Cystic Kidney Disease: A Primer

Monica T. Cramer and Lisa M. Guay-Woodford

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

RENAL 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 portobiliary system. It occurs with an estimated frequency of 1 in 20,000 live births.[1] 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.[2,3] In patients who survive the first month of life, 1-year survival rates of 92% to 95% have been reported.[1]

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.[4] Infants often have hyponatremia, presumably because of defects in free water excretion.[4] 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.[2] Age of ESRD onset is somewhat correlated with age at ARPKD diagnosis.[5]

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.[1] Portal hypertension is the predominant clinical manifestation and may cause gastroesophageal varices and hypersplenism.[1] 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.[1] 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.[3,6,7] *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.[7] A number of alternatively spliced transcripts have been identified; however, the exact function and clinical significance of these isoforms have not been elucidated.[8] Almost 750 pathogenic *PKHD1* mutations have been identified to date (http://www.humgen.rwth-aachen.de/), with approximately 44% classified as missense mutations.[9,10] A small number of relatively common mutations (eg, p.T36 M) account for ~10% of all *PKHD1* pathogenic variants.[11] Most affected patients are compound heterozygotes, carrying 2 different mutant alleles.[12]

From Division of Pediatric Nephrology, Children's Hospital of Alabama, Birmingham, AL; and Center for Translational Science, Children's National Health System, Washington, DC.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Address correspondence to Monica T. Cramer, MPH, DO, Department of Pediatrics, Pediatric Nephrology, University of Alabama Birmingham, Lowder Building 516, 1600, 7th Avenue South, Birmingham, AL 35233. E-mail: mtucci@peds.uab.edu

1548-5595/$36.00
http://dx.doi.org/10.1053/j.ackd.2015.04.001

Phenotype-genotype studies suggest that patients carrying a truncating mutation on both parental alleles have a more severe phenotype leading to perinatal demise.[10,13,14]

However, there are notable exceptions, for example, a child homozygous for a large *PKHD1* deletion who survived well past the neonatal period.[15] 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.[16] FPC has been identified as a structural component of primary cilia in kidney tubular epithelial cells and cholangiocytes of bile ducts.[7,17-19] 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 syndromes) also localize to the primary cilia/basal body (Fig 1), suggesting a role for primary cilium in the development and maintenance of kidney tubular architecture.[1]

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 hypoechoic halo.[20]

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.[1]

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.

ARPKD kidneys in utero are hyperechoic and display "decreased" corticomedullary differentiation because of the hyperechoic medulla. In comparison, ADPKD kidneys in utero tend to be moderately enlarged with a hyperechoic cortex and relatively hypoechoic medulla causing "increased" corticomedullary differentiation.[20] In addition, high-resolution US can detect the dilatations of branching collecting ducts that are readily distinguished from the round cysts of ADPKD.[20] Renal US evaluation of the parents may be useful. Absence of cysts in the parents (particularly if they are >30 years) suggests ARPKD rather than ADPKD.[20,21] However, it is important to note that in 5% to 10% of patients, ADPKD can result from spontaneous mutations.

A number of commercial genetic testing laboratories offer gene-based testing for ARPKD. Most laboratories offer direct sequencing of the entire coding region, but the expected mutation detection rate with current technologies is only 80%. An additional challenge in establishing a molecular diagnosis is that several other diseases can mimic the clinical presentation of ARPKD. For example, patients with mutations in the ADPKD genes, *PKD1* and *PKD2*, can present with early-onset renal cystic disease indistinguishable from ARPKD.[4] Thus, mutational analysis of *PKHD1* using current single-gene testing methodologies should not be considered as a first-line diagnostic approach for infants and children presenting with an ARPKD-like phenotype,[4] and genetic testing should be largely reserved for prenatal testing and preimplantation genetic diagnosis.[1]

There are currently no specific therapies for ARPKD. Postnatal management of ARPKD infants should focus on respiratory support. Several small studies have advocated for nephrectomy to improve nutrition and enable weaning of ventilator support; however, there are no current guidelines for routine nephrectomy. Decision for nephrectomy must be made on a case-by-case basis understanding the risks of surgery and complications associated with neonatal dialysis.[4] Hypertension should be aggressively managed and may require multiple antihypertensive agents. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are considered first-line therapy.[4]

CLINICAL SUMMARY

- 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.

Patients should be monitored for development of splenomegaly by abdominal examination, and annual complete blood and platelet counts should be obtained.[4] Abdominal US should be obtained at age 5, and if negative, follow-up is recommended every 2 to 3 years.[4] Cholangitis should be considered in any ARPKD patient with unexplained fever.[4]

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.[22]

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.[23,24] This early anemia may be secondary to impaired function or

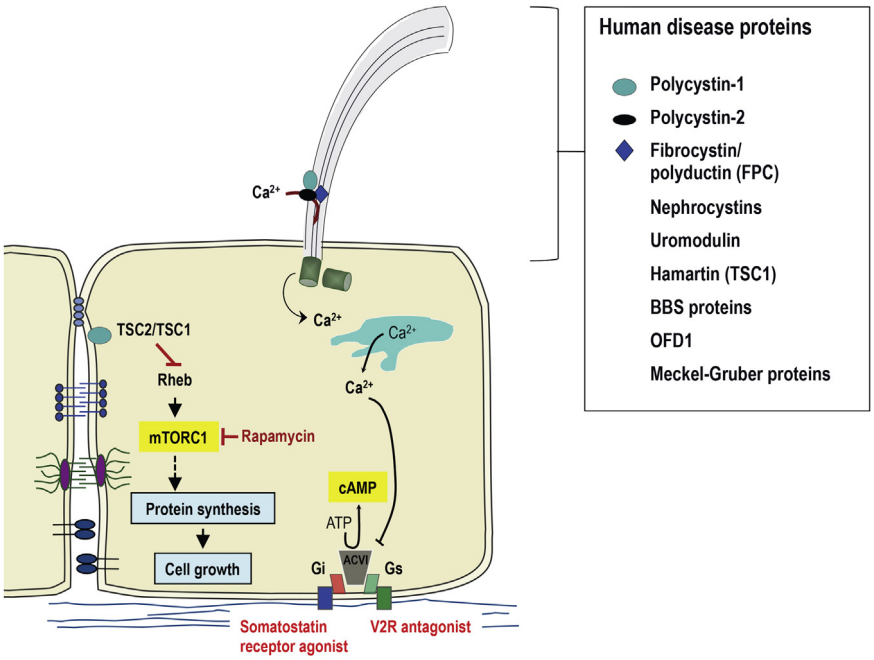

Figure 1. The primary cilium and cystoproteins. The cilium concentrates and organizes a number of channels, receptors, and effectors, for example, transcription factors and proteolytic fragments of cystoproteins. It, therefore, plays a critical role in transmitting information regarding the external milieu back into the cell and ultimately in regulating cellular and tubular differentiation and homeostasis. Almost all cystoproteins, including the polycystins, FPC, the nephrocystins, the BBS proteins, OFD1 protein, and the TSC1 protein, hamartin, localize to the cilia/centrosome complex—providing compelling evidence that this complex is critical in the pathogenesis of renal cystic disease. Cilia appear to play a role in maintaining the balance between cell proliferation and differentiation through sensing the extracellular milieu, responding to mechanical cues and modulating different signaling cascades. Ciliary dysfunction contributes to increased intracellular accumulation of cAMP and activation of mTOR, features common to cystic epithelia in human and rodent models of renal cystic disease. These abnormal signaling pathways represent potential targets for therapeutic intervention using agents that modulate the V2R (V2R antagonists or somatostatin receptor agonists) or inhibit mTORC1 (rapamycin). Abbreviations: FPC, fibrocystin-polyductin complex; BBS, Bardet-Biedl syndrome; cAMP, cyclic adenosine monophosphate; mTORC1, mammalian target of rapamycin complex 1; OFD1, oral-facial digital syndrome, type 1; TSC1, tuberous sclerosis type 1; V2R, vasopressin 2 receptor.

regulation of erythropoietin-producing cells.[24] Growth retardation, out of proportion to the degree of renal impairment, is a common finding.[25] An exception to this clinical presentation is the infantile variant, resulting primarily from mutations in the *NPHP2* or *NPHP3* genes, in which patients present in the first few months of life with kidney insufficiency and hypertension with rapid progression to ESRD.[26] 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.[25]

Genetics and Molecular Pathogenesis. To date, 19 causative genes have been identified (*NPHP1-19*). Homozygous deletions in the *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.[25] 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.[25,27]

Diagnosis and Management. Kidneys appear to be normal in size or hypoplastic, except in the infantile form, where nephromegaly is present.[27] Cysts can be observed at the corticomedullary 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.[27] 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 *NPHP* genes.[28] Current treatment of NPHP is entirely supportive.

Glomerulocystic Kidney Disease

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, hepatocyte 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.[29,30] Hereditary forms involve mutations in genes whose proteins are expressed in renal tubular primary cilia or the centrosome.[30]

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.[31] MRI may be more reliable for diagnosis and demonstrates small kidney cysts with a predominant cortical and subcapsular distribution.[31] Histopathology shows glomerular cysts defined as Bowman space dilatation greater than 2 to 3 times the normal dimension.[30] 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.[32]

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.[25] 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.[33] 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.[33] 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 *MUC1* 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 *MUC1* gene that encodes mucin 1.[34] 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.[35]

Diagnosis and Management. Diagnosis is suspected in individuals with a positive family history of kidney disease, bland urinary sediment, and characteristic sonographic findings.[33] 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 sequelae 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.[36] The description of *HNF1B* mutations as a cause of renal cystic disease originates from observations in families with monogenic diabetes.[37] 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.[37] Diabetes has been described in 58% of reported *HNF1B* mutation carriers, with mean age of diagnosis 26 years.[37] Kidney function is usually impaired, and approximately 15% of patients reach ESRD.[37]

A number of different renal pathologies have been described including hypoplastic GCKD, cystic renal dysplasia, and oligomeganephronia.[36] Other morphologic kidney abnormalities include solitary kidney and horseshoe kidney.[37] *HNF1B* mutations are a common cause of echogenic kidneys in fetuses and neonates and phenocopies ARPKD.[38] Other clinical features include uterine malformations, abnormal liver function tests, and gout.[36]

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.[39] *HNF1B* has been shown to control the transcription of known PKD genes, *UMOD*, *PKHD1*, and *PKD2*.[40]

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.[36] Diagnosis of *HNF1B*-related nephropathy may be challenging given that approximately 30% to 50% of patients have de novo mutations.[36,41] 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.[41]

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.[42] 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.[42]

Renal Manifestations. Renal lesions are evident in up to 80% of TSC individuals.[42] 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%.[43] 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.[43] In addition, AMLs may encroach on normal kidney tissue as they enlarge, contributing to the CKD.[43]

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).[44] 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.[44] Renal cell carcinoma occurs in less than 2% of the TSC population, typically at a younger age than in the general population.[43]

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.[45] *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).[43] 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.[42] The 2012 International Tuberous Sclerosis Complex Consensus Group published updated diagnostic criteria and recommended genetic testing as an independent diagnostic criterion.[42] Up to 25% of TSC patients have no identifiable mutation by genetic testing; therefore, a normal result does not exclude TSC.[42]

Table 1. Tuberous Sclerosis Complex Clinical Diagnostic Criteria

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

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 cerebral 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.[42]

Renal evaluation includes abdominal imaging to assess renal cystic disease and angiomyolipomata. MRI is the preferred imaging technique as fat poor AMLs may not be detected by computerized tomography or US.[46] 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.[47] Abdominal MRI should be obtained annually to monitor size and progression of renal angiomyolipomata. 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.[48] Results from Examining Everolimus in a Study of Tuberous Sclerosis Complex-1 trial demonstrated that everolimus was effective in reducing angiomyolipoma lesion volume and had an acceptable safety profile.[49] 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 life-long treatment.[50]

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.[51]

The clinical diagnosis of BBS is established if at least 4 major criteria are present[52] (Table 2). Renal anomalies are a cardinal feature of BBS and account for the major morbidity in these patients.[53] Sonography reveals structural defects including fetal lobulation, calyceal blunting, clubbing or diverticula, and medullary and cortical cysts.[54] Twenty-five percent of BBS patients have chronic kidney failure by age 48 and 10% develop ESRD in childhood.[53] Hypertension occurs in most patients at a median age of 34 years.[54] Developmental delay, cognitive deficits, and speech delay are common in BBS.[55]

Table 2. Clinical Diagnostic Criteria of Bardet-Biedl Syndrome

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

Clinical diagnosis requires 4 primary features or 3 primary features plus 2 secondary features.
Adapted from Beales et al.[52]

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.[56] *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).[57] 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.[51]

Diagnosis and Management. The diagnosis of BBS is based on clinical findings and confirmed by genetic sequencing.[52] 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.[62] On US, simple cysts appear sharply defined with thin, smooth walls without internal debris or septae.[63]

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).[62] 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.[62] Approximately 40% to 60% of Bosniak class III and 85% to 100% of Bosniak class IV cysts prove to be malignant.[62] 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.[63,64]

Table 3. Other Syndromic Disorders Associated With Renal Cystic Disease

Disease	Inheritance	Characteristics	Gene
OFD1[58]	X-linked dominant	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.	*OFD1*
JS[59]	Autosomal recessive	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.	*DYNC2H1* *IFT80* *TTC21 B* *NEK1*
MKS[60]	Autosomal recessive	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.	*MKS1* *TMEM216* *TMEM67* *CEP290* *RPGRIP1L* *CC2D2A* *NPHP3* *TCTN2* *B9D1* *B9D2* *TMEM231*
VHL[61]	Autosomal dominant	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.	*VHL*

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.

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 4. Nongenetic Renal Cystic Diseases

Disease	Characteristics	Management
Simple kidney cysts		
Category I renal cyst[63,64]	CT imaging: cyst with a hairline wall that does not contain septa, calcifications or solid components.	• Typically does not require follow-up unless ≥3 cm
Category II renal cyst[63,64]	CT imaging: cyst that may contain few hairline thin septa. Fine calcification may be present in the wall or septa.	• Must be distinguished from renal cystic disease and complex cysts
Category IIF renal cyst[63,64]	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.	• Requires follow-up • Consider imaging at 3, 6, and 12 months and then annual
Multilocular cysts		
Category III renal cyst[63,64]	CT imaging: cyst with thickened irregular walls or septa in which measurable enhancement is present.	• Close radiographic follow-up and/or surgical excision because of the risk of malignancy
Category IV cyst	CT imaging: cyst wall and septae with irregular thickening. Thick, nodular, irregular calcifications are present. There is enhancement of the tissue and cyst.	• Surgical

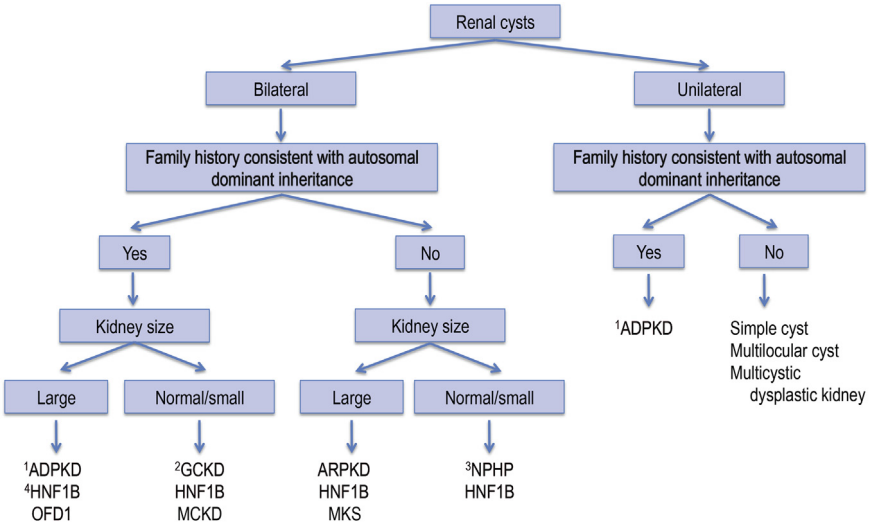

Figure 2. Algorithm for screening infants/children with kidney cysts. [1]ADPKD = De novo mutations account for 5% to 10% of cases; [2]GCKD = typically kidneys are small to normal size, but there are cases with enlarged kidneys; [3]NPHP = the exception is infantile NPHP (*NPHP2* and *NPHP3*) where patients typically present with enlarged kidneys; [4]HNF1B-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

1. Hartung EA, Guay-Woodford LM. Autosomal recessive polycystic kidney disease: a hepatorenal fibrocystic disorder with pleiotropic effects. *Pediatrics.* 2014;134:e833-e845.
2. Bergmann C, Senderek J, Windelen E, et al. Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). *Kidney Int.* 2005;67(3):829-848.
3. Guay-Woodford LM, Desmond RA. Autosomal recessive polycystic kidney disease: the clinical experience in North America. *Pediatrics.* 2003;111(5 Pt 1):1072-1080.
4. Guay-Woodford LM, Bissler JJ, Braun MC, et al. Consensus expert recommendations for the diagnosis and management of autosomal recessive polycystic kidney disease: report of an international conference. *J Pediatr.* 2014;165(3):611-617.
5. Adeva M, El-Youssef M, Rossetti S, et al. Clinical and molecular characterization defines a broadened spectrum of autosomal recessive polycystic kidney disease (ARPKD). *Medicine.* 2006;85(1):1-21.
6. Gunay-Aygun M, Avner ED, Bacallao RL, et al. 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(2):159-164.
7. Onuchic LF, Furu L, Nagasawa Y, et al. PKHD1, the polycystic kidney and hepatic disease 1 gene, encodes a novel large protein containing multiple immunoglobulin-like plexin-transcription-factor domains and parallel beta-helix 1 repeats. *Am J Hum Genet.* 2002;70(5):1305-1317.
8. Boddu R, Yang C, O'Connor AK, et al. Intragenic motifs regulate the transcriptional complexity of Pkhd1/PKHD1. *J Mol Med (Berl).* 2014;92(10):1045-1056.
9. Brüchle NO, Zerres K. *Mutation database autosomal recessive polycystic kidney disease (ARPKD/PKHD1).* 2014. Available at: http://www.humgen.rwth-aachen.de. Accessed January 15, 2015.
10. Gunay-Aygun M, Tuchman M, Font-Montgomery E, et al. PKHD1 sequence variations in 78 children and adults with autosomal recessive polycystic kidney disease and congenital hepatic fibrosis. *Mol Genet Metab.* 2010;99(2):160-173.
11. Bergmann C, Kupper F, Dornia C, Schneider F, Senderek J, Zerres K. Algorithm for efficient PKHD1 mutation screening in autosomal recessive polycystic kidney disease (ARPKD). *Hum Mutat.* 2005;25(3):225-231.
12. Rossetti S, Harris PC. Genotype-phenotype correlations in autosomal dominant and autosomal recessive polycystic kidney disease. *J Am Soc Nephrol.* 2007;18(5):1374-1380.
13. Bergmann C, Senderek J, Schneider F, et al. PKHD1 mutations in families requesting prenatal diagnosis for autosomal recessive polycystic kidney disease (ARPKD). *Hum Mutat.* 2004;23(5):487-495.
14. Sharp AM, Messiaen LM, Page G, et al. Comprehensive genomic analysis of PKHD1 mutations in ARPKD cohorts. *J Med Genet.* 2005;42(4):336-349.
15. Zvereff V, Yao S, Ramsey J, Mikhail FM, Vijzelaar R, Messiaen L. Identification of PKHD1 multiexon deletions using multiplex ligation-dependent probe amplification and quantitative polymerase chain reaction. *Genet Test Mol Biomarkers.* 2010;14(4):505-510.
16. Ward CJ, Hogan MC, Rossetti S, et al. The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein. *Nat Genet.* 2002;30(3):259-269.
17. Menezes LF, Cai Y, Nagasawa Y, et al. Polyductin, the PKHD1 gene product, comprises isoforms expressed in plasma membrane, primary cilium, and cytoplasm. *Kidney Int.* 2004;66(4):1345-1355.
18. Wang S, Luo Y, Wilson PD, Witman GB, Zhou J. The autosomal recessive polycystic kidney disease protein is localized to primary cilia, with concentration in the basal body area. *J Am Soc Nephrol.* 2004;15(3):592-602.
19. Masyuk TV, Huang BQ, Ward CJ, et al. Defects in cholangiocyte fibrocystin expression and ciliary structure in the PCK rat. *Gastroenterology.* 2003;125(5):1303-1310.
20. Chung EM, Conran RM, Schroeder JW, Rohena-Quinquilla IR, Rooks VJ. From the radiologic pathology archives: pediatric polycystic kidney disease and other ciliopathies: radiologic-pathologic correlation. *Radiographics.* 2014;34(1):155-178.
21. Sweeney WE Jr, Avner ED. Diagnosis and management of childhood polycystic kidney disease. *Pediatr Nephrol.* 2011;26(5):675-692.

22. Hildebrandt F, Otto E. Cilia and centrosomes: a unifying pathogenic concept for cystic kidney disease? *Nat Rev Genet.* 2005; 6(12):928-940.
23. Hildebrandt F, Zhou W. Nephronophthisis-associated ciliopathies. *J Am Soc Nephrol.* 2007;18(6):1855-1871.
24. Ala-Mello S, Kivivuori SM, Ronnholm KA, Koskimies O, Siimes MA. Mechanism underlying early anaemia in children with familial juvenile nephronophthisis. *Pediatr Nephrol.* 1996;10(5):578-581.
25. Guay-Woodford L. Other cystic diseases. In: Feehally RJaJ, ed. *Comprehensive Clinical Nephrology.* 5th ed. London, UK: Mosby; 2014:549-564.
26. Tory K, Rousset-Rouviere C, Gubler MC, et al. Mutations of NPHP2 and NPHP3 in infantile nephronophthisis. *Kidney Int.* 2009;75(8):839-847.
27. Wolf MT, Hildebrandt F. Nephronophthisis. *Pediatr Nephrol.* 2011;26(2):181-194.
28. Renkema KY, Stokman MF, Giles RH, Knoers NV. Next-generation sequencing for research and diagnostics in kidney disease. *Nat Rev Nephrol.* 2014;10(8):433-444.
29. Lennerz JK, Spence DC, Iskandar SS, Dehner LP, Liapis H. Glomerulocystic kidney: one hundred-year perspective. *Arch Pathol Lab Med.* 2010;134(4):583-605.
30. Bissler JJ, Siroky BJ, Yin H. Glomerulocystic kidney disease. *Pediatr Nephrol.* 2010;25(10):2049-2056. quiz 2056–2049.
31. Wood CG III, Stromberg LJ III, Harmath CB, et al. CT and MR imaging for evaluation of cystic renal lesions and diseases. *Radiographics.* 2015;35(1):125-141.
32. Loftus H, Ong AC. Cystic kidney diseases: many ways to form a cyst. *Pediatr Nephrol.* 2013;28(1):33-49.
33. Iorember FM, Vehaskari VM. Uromodulin: old friend with new roles in health and disease. *Pediatr Nephrol.* 2014;29(7):1151-1158.
34. Kirby A, Gnirke A, Jaffe DB, et al. Mutations causing medullary cystic kidney disease type 1 lie in a large VNTR in MUC1 missed by massively parallel sequencing. *Nat Genet.* 2013;45(3):299-303.
35. Vyletal P, Bleyer AJ, Kmoch S. Uromodulin biology and pathophysiology—an update. *Kidney Blood Press Res.* 2010;33(6):456-475.
36. Edghill EL, Bingham C, Ellard S, Hattersley AT. Mutations in hepatocyte nuclear factor-1beta and their related phenotypes. *J Med Genet.* 2006;43(1):84-90.
37. Bingham C, Hattersley AT. Renal cysts and diabetes syndrome resulting from mutations in hepatocyte nuclear factor-1beta. *Nephrol Dial Transplant.* 2004;19(11):2703-2708.
38. Decramer S, Parant O, Beaufils S, et al. Anomalies of the TCF2 gene are the main cause of fetal bilateral hyperechogenic kidneys. *J Am Soc Nephrol.* 2007;18(3):923-933.
39. Bellanne-Chantelot C, Clauin S, Chauveau D, et al. Large genomic rearrangements in the hepatocyte nuclear factor-1beta (TCF2) gene are the most frequent cause of maturity-onset diabetes of the young type 5. *Diabetes.* 2005;54(11):3126-3132.
40. Gresh L, Fischer E, Reimann A, et al. A transcriptional network in polycystic kidney disease. *EMBO J.* 2004;23(7):1657-1668.
41. Faguer S, Decramer S, Chassaing N, et al. Diagnosis, management, and prognosis of HNF1B nephropathy in adulthood. *Kidney Int.* 2011;80(7):768-776.
42. Northrup H, Krueger DA. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol.* 2013;49(4):243-254.
43. Siroky BJ, Yin H, Bissler JJ. Clinical and molecular insights into tuberous sclerosis complex renal disease. *Pediatr Nephrol.* 2011;26(6):839-852.
44. Brook-Carter PT, Peral B, Ward CJ, et al. Deletion of the TSC2 and PKD1 genes associated with severe infantile polycystic kidney disease—a contiguous gene syndrome. *Nat Genet.* 1994;8(4): 328-332.
45. Dabora SL, Jozwiak S, Franz DN, et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. *Am J Hum Genet.* 2001;68(1):64-80.
46. Halpenny D, Snow A, McNeill G, Torreggiani WC. The radiological diagnosis and treatment of renal angiomyolipoma—current status. *Clin Radiol.* 2010;65(2):99-108.
47. Dixon BP, Hulbert JC, Bissler JJ. Tuberous sclerosis complex renal disease. *Nephron Exp Nephrol.* 2011;118(1):e15-e20.
48. Krueger DA, Northrup H. Tuberous sclerosis complex surveillance and management: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. *Pediatr Neurol.* 2013;49(4):255-265.
49. Kingswood JC, Jozwiak S, Belousova ED, et al. The effect of everolimus on renal angiomyolipoma in patients with tuberous sclerosis complex being treated for subependymal giant cell astrocytoma: subgroup results from the randomized, placebo-controlled, phase 3 trial EXIST-1. *Nephrol Dial Transpl.* 2014;29(6):1203-1210.
50. Bissler JJ, McCormack FX, Young LR, et al. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. *N Engl J Med.* 2008;358(2):140-151.
51. Forsythe E, Beales PL. Bardet-Biedl syndrome. *Eur J Hum Genet.* 2013;21(1):8-13.
52. Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. *J Med Genet.* 1999;36(6):437-446.
53. O'Dea D, Parfrey PS, Harnett JD, Hefferton D, Cramer BC, Green J. The importance of renal impairment in the natural history of Bardet-Biedl syndrome. *Am J Kidney Dis.* 1996;27(6):776-783.
54. Moore SJ, Green JS, Fan Y, et al. Clinical and genetic epidemiology of Bardet-Biedl syndrome in Newfoundland: a 22-year prospective, population-based, cohort study. *Am J Med Genet A.* 2005; 132A(4):352-360.
55. Putoux A, Attie-Bitach T, Martinovic J, Gubler MC. Phenotypic variability of Bardet-Biedl syndrome: focusing on the kidney. *Pediatr Nephrol.* 2012;27(1):7-15.
56. Katsanis N, Ansley SJ, Badano JL, et al. Triallelic inheritance in Bardet-Biedl syndrome, a Mendelian recessive disorder. *Science.* 2001;293(5538):2256-2259.
57. Jin H, Nachury MV. The BBSome. *Curr Biol.* 2009;19(12):R472-R473.
58. Macca M, Franco B. The molecular basis of oral-facial-digital syndrome, type 1. *Am J Med Genet C Semin Med Genet.* 2009; 151C(4):318-325.
59. Poyner SE, Bradshaw WT. Jeune syndrome: considerations for management of asphyxiating thoracic dystrophy. *Neonatal Netw.* 2013; 32(5):342-352.
60. Logan CV, Abdel-Hamed Z, Johnson CA. Molecular genetics and pathogenic mechanisms for the severe ciliopathies: insights into neurodevelopment and pathogenesis of neural tube defects. *Mol Neurobiol.* 2011;43(1):12-26.
61. Maher ER, Neumann HP, Richard S. von Hippel-Lindau disease: a clinical and scientific review. *Eur J Hum Genet.* 2011;19(6):617-623.
62. Eknoyan G. A clinical view of simple and complex renal cysts. *J Am Soc Nephrol.* 2009;20(9):1874-1876.
63. Simms RJ, Ong AC. How simple are 'simple renal cysts'? *Nephrol Dial Transpl.* 2014;29(suppl 4):iv106-iv112.
64. Israel GM, Bosniak MA. An update of the Bosniak renal cyst classification system. *Urology.* 2005;66(3):484-488.