family with a positive history of kidney disease, and there may be a history of polydipsia and polyuria. Blood pressure is usually normal or borderline low due to the urinary concentration defects observed in this disorder.

**Diagnosis and Management.** GCKD is typically transmitted as an autosomal dominant trait. The diagnosis of GCKD is often based on clinical suspicion, with findings of echogenic kidneys on US with or without glomerular cysts. The cysts may be difficult to define at US, and cortical hyperechogenicity may be seen instead of the typical anechoic appearance of simple cysts. MRI may be more reliable for diagnosis and demonstrates small kidney cysts with a predominant cortical and subcapsular distribution. Histopathology shows glomerular cysts defined as Bowman space dilatation greater than 2 to 3 times the normal dimension. Genetic testing should be considered in patients with associated diabetes or early-onset gout. The treatment of GCKD is symptomatic. The prognosis depends on the underlying cause and is determined by the rate of kidney function decline.

**AUTOSOMAL DOMINANT TUBULOINTERSTITIAL KIDNEY DISEASE**

**Medullary Cystic Kidney Disease**

**Disease Characteristics.** Medullary cystic kidney disease (MCKD) is an autosomal dominant disorder that typically presents in the third to sixth decade of life. Despite its designation, cysts are often absent in MCKD. MCKD is now more appropriately characterized as an autosomal dominant tubulointerstitial kidney disease, which is defined as a group of disorders characterized by autosomal dominant inheritance, bland urinary sediment with minimal blood and protein, pathologic changes of tubular and interstitial fibrosis, and slowly progressive chronic kidney disease. Patients present with CKD and bland urine with decreased urinary concentrating ability. As in NPHP, there may be a history of polydipsia and polyuria. Blood pressure is usually normal or borderline low because of salt wasting. Hyperuricemia and gout may be present. MCKD presents later than NPHP, with most patients reaching ESRD between the third and sixth decade of life.

**Genetics and Molecular Pathogenesis.** Medullary cystic disease of type 1 (MIM 174000) is caused by heterozygous mutations in the UMOD gene. The MCKD1 gene was localized more than a decade ago to a 2 Mb region on chromosome 1, but only recently, with studies using next-generation sequencing technologies, were novel mutations identified in a coding variable-number tandem repeat sequence within the UMOD gene that encodes mucin 1. Medullary cystic disease of type 2 (MIM 162000) is associated with heterozygous mutations in the uromodulin gene (UMOD). Uromodulin is a glycosylphosphatidylinositol-anchored protein found exclusively on the apical membrane of thick ascending limb (TAL) cells, which suggests a role in vesicle trafficking and signal transduction. In addition, it has been postulated that uromodulin serves as a physical barrier to water permeability in the TAL, suggesting that mutated uromodulin may lead to the urinary concentration defects observed in this disorder.

**Diagnosis and Management.** Diagnosis is suspected in individuals with a positive family history of kidney disease, bland urinary sediment, and characteristic sonographic findings. Kidneys are often echogenic and normal to small in size on US, and medullary cysts are typically not observed. The presence of gout in MCKD2 patients distinguishes this disorder from MCKD1. Genetic testing for known UMOD mutations confirms the diagnosis if positive but may not be definitive in the case of new mutations. There are no specific treatments for MCKD. Patients should be monitored for associated sequela including gout. All related potential kidney donors should be evaluated to identify the family-specific MUC1 or UMOD mutation. Only those individuals without the mutation are suitable candidate donors.

**HNF1B-Related Kidney Disease**

**Disease Characteristics.** Mutations in the HNF1B gene (also known as TCF2) are associated with abnormalities of the kidney, pancreas, liver, and genital tract. The description of HNF1B mutations as a cause of renal cystic disease originates from observations in families with monoclonic diabetes. Mutations in HNF1B were first described as a rare cause of maturity-onset diabetes of young, a form of early-onset (usually diagnosed <25 years), non-insulin-dependent diabetes, resulting from pancreatic β-cell dysfunction. Diabetes has been described in 58% of reported HNF1B mutations carriers, with mean age of diagnosis 26 years. Kidney function is usually impaired, and approximately 15% of patients reach ESRD. A number of different renal pathologies have been described including hypoplastic GCKD, cystic renal dysplasia, and oligomeganephronia. Other morphologic kidney abnormalities include solitary kidney and horseshoe kidney. HNF1B mutations are a common cause of echogenic kidneys in fetuses and neonates and phenocopies ARPKD. Other clinical features include uterine malformations, abnormal liver function tests, and gout.
**Genetics and Molecular Pathogenesis.** HNF1B-related kidney disease is inherited as an autosomal dominant trait. HNF1B, a transcription factor expressed in kidney, pancreas, liver, and the Mullerian duct, controls gene expression during embryonic development. Whole-gene deletions are responsible for approximately 30% of mutations, whereas the remainder are point mutations. HNF1B has been shown to control the transcription of known PKD genes, UMOD, PKHD1, and PKD2.

**Diagnosis and Management.** HNF1B-related nephropathy requires a high index of suspicion, and knowledge of the phenotypic variability present of this disorder can improve its recognition. Genetic testing for HNF1B mutations should be considered in patients with unexplained kidney cysts (including GCKD), especially when associated with diabetes, early-onset gout, or uterine abnormalities. Diagnosis of HNF1B-related nephropathy may be challenging given that approximately 30% to 50% of patients have de novo mutations. Treatment is entirely symptomatic. Patients with identified HNF1B mutations should have careful monitoring of glucose levels. These patients are good candidates for kidney transplant but are at increased risk of developing diabetes in the post-transplant period. In diabetic individuals with ESRD, combined pancreatic and kidney transplantation should be considered.

**Renal Cystic Diseases Associated with Syndromic Disorders**

**Renal Manifestations of the TSC**

**Disease Characteristics.** TSC is an autosomal, dominant systemic disorder that has an estimated incidence of 1:6000 to 1:10,000 live births. It is characterized by benign tumors (hamartomas) in multiple organ systems, including the central nervous system, skin, heart, kidney, and lung. The phenotypic presentation of TSC is variable with clinical manifestations varying widely even among closely related affected individuals.

**Renal Manifestations.** Renal lesions are evident in up to 80% of TSC individuals. Patients often have bilateral and multiple renal angiomyolipomas (AMLs), which are slow growing, benign mesenchymal tumors, composed of abnormal vascular elements, smooth muscle, and fat cells. Overall, the estimated incidence of AMLs in TSC patients is 49% to 75%. Approximately 60% of children with TSC develop AMLs by age 10.5 years. AMLs contain abnormal vasculature and often develop aneurysms that may rupture and cause life-threatening bleeding. The risk of hemorrhage is greatest when AMLs are more than 3 cm in diameter. In addition, AMLs may encroach on normal kidney tissue as they enlarge, contributing to the CKD.

TSC patients also develop renal cystic lesions that range in severity from microscopic disease to a polycystic phenotype. The TSC2 gene and the PKD1 gene lie adjacent to each other on chromosome 16p13. Approximately 2% to 3% of TSC deletions involve both TSC2 and PKD1, resulting in the contiguous gene deletion syndrome (MIM 600273). These patients have early-onset renal cystic disease, with kidney enlargement and radiological appearances similar to those with advanced ADPKD, and reach ESRD at a much younger age than ADPKD alone. Renal cell carcinoma occurs in less than 2% of the TSC population, typically at a younger age than in the general population.

**Genetics and Molecular Pathogenesis.** TSC is caused by mutations in one of the tumor suppressor genes, TSC1 (MIM 191100) or TSC2 (MIM 613254). Although considered an autosomal dominant disorder, more than 80% of affected individuals harbor a spontaneous heterozygous mutation in one of the TSC genes. No identifiable mutations are detected in 20% to 25% of TSC patients. TSC1 and TSC2 encode the proteins, hamartin and tuberin, respectively, which function as tumor suppressor genes and are co-expressed in multiple organs, including kidney, brain, lung, and pancreas. These proteins interact to form the hamartin-tuberin (TSC1/TSC2) complex, which inhibits the downstream activation of the mammalian target of rapamycin (mTOR; Fig. 1). A serine-threonine kinase, mTOR, functions in a protein complex (mTORC1) to regulate protein synthesis, cellular metabolism, differentiation, and growth and proliferation. A loss of hamartin and tuberin results in unregulated activation of mTOR leading to uncontrolled cellular growth and proliferation.

**Diagnosis and Management.** The clinical diagnosis of TSC is established by the presence of 2 major or 1 major and 2 minor features (Table 1). A possible diagnosis is made with either 1 major or 2 minor features. The 2012 International Tuberous Sclerosis Complex Consensus Group published updated diagnostic criteria and recommended genetic testing as an independent diagnostic criterion. Up to 25% of TSC patients have no identifiable mutation by genetic testing; therefore, a normal result does not exclude TSC.

<table>
<thead>
<tr>
<th>Major Features</th>
<th>Minor Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomelanotic macules (≥3, at least 5-mm diameter)</td>
<td>&quot;Confetti&quot; skin lesions</td>
</tr>
<tr>
<td>Angiofibromas (≥3) or fibrous cephalic plaque</td>
<td>Dental enamel pits (≥3)</td>
</tr>
<tr>
<td>Ungual fibromas (≥2)</td>
<td>Intraoral fibromas (≥2)</td>
</tr>
<tr>
<td>Shagreen patch</td>
<td>Retinal achromic patch</td>
</tr>
<tr>
<td>Multiple retinal hamartomas</td>
<td>Multiple kidney cysts</td>
</tr>
<tr>
<td>Cortical dysplasias</td>
<td>Nonrenal hamartomas</td>
</tr>
<tr>
<td>Subependymal nodules</td>
<td></td>
</tr>
<tr>
<td>Subependymal giant cell astrocytoma</td>
<td></td>
</tr>
<tr>
<td>Cardiac rhabdomyoma</td>
<td></td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis*</td>
<td></td>
</tr>
<tr>
<td>Angiomyolipomas (≥2)†</td>
<td></td>
</tr>
</tbody>
</table>

Definite diagnosis: 2 major features or 1 major feature with ≥ 2 minor features; possible diagnosis: either 1 major feature or ≥ 2 minor features.

*Includes tubers and cerebellar white matter radial migration lines. †A combination LAM and angiomyolipomas, without other features, does not meet criteria for a definite diagnosis.

Adapted from Northrup and Krueger.
Renal evaluation includes abdominal imaging to assess renal cystic disease and angiomyolipomatosa. MRI is the preferred imaging technique as fat poor AMLs may not be detected by computerized tomography or US. Kidney function and blood pressure should be measured on an annual basis. Management of hypertension is important given that the most patients have CKD. Renal cystic disease is a significant risk factor for hypertension in this population and responds well to angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Abdominal MRI should be obtained annually to monitor size and progression of renal angiomyolipomatosa. Based on the 2012 International Tuberous Sclerosis Consensus Group recommendations, asymptomatic AMLs larger than 3 cm should be treated with an mTOR inhibitor as first-line therapy. Results from Examining Everolimus in a Study of Tuberous Sclerosis Complex-1 trial demonstrated that everolimus was effective in reducing angio-myolipoma lesion volume and had an acceptable safety profile. AMLs presenting with acute hemorrhage require embolization. Embolization or nephron-sparing resection may also be considered for asymptomatic AMLs that are larger than 3 cm. A majority of subependymal giant cell astrocytomas (SEGAs) and AMLs return to original volume after withdrawal of mTOR inhibitors, suggesting that TSC patients require lifelong treatment.

Bardet-Biedl Syndrome

**Disease Characteristics.** Bardet-Biedl syndrome (MIM 209900) is a multisystem disorder characterized by renal structural anomalies, obesity, visual, and cognitive impairment; postaxial polydactyly; and hypogenitalism. The estimated prevalence of BBS is 1:125,000 to 1:175,000 in Europe and North America. The clinical diagnosis of BBS is established if at least 4 major criteria are present (Table 2). Renal anomalies are a cardinal feature of BBS and account for the major morbidity in these patients. Sonography reveals structural defects including fetal lobulation, calyceal blunting, clubbing or diverticula, and medullary and cortical cysts. Twenty-five percent of BBS patients have chronic kidney failure by age 48 and 10% develop ESRD in childhood. Hypertension occurs in most patients at a median age of 34 years. Developmental delay, cognitive deficits, and speech delay are common in BBS.

**Genetics and Molecular Pathogenesis.** BBS is a genetically heterogeneous disorder with 19 causative genes identified to date. BBS is considered an autosomal recessive disorder, although a oligogenic inheritance pattern has been described in which the resultant phenotype reflects the modulation of mutations in 1 BBS gene by a third mutation in another BBS gene. BBS1 (MIM 209901) and BBS10 (MIM 610148) are the most frequently mutated genes and have been identified in 33% of BBS families.

BBS proteins affect ciliary function and can be classified into 2 major categories: the BBSome (BBS1, BBS2, BBS4, BBS5, BBS7, BBS8, and BBS9) and the chaperonin-like superfamily (BBS6, BBS10, and BBS12). The BBSome promotes trafficking of vesicles to cilia and is involved in ciliogenesis and cilia maintenance, whereas the chaperonin-like superfamily regulates BBSome assembly. The remaining known causative genes have variable predicted functions.

**Diagnosis and Management.** The diagnosis of BBS is based on clinical findings and confirmed by genetic sequencing. Causative mutations are identified in 80% of patients. Surveillance includes regular eye examinations, monitoring of kidney function, glucose and lipid profiles, and also weight and blood pressure measurements.

Other single-gene disorders associated with renal cystic disease and syndromic features are summarized in Table 3.

**NONHEREDITARY KIDNEY CYSTS**

Simple kidney cysts rarely occur before age 20 but thereafter begin to increase in frequency with a prevalence of 7% to 10% in the general population. Simple cysts are variable in size, typically 1 cm or less but increase slowly over time in 25% of cases. On US, simple cysts appear sharply defined with thin, smooth walls without internal debris or septae.

As a rule, sharply defined cysts with well-transmitted sound waves and absence of any echoes on ultrasonography define a simple cyst. Any complexity that deviates from this should be further evaluated by computed tomography (CT). Features on CT that identify complex cysts and potential increased risk of malignancy include presence of calcification, septae, loculation, wall thickening, and increased density after dye injection. Approximately 40% to 60% of Bosniak class III and 85% to 100% of Bosniak class IV cysts prove to be malignant. The Bosniak classification system of renal cystic masses divides renal cystic masses into 5 categories based on imaging characteristics on contrast-enhanced CT. This system (summarized in Table 4) is helpful in predicting the risk of malignancy and suggesting management approaches.

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**Table 2. Clinical Diagnostic Criteria of Bardet-Biedl Syndrome**

<table>
<thead>
<tr>
<th>Primary Features</th>
<th>Secondary Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal anomalies</td>
<td>Speech disorder/delay</td>
</tr>
<tr>
<td>Rod-cone dystrophy</td>
<td>Strabismus/cataracts/astigmatism</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>Brachydactyly/syndactyly</td>
</tr>
<tr>
<td>Obesity</td>
<td>Developmental delay</td>
</tr>
<tr>
<td>Learning disabilities</td>
<td>Polyuria/polydipsia (nephrogenic</td>
</tr>
<tr>
<td>Hypogonadism in male</td>
<td>diabetes insipidus</td>
</tr>
<tr>
<td></td>
<td>Ataxia/poor coordination/imbalance</td>
</tr>
<tr>
<td></td>
<td>Mild spasticity (especially lower</td>
</tr>
<tr>
<td></td>
<td>limbs)</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Dental crowding/hypodontia/small</td>
</tr>
<tr>
<td></td>
<td>roots/high arched palate</td>
</tr>
<tr>
<td></td>
<td>Left ventricular hypertrophy/congenital</td>
</tr>
<tr>
<td></td>
<td>congenital heart disease</td>
</tr>
<tr>
<td></td>
<td>Hepatic fibrosis</td>
</tr>
</tbody>
</table>

Clinical diagnosis requires 4 primary features or 3 primary features plus 2 secondary features.

Adapted from Beales et al.

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Cramer and Guay-Woodford
In summary, disorders associated with kidney cysts may be inherited or acquired. Their manifestations may be confined to the kidney or expressed systemically. The kidney cysts may be single or multiple, and associated renal impact may range from clinical insignificance to progressive parenchymal destruction with resultant renal insufficiency. For those disorders associated with systemic manifestations, such as TSC and Bardet-Biedl syndrome, the associated extrarenal features may provide other important differential diagnostic clues. However, in some patients with atypical presentations, more extensive imaging studies and/or genetic testing may be required to establish the diagnosis.

The algorithm provided in Figure 2 outlines a diagnostic guide, based on family history, the laterality of the cystic findings, and kidney size on renal imaging. This clinical guide is primarily useful in children with renal cystic disease. Genetic testing resources for inherited renal cystic diseases are available at Gene Tests (http://www.genetests.org) and the NIH Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr).

<table>
<thead>
<tr>
<th>Disease</th>
<th>Inheritance</th>
<th>Characteristics</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFD1</td>
<td>X-linked dominant</td>
<td>Renal ultrasound: bilateral kidney cysts similar to autosomal dominant polycystic kidney disease. Clinical manifestations: craniofacial and oral anomalies, malformations of the digits in the hand, and CNS malformations.</td>
<td>OFD1</td>
</tr>
<tr>
<td>JS</td>
<td>Autosomal recessive</td>
<td>Renal ultrasound: bilateral kidney cysts. Clinical manifestations: skeletal abnormalities including a narrow chest, limb shortening, brachydactyly, and short stature. Early development of hypertension and renal insufficiency.</td>
<td>DYNC2H1, IFT80, TTC21B, NEK1</td>
</tr>
<tr>
<td>MKS</td>
<td>Autosomal recessive</td>
<td>Renal ultrasound: enlarged kidneys with varying degrees of cyst formation. Clinical manifestations: occipital encephalocele (present in 90%), postaxial polydactyly, skeletal dysplasia, microphthalmia, genital anomalies, cleft lip and palate, and heart defects.</td>
<td>MKS1, TMEM216, TMEM67, CEP290, RPGRIP1L, CC2D2A, NPHP3, TCTN2, B9D1, B9D2, TMEM231</td>
</tr>
<tr>
<td>VHL</td>
<td>Autosomal dominant</td>
<td>Renal ultrasound: bilateral kidney cysts and bilateral multifocal renal cell carcinoma. Clinical manifestations: tumors develop in both kidneys, adrenal glands, pancreas, brain or spine, eyes, and inner ears.</td>
<td>VHL</td>
</tr>
</tbody>
</table>

CNS, central nervous system; JS, Jeune syndrome; MKS, Meckel-Gruber syndrome; OFD1, Orofacial Digital Syndrome 1; VHL, von Hippel-Lindau syndrome.

### APPROACH TO DIAGNOSTIC EVALUATION

In summary, disorders associated with kidney cysts may be inherited or acquired. Their manifestations may be confined to the kidney or expressed systemically. The kidney cysts may be single or multiple, and associated renal impact may range from clinical insignificance to progressive parenchymal destruction with resultant renal insufficiency. For those disorders associated with systemic manifestations, such as TSC and Bardet-Biedl syndrome, the associated extrarenal features may provide other important differential diagnostic clues. However, in some patients with atypical presentations, more extensive imaging studies and/or genetic testing may be required to establish the diagnosis.

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### Table 4. Nongenetic Renal Cystic Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple kidney cysts Category I renal cyst</td>
<td>CT imaging: cyst with a hairline wall that does not contain septa, calcifications or solid components.</td>
<td>Typically does not require follow-up unless ( \geq 3 \text{ cm} )</td>
</tr>
<tr>
<td>Category II renal cyst</td>
<td>CT imaging: cyst that may contain few hairline thin septa. Fine calcification may be present in the wall or septa.</td>
<td>Must be distinguished from renal cystic disease and complex cysts</td>
</tr>
<tr>
<td>Category IIF renal cyst</td>
<td>CT imaging: cyst that may contain multiple hairline thin septa or minimal smooth thickening of the wall or septa. The wall or septa may contain calcification that may be thick and nodular.</td>
<td>Requires follow-up; Consider imaging at 3, 6, and 12 months and then annual</td>
</tr>
<tr>
<td>Multilocular cysts Category III renal cyst</td>
<td>CT imaging: cyst with thickened irregular walls or septa in which measurable enhancement is present.</td>
<td>Close radiographic follow-up and/or surgical excision because of the risk of malignancy</td>
</tr>
<tr>
<td>Category IV cyst</td>
<td>CT imaging: cyst wall and septae with irregular thickening. Thick, nodular, irregular calcifications are present. There is enhancement of the tissue and cyst.</td>
<td>Surgical</td>
</tr>
</tbody>
</table>
Figure 2. Algorithm for screening infants/children with kidney cysts. 1ADPKD = De novo mutations account for 5% to 10% of cases; 2GCKD = typically kidneys are small to normal size, but there are cases with enlarged kidneys; 3NPHP = the exception is infantile NPHP (NPHP2 and NPHP3) where patients typically present with enlarged kidneys; 4HNF1B-related cystic disease = De novo mutations account for 30%-50% of cases, kidneys can be quite variable in size. ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; GCKD, glomerulocystic kidney disease; HNF1B, hepatocyte nuclear factor-1 beta; MCKD, Medullary cystic kidney disease; MKS, Meckel-Gruber syndrome; NPHP, nephronophthisis; OFD1, orofacial digital syndrome 1.

REFERENCES


