Review Article

Cystic Diseases of the Kidneys: From Bench to Bedside

Rupesh Raina[1,2*], Francis Lomanta[4], Siddhartha Singh[1,2*], Alisha Anand[5], Riti Kalra[6], Vignasiddh Enukonda[2], Oren Barat[3], Davinder Pandher[2], Sidharth K Sethi[7]

[1]Department of Pediatric Nephrology, Akron Children's Hospital, Akron, Ohio, [2]Department of Nephrology, Akron Nephrology Associates/ Cleveland Clinic Akron General Medical Center, Akron, [3]College of Medicine, Northeast Ohio Medical University, Rootstown, [4]Department of Nephrology, Akron Children's Hospital, Akron, [5]Faculty of Science, McMaster University, Hamilton, ON, Canada, [6]College of Arts and Sciences, Case Western Reserve University, Cleveland, OH, USA, [7]Kidney and Renal Transplant Institute, Medanta, The Medicity Hospital, Gurugram, Haryana, India

[*]Both are co-first authors

Abstract

Exploration into the causes of hereditary renal cystic diseases demonstrates a deep-rooted connection with the proteomic components of the cellular organelle cilia. Cilia are essential to the signaling cascades, and their dysfunction has been tied to a range of renal cystic diseases initiating with studies on the oak ridge polycystic kidney (ORPK) mouse model. Here, we delve into renal cystic pathologies that have been tied with ciliary proteosome and highlight the genetics associated with each. The pathologies are grouped based on the mode of inheritance, where inherited causes that result in cystic kidney disease phenotypes include autosomal dominant and autosomal recessive polycystic kidney disease, nephronophthisis (Bardet–Biedl syndrome and Joubert Syndrome), and autosomal dominant tubulointerstitial kidney disease. Alternatively, phakomatoses-, also known as neurocutaneous syndromes, associated cystic kidney diseases include tuberous sclerosis (TS) and Von Hippel–Lindau (VHL) disease. Additionally, we group the pathologies by the mode of inheritance to discuss variations in recommendations for genetic testing for biological relatives of a diagnosed individual.

Keywords: *Bardet–Biedl syndrome, ciliopathy, genetic counseling, Joubert syndrome, kidney disease, nephronophthisis, polycystic kidney disease, renal cystic disease, tuberous sclerosis, Von Hippel–Lindau, Zellweger spectrum disorders*

Introduction

Renal cystic disease encompasses a wide range of hereditary, non-hereditary, and acquired pathologies that demand a multidisciplinary approach to treatment. This may accompany extrarenal abnormalities or be a part of a well-defined syndrome. In 1964, Potter and Osathanondh pioneered a classification system based on microdissections of cystic kidneys, and hypothesized the mechanisms of cyst formation by localizing the cysts to specific segments of the nephrons.[1] Newly elucidated genetic and pathophysiologic concepts further refined the classification in 1969.[2] Ongoing research continue to clarify clinicopathologic correlations in the more recent classifications [Table 1].[3]

Cysts form in the kidney through a myriad of unspecified mechanisms where the consensus considers cysts secondary to obstructive, degenerative, or neoplastic mechanisms. Recent data provides compelling evidence that inherited cystic disease is linked to alterations in different genes involved in the formation and function of both the cilia of the embryonic node and cilia in epithelial renal tubes.[4] Inherited causes that result in the cystic kidney disease phenotype as well as ciliopathy-associated (related to the structure/function of the primary cilia complex) cystic kidney diseases will be further examined.

Role of cilia in cystic kidney disease

The primary cilium is a ubiquitous organelle involved in chemosensation, signal transduction, and cell growth. Primary cilia are arranged in a 9+0 axoneme (versus 9+2 axoneme in motile cilia) which warp orientation in reaction to fluid flow. Research on cilia conducted through the ORPK mouse (model system with intraflagellar transport (IFT) protein localized in the cilia) demonstrated an association between shortened/absent cilia and autosomal recessive polycystic kidney disease (ARPKD).[11,12] In the kidneys, the cilium's unique position as a projection into the lumen of the duct from epithelial cells allows for its principal function to sense the locale and provide control over proliferation and differentiation.

How to cite this article: Raina R, Lomanta F, Singh S, Anand A, Kalra R, Enukonda V, *et al.* Cystic diseases of the kidneys: From bench to bedside. Indian J Nephrol 2023;33:83-92.

Received: 21-07-2021
Revised: 21-03-2022
Accepted: 18-04-2022
Published: 20-02-2023

Address for correspondence:
Dr. Rupesh Raina, Department of Nephrology, Cleveland Clinic Akron General and Akron Children's Hospital, Akron, Ohio, Faculty Staff at Case Western Reserve University, School of Medicine Cleveland Ohio, USA.
E-mail: rraina@akronchildrens.org

Access this article online

Website: https://journals.lww.com/ijon

DOI: 10.4103/ijn.ijn_318_21

Quick Response Code:

The signaling process is still poorly understood; however, proposed models suggest an interaction between luminal flow and paracrine signaling.[13] Kidney function depends on flow through nephrons, this flow is sensed by the primary cilia of the nephrons and deflected by the fluid passing to increase intracellular calcium. Normally, this increase causes regulation of a calcium-dependent channel. However, disruption of cilia formation is proposed to result in both defects in the channel and ultimately, polycystic kidney disease (PKD). Similar mechanistic disruptions occur on extrarenal systems: pulmonary hypoplasia or bronchiectasis, hypogonadism, intellectual disability, congenital heart defects, skeletal malformations and visual disturbances are all associated with ciliopathies.[1,2,12,13]

Genes involved in cystic kidney diseases have been shown to encode proteins involved in cilia formation/function [Figure 1].[5,14,15] Models using non-biased forward genetic screening for cystic kidney mutations in non-human models found defects in cilia associated with abnormal cytogenesis [Supplement A].[6,7] Mutations in the *hi409*, *hi221*, and *hi3417* genes disrupt the creation of portions of the IFT particle required for cilia formation.[16] In conclusion, the overarching cause of PKD involves mutations in ciliary genes, and specific gene targets are possible options for therapy in human diseases involving kidney cyst formation. A summary of pathophysiologic and imaging characteristics used to confirm the diagnosis of cystic kidney diseases is summarized in Table 2.

The signaling pathway connecting cilia to cell proliferation is largely unknown; polycystin-1 and polycystin-2 have been implicated in numerous pathways including JAK-STAT, Wnt, β-catenin, protein kinase C, cAMP, G-protein, and Ca^{2+} signaling pathways.[17] IFT genes have been implicated in hedgehog signaling, and the lack of cilia is reported to activate β-catenin signaling.[18] Analyzing mutant phenotypes suggests that cilia link extracellular signals to intracellular events such as cell proliferation. Further research will be paramount in dissecting the signaling network of cilia's role in coordinated cellular responses.

Table 1: Classification of cystic kidney diseases[1,3-10]

Classification of Cystic Kidney Diseases	
Genetic	
Ciliopathy associated	Autosomal dominant polycystic kidney disease (ADPKD)
	Autosomal recessive polycystic kidney disease (ARPKD)
	Nephronophthisis-related isolated syndrome
	Bardet–Biedl syndrome
	Joubert syndrome
	Meckel–Gruber syndrome
Phakomatoses associated	Tuberous sclerosis
	Von Hippel–Lindau syndrome
Cystic Dysplasia associated	Multicystic dysplastic kidney (MCDK)
	Posterior urethral valve (PUV)
	Reflux nephropathy
	Hypodysplastic kidneys
Autosomal dominant tubulointerstitial kidney disease (ADTKD)	ADTKD-uromodulin kidney disease (ADTKD-UMOD)
	ADTKD-renin mutation (ADTKD-REN)
	ADTKD-mucin-1 mutation (ADTKD-MUC1)
	Hepatocyte nuclear factor-1beta (HNF1β)–associated kidney disease
Miscellaneous	Acquired cystic kidney disease
	Glycogen storage disease
	Leukemia or lymphoma
	Nephroblastomatosis
	Pyelonephritis

Hepatorenal fibrocystic disease

Hepatorenal fibrocystic diseases are monogenic disorders characterized by fibrocystic abnormalities of the kidney and dysgenesis of the portobiliary tract. Clinical presentation is variable and includes oligohydramnios, enlarged kidneys, hypertension, and Potter sequence.

Development of hepatic bile ducts starts at gestational age (GA) six to eight weeks, initiating from the contact of primitive epithelial cells with portal vein mesenchyme.[19,20] A ductal plate begins differentiation from unknown developmental signals around GA 13–17 weeks where any interruption can lead to

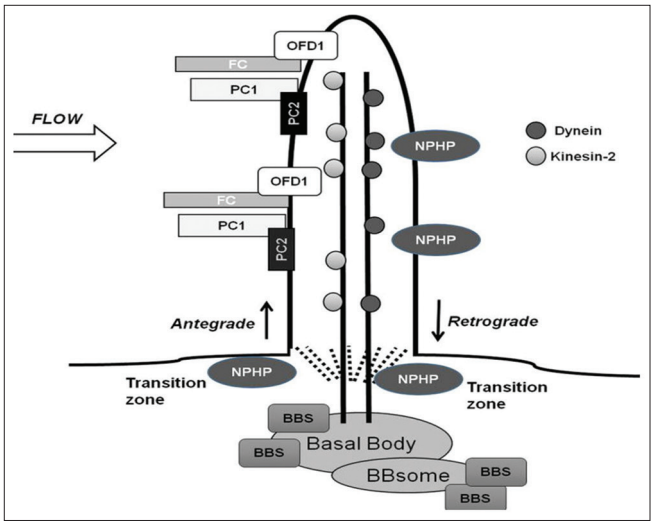

Figure 1: Representation of the ciliary structure and associated renal cystic proteasome. Each associated pathology shows overlap as the depicted protein products are all involved in the homeostatic function of the cilium. Abbreviations: BBS, Bardet–Biedl syndrome; NPHP, Nephronophthisis; OFD1, Oral-facial-digital syndrome 1; PC, Polycystin; PC1/PC3, Prohormone convertase 1/2

Table 2: Pathophysiologic and imaging characteristics of renal cystic diseases[1–8,10–32]

Pathophysiologic and Imaging Characteristics of Renal Cystic Diseases		
Disease type	**Pathophysiologic Characteristics**	**Image Findings**
Acquired cystic kidney disease	Hyperplasia of tubular epithelium due to↑mitogenic growth factors and activation of proto-oncogenes with↑fluid secretion	Bilateral small kidneys with multiple cysts, ↑risk of intracystic hemorrhage, and development of renal cell carcinomas
Medullary sponge kidney	Disruption of the embryonic interface between the developing ureteral bud and the metanephric blastema during embryogenesis	Medullary nephrocalcinosis and cysts, paint-like appearance at urography, multiple renal calculi
Multicystic dysplastic kidney	Abnormal metanephric-mesenchymal differentiation in the setting of urinary tract obstruction during embryogenesis	Non-reniform, non-functional kidney with multiple peripheral cysts and central solid components
Localized renal cystic disease	Acquired maldevelopmental origin is hypothesized	Conglomerate mass of multiple simple cysts of various sizes, separated by enhancing or atrophic renal tissue without definite capsule
Autosomal dominant polycystic kidney disease	Dysregulation function of renal cilium with↑proliferation of renal tubular epithelium and↑fluid secretion	Bilateral enlarged kidneys with multiple expansile cysts
Autosomal Recessive polycystic kidney disease	Altered molecular and cellular pathways causing abnormal cellular proliferation, fluid secretion and alterations in extracellular matrix.	Bilaterally enlarged echogenic kidneys.
Hepatocyte nuclear factor -1beta–associated kidney disease	HNF1β mutations leads to abnormal nephron development and affects many genes involved in the pathogenesis of renal cystic disease	Hyperechogenic kidneys with normal or slightly enhanced size
Medullary cystic kidney disease	Ciliary dysfunction postulated to be secondary to altered interaction of MCKD1 or MCKD2 protein with nephrocystin	Multiple cysts at the corticomedullary junction and in medulla
Von Hippel–Lindau disease	Upregulation of HIF with resultant↑in downstream effectors. Dysregulation of ciliary assembly and mechanosensory function of renal cilium	Multiple, variably sized cysts in kidneys; multiple interspersed cystic solid renal cell carcinomas
Tuberous sclerosis complex	Uncontrolled activation of mTOR and downstream effectors. Defects in ciliary function and epithelial cells polarity.	Multiple bilateral renal cysts intermixed with multiple angiomyolipomas

malformation. Dysregulated proliferation leads to dilated ductule and the initial hepatic lesions, subsequent liver damage, and inflammation can cause fibrosis and cirrhosis. This pattern is seen in a variety of fibrocystic syndromes including Meckel–Gruber syndrome (MKS), Renal–Hepatic–Pancreatic Dysplasia or Ivemark's syndrome (RHPD), and Jeune Syndrome (JATD1–5).[21]

Meckel–Gruber syndrome (MKS) is a rare congenital and lethal autosomal recessive condition characterized by the triad of occipital encephalocele, large polycystic kidneys, and postaxial polydactyly. MKS has variable expressivity and allelism similar to other ciliopathies such as Joubert syndrome, which attributes to its rare diagnosis.[22] Asphyxiating thoracic dystrophy, or Jeune syndrome, is one of several ciliopathies associated with skeletal disorders. In addition to changes in the hedgehog signaling pathway, genes associated with "skeletal ciliopathies" continue to be discovered, but the conditions can have mutations in the dynein motor (e.g., DYNC2H1), intraflagellar transport complexes (e.g., IFT80), and the basal body (e.g., NEK1).[22] A more comprehensive list of causes for hepatorenal fibrocystic diseases can be found in Table 3.

Polycystic kidney diseases

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD, OMIM: 618061) is the most common hereditary kidney disease worldwide, characterized by bilateral kidney enlargement with numerous cysts and a variable rate of chronic kidney disease (CKD) progression. Common comorbidities include hypertension, nephrolithiasis, urinary tract infections (UTIs), and extrarenal complications.[8] Since the approval of tolvaptan, the first treatment for patients with high risk of progressive ADPKD, emphasis on risk assessment of ADPKD progression has become clinically significant.[34,35]

In clinically ascertained samples, mutations in PKD1 and PKD2 are responsible for 60%–78% and 15%–26% of ADPKD, respectively (A8, A9). Additionally, about 10%–15% of patients with apparent ADPKD have no identifiable *PKD1* or *PKD2* mutation; however, whole-exome

Table 3: Causes of hepatorenal fibrocystic diseases [1–8,10–33]

Fibrocystic Disease	Gene and Protein	Renal Impairment	Hepatic Association	Extra-hepatorenal Implications
Autosomal dominant polycystic kidney disease	PKD (Polycystin-1) PKD2 (Polycystin-2)	Cysts over whole nephron	Nodular hepatomegaly, hepatic cysts, pancreatic cysts	Hypertension, retinal dysplasia, aneurysm
Autosomal recessive polycystic kidney disease	PKHD1 (Fibrocystin)	Cysts towards collecting ducts	Congenital hepatic fibrosis, portal hypertension	Hypoplastic lung, splenomegaly, hypersplenism, cholangitis
Bardet–Biedl syndrome	BBS1-21 (BBSome)	Structural impairment, cyst formation, urinary tract malformation	Non-alcoholic steatohepatitis	Retinal dystrophy, obesity, polydactyly, hypogonadism, mental retardation
Joubert syndrome	AHI1, CPLANE1, CC2D2A, CEP290, CSPP1, INPP5E, KIAA0586, MKS1, NPHP1, RPGRIP1L, TCTN2, TMEM67, TMEM216	Cystic dysplasia	Congenital hepatic fibrosis	Muscle control (ataxia), coloboma, polydactyly, encephalocele
Zellweger syndrome	PEX1 (Pex1p)	Cortical microcysts	Fibrosis, cirrhosis, hepatomegaly	Craniofacial abnormality, hypomyelination, chondrodysplasia
Von Hippel–Lindau	VHL (pVHL)	Clear cell RCC	Tumor	PNET, pancreatic cysts, pheochromocytoma, hemangioblastoma, ovarian cysts
Jeune syndrome	Several implicated genes	Cystic dysplasia	Fibrosis	Skeletal dysplasia (small thorax), pancreatic cysts, retinal abnormality
Nephronophthisis	NPHP1–18	Hyperechogenic kidneys, reduced size, and corticomedullar cysts	Congenital hepatic fibrosis	Tapetoretinal degeneration, ocular motor apraxia, and cone-shaped epiphysis

Abbreviations: AML, angiomyolipoma; PNET, pancreatic neuroendocrine tumors; RCC, renal cell carcinoma; SEGA, subependymal giant cell astrocytoma

sequencing studies have identified additional genes (i.e., *GANAB*, *DNAJB11*) mutated in a small proportion of patients (<1%).[9,36] Both genic and allelic heterogeneity contribute to phenotype severity in ADPKD. Mutations in PKD1 lead to a more severe phenotype with larger kidneys, earlier onset of end-stage renal disease (ESRD), hemorrhage into cysts, and gross hematuria when compared to mutations in *PKD2*. Protein-truncating mutations caused by nonsense, frameshift, or canonical splice-site mutations, lead to a more severe disease than non-truncating mutation (i.e., in-frame insertion and deletions (indels), missense mutations, and atypical splicing mutations).[37]

The study of intrafamilial kidney disease discordance provides an opportunity to delineate genetic and environmental modifiers impacting the predictability of kidney disease progression in ADPKD. One potential explanation for intrafamilial disease discordance is compound heterozygosity or digenic inheritance of an additional mutation in a cystogenic gene, including *PKD1* and *PKD2*.[38] Mosaicism, in which two populations of cells with different genotypes exist in the same person, can lead to intrafamilial kidney disease discordance.[39] While mosaicism can lead to intrafamilial kidney disease discordance, its prevalence in ADPKD remains poorly defined.[40]

Mutations in additional disease modifiers, including *COL4A1* and *HNF1B* have been described and could create intrafamilial variations under heterozygous conditions.[41] Genetic variants may modify the kidney disease severity of ADPKD, exemplified by DKK3, and a polygenic component with numerous genetic variants causing accumulation of small microaggressions contributing to disease progression.[42] Comorbidities including obesity, diabetes, vascular disease, acute kidney injury, and environmental factors such as cigarette smoking, diet, and water intake could also contribute to intrafamilial kidney disease discordance in ADPKD.[43,44]

Autosomal Recessive Polycystic Kidney Disease

Autosomal recessive polycystic kidney disease (ARPKD; MIM 263200) is another hereditary cause of CKD, with an estimated incidence of 1 in 20,000 live births.[23] Neonates typically present with history of oligohydramnios, enlarged kidneys, respiratory insufficiency secondary to pulmonary hypoplasia, and perinatal death in approximately 30% of affected newborns.

ARPKD is caused by mutations in *PKHD1*, a large ~500-kb gene with a complex splicing pattern located on chromosome 6p21.1-p12.[45] The product of *PKHD1*, fibrocystin/polyductin (FPC), is a single membrane spanning protein with multiple isoforms expressed predominantly in the kidneys (collecting ducts and thick ascending loops of Henle), liver (in bile duct epithelia), and pancreas.[46] In renal tubular and biliary epithelial cells, FPC localizes to apical membranes, which are the primary cilia/basal body.[47] The function of FPC remains unclear, yet the role for the primary cilium in renal tubular architecture has led aforementioned disorders to be categorized as ciliopathies. Through its interactions with the ADPKD protein polycystin-2, FPC forms a common signaling pathway with polycystin-1.[48]

Numerous groups have attempted to categorize sequence variations based on the likelihood of pathogenicity, many of which are catalogued in the ARPKD mutation database.[49,50] However, because many patients have novel *PKHD1* variants, interpretation of genetic testing results can be challenging. Genetic modifiers likely play a significant role in disease expression as illustrated by significant phenotypic variability in family subsets; for example, in a study of 126 unrelated families, 20 siblings showed widely discordant phenotypes (perinatal death in one sibling and survival into childhood in the other).[24]

Nephronophthisis

Nephronophthisis (NPHP) is an autosomal recessive kidney disease, typically causing ESRD within the first three decades of life.[51] Traditionally diagnosed clinically through onset of insidious chronic renal failure (CRF) followed by histological confirmation, advancements in molecular diagnostics have provided insight into the underlying mechanisms of NPHP.[22] NPHP genes encode proteins expressed ubiquitously in centrosomes and primary cilia. NPHP is, therefore, considered to be a ciliopathy, consistent with the fact that extrarenal manifestations occur in around 20% of cases. Reviewing clinical and histological features of the disease highlights the multiple ciliopathic syndromes associated with NPHP.[22]

With more than 25 mutated genes now affiliated with NPHP, reviewing genetic causes provides mechanistic insights into the pathogenesis of NPHP.[22] A number of these genetic mutations appear to be associated with the centrosome/basal body/primary cilium [Table 4]. Two studies, one which identified nine NPHP genes, and another identifying 25 genes, found similar prevalence of mutations in *NPHP1*, a large homozygous deletion, accounting for ~20% of NPHP.[22,25,27] The remaining known mutations accounted for approximately 1% of all NPHP cases which suggest that up to two-thirds of cases remain unsolved.[25] Genotypic mutations in NPHP may lead to a wide spectrum of phenotypes including isolated NPHP, NPHP with additional features (Senior–Løken syndrome and Joubert syndrome), and lethal neonatal forms (Meckel–Gruber syndrome).

Bardet–Biedl Syndrome

Bardet–Biedl syndrome (BBS; MIM 209900) is a genetic disorder characterized by defects in multiple organ systems, and the estimated prevalence ranges from 1 in 160,000 in northern European populations to as high as 1 in 13,500 in Kuwait and Newfoundland.[26,52,53] BBS is a disorder of locus and allelic heterogeneity. It is typically inherited in an autosomal recessive fashion, under which model mutations in 14 loci (BBS1–12, MKS1, centrosomal protein 290 kDa/nephronophthisis 6 [CEP290/NPHP6]) have been identified.[54,55]

Joubert syndrome

Joubert syndrome (JS) and disorders (JSRD, OMIM: 213300) are a genetically heterogenous group of congenital disorders that affect brain development and other organs such as the eye, kidney, or lungs.[56] Other names referring to Joubert syndrome in the past include COACH syndrome, cerebellar ocular renal syndrome, and Cogan type oculomotor apraxia. The latter being characterized by impairment of voluntary horizontal eye movements. Multi-organ symptoms manifest as retinal dystrophy, NPHP, and retinal cystic dysplasia with renal involvement are accounted for in 25%-30% of patients with JSRD. Incidence rates of JSRD range between 1 in 80,000–100,000 in neonatal populations; however, these rates tend to range at the lower estimate of the confidence interval (CI) due to the continual discovery of more causative genes.[56] JSRD was first described in isolated groups with high rates of consanguinity, including French–Canadian, Arab, and Ashkenazi Jewish populations. The genetic causes of cerebellar-ocular-renal syndrome can be largely attributed to mutations in JBTS5, caused by mutation in the CEP290 gene, also called NPHP6, on chromosome 12q21; JBTS3, caused by mutation in the AHI1 gene on chromosome 6q23; JBTS6 caused by mutation in the TMEM67 gene on chromosome 8q21; JBTS4 caused by mutation in the NPHP1 gene on chromosome 2q13.[27,57,58]

Autosomal dominant tubulointerstitial kidney disease

Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) contains a group of diseases that affect tubules of the kidney and can lead to CKD. Uniquely, this disease is associated with elevated uric acid concentrations in the blood, leading to gout in as early as teenage years for several of its associated subtypes.[59] These types include uromodulin kidney disease (ADTKD-UMOD), renin mutation (ADTKD-REN), or mucin-1 mutation (ADTKD-MUC1) subtype. The UMOD subtype has a mutation in uromodulin, also called Tamm–Horsfall protein, which is a protein made in the kidney that is associated with gout when elevated.[59]

Table 4: Primary NPHP genetic mutations[27]

Gene	Locus	Protein	Location	Function	Disorder
NPHPI	2q12.3	Nephrocystin-l	Adherens, focal adhesion, transition zone	Cellular scaffolding and cell-cell adhesion/signalling	NPHP, SLSN, JBTS
NPHP2/INVS	9q21-22	Inversin	Inversin compartment	Wnt pathway for cell polarity	iNPHP, SLSN, Situs Inversus, cHeart Defects
NPHP3	3q22.1	Nephrocystin-3	Inversin compartment, axoneme	Wnt inhibitor	NPHP, RP, Situs inversus, MKS, SLSN
NPHP4	Ip36.31	Nephrocystin-4	Transition Zone	Wnt inhibitor, Hippo pathway	jNPHP, RP, OMA, SLSN
NPHP5/IQCB1	3q13.33	Nephrocystin5/1Q Motif Bl	Transition Zone, centrosome	RPGR Complex	jNPHP, RP, LCA
NPHP6/CEP290	12q21.32	Nephrocystin6/CEP 290	Transition Zone, centrosome	ATF4/CREB 2 regulation, cAMPdependent cyst, DDR	NPHP, RP, LCA, JBTA, MKS
NPHP7/GLIS2	16p13.3	Nephrocystin7/GLl S-2	Nucleus	Hh Regulation	NPHP
NPHP8/RPGRIPIL	16q12.2	Nephrocystin9/ RPGRIP1-like	Transition Zone	Shh Signalling	jNPHP, JBTS, MKS, RP, LCA, COACH
NPHP9/NEK8	17q11.1	Nephrocystin9/ NIMA-related kinase 8	Basal Body	DDR Signaling	jNPHP, RP, SLSN, BBS
NPHPI0/SDC CAG8	Iq43q44	Nephrocystin10/ Serologically defined colon cancer antigen	Transition Zone	Cellular structure and centrosome migration	NPHP, JBTS, MKS, COACH

NPHP, Nephronophthisis; INVS, Inversin; SLSN, Senior Loken Syndrome; JBTS, Joubert Syndrome; cHeart Defects, congenital heart defects; RP, retinitis pigmentosa; MKS, Meckel Gruber Syndrome; jNPNP, Juvenile Nephronophthisis; OMA, oculomotor apraxia; LCA, Leber's congenital amaurosis; COACH, COACH syndrome

The subtype with mucin-1 mutations differs from both the UMOD and REN subtypes because it is the only type to not be associated with increased risk of gout, but rather an insidious, gradually progressive kidney disease that presents in the sixth decade of life.[59]

Hepatocyte nuclear factor-1beta–associated kidney disease

Hepatocyte nuclear factor-1beta (HNF1β)–associated kidney disease is a newly recognized disease with multisystem phenotypical expression and renal cysts as a common presentation. It is closely associated with maturity onset diabetes of the young. Decline in renal function along with renal cysts prior to the onset of diabetes is often noticed. HNF1β transcription factor is involved in the development of ureteric bud giving ureter, renal pelvis, collecting ducts and mesenchyme, pancreas, liver and brain. Any mutation can lead to a wide variety of phenotypical expressions and developmental renal abnormalities, such as renal cysts preceding diabetes, hyperechogenic kidneys with slightly enhanced or normal kidney size on ultrasound, hypoplastic glomerulocystic kidney disease, hyperuricemia or hypomagnesemia.

Ciliopathy-associated cystic kidney diseases

Tuberous Sclerosis: Tuberous sclerosis complex (TSC, OMIM: 19100) is a multisystemic neurocutaneous condition with autosomal dominant inheritance, characterized by renal cysts, hamartomas across multiple organs, skin, central nervous system, heart, lungs, and kidney.[54] The condition affects 1 in 6,000–10,000 individuals and can affect both sexes and all ethnic groups equally.[55] TSC occurs due to the deletion, rearrangement, or inactivation mutations of tumor suppressor genes, *TSC1* or *TSC2*, leading to abnormal proteins hamartin and tuberin, codified in the loci 9p34 and 16p13, respectively.[29,60,61,62-68] In countries where genetic analysis is scarce, establishing TSC remains a clinical diagnosis.[69] Renal manifestations include angiomyolipoma (AML), hemorrhage, CKD, anemia, and hypertension often diagnosed through radiological findings (MRI, CT, Ultrasound) or needle biopsy if without definitive imaging.[70,71]

Zellweger Syndrome: The Zellweger spectrum disorders (ZSDs) are a heterogeneous group of autosomal recessive disorders characterized by a defect in peroxisome formation and are caused by mutations in one of 13 PEX genes.[29,60] Defects in peroxisome formation are associated with ZSD patients accumulating very long chain fatty acids (VLCFAs), phytanic- and pristanic acid, C27-bile acid intermediates and pipecolic acid in plasma, and deficiency of plasmalogens in erythrocytes.[61,69,62-68] Clinically, ZSDs are highly heterogeneous, but the core features are liver and adrenocortical dysfunction, developmental delay, hearing and vision impairment, and other neurological abnormalities.

Von Hippel–Lindau: Von Hippel–Lindau (VHL) disease (MIM #193300) occurs as the result of germline mutations in

the *VHL* tumor suppressor gene, located on chromosome 3p25–26.[70] Patients with VHL disease are at risk of developing visceral cysts and tumors throughout the body including simple cysts, hemangioblastomas (HBs) of the retina and central nervous system, clear cell renal cell carcinomas (RCCs), pheochromocytomas, pancreatic neuroendocrine tumors (PNETs), pancreatic serous cystadenomas, and endolymphatic sac tumors (ELSTs).[71,72] VHL gene is composed of three exons coding for two isoforms of the protein pVH, which form part of a multiprotein complex including elongin B, elongin C, and Cullin 2 (CUL2) responsible for ubiquitination and degradation of the α subunits of hypoxia-inducible factors (HIFs) 1 and 2.[73] VHL is almost completely penetrative: Most individuals with mutations in *VHL* tumor suppressor gene have VHL disease–related symptoms by the age of 65.[74] The estimated incidence of sporadic mutations in VHL disease is 1 in 36,000 live births with no known parental age affect.

Genetic counseling

Prenatal and pre-implantation genetic testing plans should be highly considered for families with high-risk pregnancies that are predisposed to pathogenic gene mutations for cystic diseases.[75,76] The families should be referred to a genetic counselor who will review family history and clinical findings to provide pre-implantation, prenatal, and postnatal genetic testing options. Genetic testing may involve the use of targeted next-generation sequencing (NGS); however, the specific testing options provided may vary based on the history of ciliopathy present, renal findings, and other inconsistencies present.

For autosomal dominant ciliopathies (ADPKD, HNF1B, BORSD, VHL), assuming one parent has the proband, all offspring have a 50% chance of inheriting the pathogenic gene mutation, increasing to 75% if both parents are afflicted. Assessing parental predisposition can be done on a macroscale with MRI or CT scan (ADPKD) or microscale with genetic testing of both parents for the proband.[30] However, these tests are imperfect as parents may have mosaicism of the gene or a proband may form from de novo mutations in utero, both resulting in minimal positive pretest probability.

In contrast, in autosomal recessive ciliopathies (isolated/syndromic nephronophthisis, ARPKD, BBS, Zellweger*)*, both parents are carriers of the gene mutation or one carrier parent and one afflicted parent. Siblings of the proband have a 25% chance of inheriting both genotypes resulting in pathology, 50% chance of becoming a carrier, and a 25% chance of not being a carrier. Siblings of the proband's parents are at 50% risk of being carriers of the pathogenic gene mutation. For high-risk pregnancies (>25% chance of autosomal recessive ciliopathy), if mutant genes have been identified in the family member, prenatal testing is available.[76] For low-risk pregnancies (no family history of ARPKD, but enlarged cystic kidneys on prenatal ultrasound), there are multiple testing options including karyotyping or array with fetal ultrasonography, molecular genetic testing, and renal ultrasound (ARPKD) of both parents assessing predisposition. De novo mutations in the proband can also affect success of risk assessment with genetic testing.[32]

As many ciliopathies are rare and not completely understood, simple Mendelian inheritance patterns cannot always be attributed to the transmittance of these pathologies; rather, oligogenic inheritance plays a role. For example, MKS has both variable expressivity and allelism similar to other ciliopathies such as Joubert syndrome. In addition to making the distinction when diagnosing these pathologies difficult, the overlapping allelism leaves the possibility of effect modifiers to play a role in each disease's manifestation. Similarly, NPHP is still not entirely understood despite the number of identified mutations having grown from 9 to 25 in just a couple of years. Thus, despite NPHP being considered an autosomal recessive disease, this disease along with other ciliopathies may have additional interactions which play a role in the resulting genotypic heterogeneity. With the varying severity of clinical presentations resulting from mutations of different subtypes in the *CEP290* gene ranging from isolated nephronophthisis to the lethal MKS phenotype, more research is needed to further understand how different factors play a role in the development of these pathologies.[30–32,76]

Currently, the decision of who should receive and the type of testing is controversial in current guidelines. This is complicated by the fact that there are more than 100 genes associated with cystic kidney diseases, as listed by Park *et al.* [Supplement A].[10] Thus, the decision should be made by the family members after the genetic counselor has extensively discussed the possible cons and benefits of genetic testing.

Conclusion

In conclusion, ciliopathies are an emerging conceptual framework to tie in the clinically relevant renal cystic diseases with the emerging cellular research into ciliopathies. By combining animal models (particularly mouse) with clinically oriented research, new insights can further the molecular basis of understanding the cystic kidney diseases and provide a novel understanding into the role of cilia in pathologic manifestations. The quintessential example is the creation of double knockout mice lacking *Pkd* genes and *Kif3a* or *Ift20*, which reduced the burden of polycystic kidney disease.

Acknowledgements

We would like to thank Dr Shweta Deshpande for creating and refining the tables for this review.

Financial support and sponsorship

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflicts of interest

The authors declare that there is no conflicts of interest.

References

1. Friedmann W, Vogel M, Dimer JS, Luttkus A, Büscher U, Dudenhausen JW. Perinatal differential diagnosis of cystic kidney disease and urinary tract obstruction: Anatomic pathologic, ultrasonographic and genetic findings. Eur J Obstet Gynecol Reprod Biol 2000;89:127-33.
2. Adams CM, Danks DM, Campbell PE. Comments upon the classification of infantile polycystic diseases of the liver and kidney, based upon three-dimensional reconstruction of the liver. J Med Genet 1974;11:234-43.
3. Bonsib SM. The classification of renal CYSTIC diseases and Other congenital malformations of the kidney and urinary tract. Published April 1, 2010. Available from: https://meridian.allenpress.com/apIm/article/134/4/554/461037/The-Classification-of-Renal-Cystic-Diseases-and. [Last accessed on 2021 Apr 15].
4. Avasthi P, Maser RL, Tran PV. Primary cilia in cystic kidney disease. Results Probl Cell Differ 2017;60:281-321.
5. Dell KM. The role of cilia in the pathogenesis of cystic kidney disease. Curr Opin Pediatr 2015;27:212-8.
6. Katabathina VS, Kota G, Dasyam AK, Shanbhogue AK, Prasad SR. Adult renal cystic disease: A genetic, biological, and developmental primer. Radiographics 2010;30:1509-23.
7. Khan Z, Pandey M, Samartha RM. Role of cytogenetic biomarkers in management of chronic kidney disease patients: A review. Int J Health Sci (Qassim) 2016;10:576-89.
8. Luciano RL, Dahl NK. Extra-renal manifestations of autosomal dominant polycystic kidney disease (ADPKD): Considerations for routine screening and management. Nephrol Dial Transplant 2014;29:247–54.
9. Rossetti S, Hopp K, Sikkink RA, Sundsbak JL, Lee YK, Kubly V, *et al*. Identification of gene mutations in autosomal dominant polycystic kidney disease through targeted resequencing. J Am Soc Nephrol 2012;23:915-33.
10. Park HC, Ryu H, Kim YC, Ahn C, Lee KB, Kim YH, *et al*. Genetic identification of inherited cystic kidney diseases for implementing precision medicine: A study protocol for a 3-year prospective multicenter cohort study. BMC Nephrol 2021;22:2.
11. Murcia NS, Sweeney WE Jr, Avner ED. New insights into the molecular pathophysiology of polycystic kidney disease. Kidney Int 1999;55:1187-97.
12. Pazour GJ, Dickert BL, Vucica Y, Seeley ES, Rosenbaum JL, Witman GB, *et al*. Chlamydomonas IFT88 and its mouse homologue, polycystic kidney disease gene tg737, are required for assembly of cilia and flagella. J Cell Biol 2000;151:709-18.
13. Praetorius HA, Spring KR. The renal cell primary cilium functions as a flow sensor. Curr Opin Nephrol Hypertens 2003;12:517-20.
14. Chiang AP, Nishimura D, Searby C, Elbedour K, Carmi R, Ferguson AL, *et al*. Comparative genomic analysis identifies an ADP-ribosylation factor-like gene as the cause of Bardet-Biedl syndrome (BBS3). Am J Hum Genet 2004;75:475-84.
15. Arjumand W, Sultana S. Role of VHL gene mutation in human renal cell carcinoma. Tumour Biol 2012;33:9-16.
16. Sun Z, Amsterdam A, Pazour G, Cole D, Miller M, Hopkins N. A genetic screen in zebrafish identifies cilia genes as a principal cause of cystic kidney. Development 2004;131:4085-93.
17. Boletta A, Germino GG. Role of polycystins in renal tubulogenesis. Trends Cell Biol 2003;13:484-92.
18. Huangfu D, Liu A, Rakeman AS, Murcia NS, Niswander L, Anderson KV. Hedgehog signalling in the mouse requires intraflagellar transport proteins. Nature 2003;426:83-7.
19. Desmet VJ. Congenital diseases of intrahepatic bile ducts: Variations on the theme "ductal plate malformation". Hepatology 1992;16:1069-83.
20. Johnson CA, Gissen P, Sergi C. Molecular pathology and genetics of congenital hepatorenal fibrocystic syndromes. J Med Genet 2003;40:311-9.
21. Majewski E, Oztürk B, Gillessen-Kaesbach G. Jeune syndrome with tongue lobulation and preaxial polydactyly, and Jeune syndrome with situs inversus and asplenia: Compound heterozygosity Jeune-Mohr and Jeune-Ivemark?. Am J Med Genet 1996;63:74-9.
22. McConnachie DJ, Stow JL, Mallett AJ. Ciliopathies and the kidney: A review. Am J Kidney Dis 2021;77:410-9.
23. Zerres K, Mücher G, Becker J, Steinkamm C, Rudnik-Schöneborn S, Heikkilä P, *et al*. Prenatal diagnosis of autosomal recessive polycystic kidney disease (ARPKD): Molecular genetics, clinical experience, and fetal morphology. Am J Med Genet 1998;76:137-44.
24. Bergmann C, Senderek J, Windelen E, Küpper F, Middeldorf I, Schneider F, *et al*. Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). Kidney Int 2005;67:829-48.
25. Hildebrandt F, Attanasio M, Otto E. Nephronophthisis: Disease mechanisms of a ciliopathy. J Am Soc Nephrol 2009;20:23-35.
26. Moore SJ, Green JS, Fan Y, Bhogal AK, Dicks E, Fernandez BA, *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: 352-60.
27. Tory K, Lacoste T, Burglen L, Morinière V, Boddaert N, Macher MA, *et al*. High NPHP1 and NPHP6 mutation rate in patients with Joubert syndrome and nephronophthisis: Potential epistatic effect of NPHP6 and AHI1 mutations in patients with NPHP1 mutations. J Am Soc Nephrol 2007;18:1566–75.
28. Zamora EA, Aeddula NR. Tuberous Sclerosis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538492/. [Updated 2020 Dec 01].
29. Steinberg S, Chen L, Wei L, Moser A, Moser H, Cutting G, *et al*. The PEX Gene screen: Molecular diagnosis of peroxisome biogenesis disorders in the Zellweger syndrome spectrum. Mol Genet Metab 2004;83:252-63.
30. Murphy EL, Droher ML, DiMaio MS, Dahl NK. Preimplantation genetic diagnosis counseling in autosomal dominant polycystic kidney disease. Am J Kidney Dis 2018;72:866-72.
31. Sweeney WE. "Polycystic Kidney Disease, Autosomal Recessive." GeneReviews®., U.S. National Library of Medicine, 14 Feb. 2019. Available from: www.ncbi.nlm.nih.gov/books/NBK1326/.
32. Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, *et al*. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature 2017;549:519-22.
33. Parisi M, Glass I. Joubert syndrome. 2003 Jul 9. In: Adam MP, Ardinger HH, Pagon RA, *et al*., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1325/. [Updated 2017 Jun 29].

34. Raina R, Chakraborty R, DeCoy ME, Kline T. Autosomal-dominant polycystic kidney disease: Tolvaptan use in adolescents and young adults with rapid progression. Pediatr Res 2021;89:894-9.
35. Torres VE. Pro: Tolvaptan delays the progression of autosomal dominant polycystic kidney disease. Nephrol Dial Transplant 2019;34:30-4.
36. Rossetti S, Consugar MB, Chapman AB, Torres VE, Guay-Woodford LM, Grantham JJ, *et al*. Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. J Am Soc Nephrol 2007;18:2143-60.
37. Cornec-Le Gall E, Audrézet MP, Chen JM, Hourmant M, Morin MP, Perrichot R, *et al*. Type of PKD1 mutation influences renal outcome in ADPKD. J Am Soc Nephrol 2013;24:1006-13.
38. Lanktree MB, Guiard E, Li W, Akbari P, Haghighi A, Iliuta IA, *et al*. Intrafamilial variability of ADPKD. Kidney Int Rep 2019;4:995-1003.
39. Tan AY, Blumenfeld J, Michaeel A, Donahue S, Bobb W, Parker T, *et al*. Autosomal dominant polycystic kidney disease caused by somatic and germline mosaicism. Clin Genet 2015;87:373-7.
40. Tan AY, Michaeel A, Liu G, Elemento O, Blumenfeld J, Donahue S, *et al*. Molecular diagnosis of autosomal dominant polycystic kidney disease using next-generation sequencing. J Mol Diagn 2014;16:216-28.
41. Cornec-Le Gall E, Chebib FT, Madsen CD, Senum SR, Heyer CM, Lanpher BC, *et al*. The value of genetic testing in polycystic kidney diseases illustrated by a family with PKD2 and COL4A1 mutations. Am J Kidney Dis 2018;72:302-8.
42. Liu M, Shi S, Senthilnathan S, Yu J, Wu E, Bergmann C, *et al*. Genetic variation of DKK3 may modify renal disease severity in ADPKD. J Am Soc Nephrol 2010;21:1510-20.
43. Halvorson CR, Bremmer MS, Jacobs SC. Polycystic kidney disease: Inheritance, pathophysiology, prognosis, and treatment. Int J Nephrol Renovasc Dis 2010;3:69-83.
44. Reiterová J, Štekrová J, Merta M, Kotlas J, Elišáková V, Lněnička P, *et al*. Autosomal dominant polycystic kidney disease in a family with mosaicism and hypomorphic allele. BMC Nephrol 2013;14:59.
45. Guay-Woodford LM, Muecher G, Hopkins SD, Avner ED, Germino GG, Guillot AP, *et al*. The severe perinatal form of autosomal recessive polycystic kidney disease maps to chromosome 6p21.1-p12: Implications for genetic counseling. Am J Hum Genet 1995;56:1101-7.
46. Zhang MZ, Mai W, Li C, Cho SY, Hao C, Moeckel G, *et al*. 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.
47. Zhang J, Wu M, Wang S, Shah JV, Wilson PD, Zhou J. Polycystic kidney disease protein fibrocystin localizes to the mitotic spindle and regulates spindle bipolarity. Hum Mol Genet 2010;19:3306-19.
48. Olson RJ, Hopp K, Wells H, Smith JM, Furtado J, Constans MM, *et al*. Synergistic Genetic Interactions between Pkhd1 and Pkd1 Result in an ARPKD-Like phenotype in murine models. J Am Soc Nephrol 2019;30:2113-27.
49. Bergmann C, Senderek J, Sedlacek B, Pegiazoglou I, Puglia P, Eggermann T, *et al*. Spectrum of mutations in the gene for autosomal recessive polycystic kidney disease (ARPKD/PKHD1). J Am Soc Nephrol 2003;14:76-89.
50. Bergmann C, Senderek J, Küpper F, Schneider F, Dornia C, Windelen E, *et al*. PKHD1 mutations in autosomal recessive polycystic kidney disease (ARPKD). Hum Mutat 2004;23:453-63.
51. Wolf MT. Nephronophthisis and related syndromes. Curr Opin Pediatr 2015;27:201-11.
52. Young TL, Woods MO, Parfrey PS, Green JS, Hefferton D, Davidson WS. A founder effect in the newfoundland population reduces the Bardet-Biedl syndrome I (BBS1) interval to 1 cM. Am J Hum Genet 1999;65:1680-7.
53. Farag TI, Teebi AS. Bardet-Biedl and Laurence-Moon syndromes in a mixed Arab population. Clin Genet 1988;33:78-82.
54. Badano JL, Kim JC, Hoskins BE, Lewis RA, Ansley SJ, Cutler DJ, *et al*. Heterozygous mutations in BBS1, BBS2 and BBS6 have a potential epistatic effect on Bardet-Biedl patients with two mutations at a second BBS locus. Hum Mol Genet 2003;12:1651-9.
55. Muller J, Stoetzel C, Vincent MC, Leitch CC, Laurier V, Danse JM, *et al*. Identification of 28 novel mutations in the Bardet-Biedl syndrome genes: The burden of private mutations in an extensively heterogeneous disease. Hum Genet 2010;127:583-93.
56. Brancati F, Dallapiccola B, Valente EM. Joubert Syndrome and related disorders. Orphanet J Rare Dis 2010;5:20.
57. Sattar S, Gleeson JG. The ciliopathies in neuronal development: A clinical approach to investigation of Joubert syndrome and Joubert syndrome-related disorders. Dev Med Child Neurol 2011;53:793-8.
58. Fleming LR, Doherty DA, Parisi MA, Glass IA, Bryant J, Fischer R, *et al*. Prospective evaluation of kidney disease in joubert syndrome. Clin J Am Soc Nephrol 2017;12:1962-73.
59. Devuyst O, Olinger E, Weber S, Eckardt KU, Kmoch S, Rampoldi L, *et al*. Autosomal dominant tubulointerstitial kidney disease. Nat Rev Dis Primers 2019;5:60.
60. Crane DI, Maxwell MA, Paton BC. PEX1 mutations in the Zellweger spectrum of the peroxisome biogenesis disorders. Hum Mutat 2005;26:167-75.
61. Klouwer FCC, Berendse K, Ferdinandusse S, Wanders RJ, Engelen M, Poll-The BT. Zellweger spectrum disorders: Clinical overview and management approach. Orphanet J Rare Dis 2015;10:151.
62. Northrup H, Koenig MK, Pearson DA, Au KS. Tuberous Sclerosis Complex. In: Adam MP, Ardinger HH, Pagon RA, *et al*., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; July 13, 1999.
63. Green AJ, Smith M, Yates JR. Loss of heterozygosity on chromosome 16p13.3 in hamartomas from tuberous sclerosis patients. Nat Genet 1994;6:193-6.
64. Povey S, Burley MW, Attwood J, Benham F, Hunt D, Jeremiah SJ, *et al*. Two loci for tuberous sclerosis: One on 9q34 and one on 16p13. Ann Hum Genet 1994;58:107-27.
65. Smith M. Mapping of the tuberous sclerosis g3enes. Int J Neurol 1991;25-26:81-8.
66. Krueger DA, Northrup H, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex surveillance and management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013;49:255-65
67. Kothare SV, Singh K, Chalifoux JR, Staley BA, Weiner HL, Menzer K, *et al*. Severity of manifestations in tuberous sclerosis complex in relation to genotype. Epilepsia 2014;55:1025-9.
68. Wilbur C, Sanguansermsri C, Chable H, Anghelina M, Peinhof S, Anderson K, *et al*. Manifestations of tuberous sclerosis complex: The experience of a provincial clinic. Can J Neurol Sci 2017;44:35-43.
69. Braverman NE, Raymond GV, Rizzo WB, Moser AB, Wilkinson ME, Stone EM, *et al*. Peroxisome biogenesis disorders in the Zellweger spectrum: An overview of current diagnosis, clinical manifestations, and treatment guidelines. Mol Genet Metab 2016;117:313-21.
70. Pericak-Vance MA, Nunes KJ, Whisenant E, Loeb DB, Small KW,

Stajich JM, *et al*. Genetic mapping of dinucleotide repeat polymorphisms and von Hippel-Lindau disease on chromosome 3p25-26. J Med Genet 1993;30:487-91.

71. Alves MR, Carneiro FC, Lavorato-Rocha AM, WH DC, IW DC, Zequi S DC, *et al*. Mutational status of VHL gene and its clinical importance in renal clear cell carcinoma. Virchows Arch 2014;465:321-30.
72. Varshney N, Kebede AA, Owusu-Dapaah H, Lather J, Kaushik M, Bhullar JS. A review of von Hippel-Lindau syndrome. J Kidney Cancer VHL 2017;4:20-9.
73. Lai Y, Song M, Hakala K, Weintraub ST, Shiio Y. Proteomic dissection of the von Hippel-Lindau (VHL) interactome. J Proteome Res 2011;10:5175-82.
74. Binderup ML, Galanakis M, Budtz-Jørgensen E, Kosteljanetz M, Luise Bisgaard M. Prevalence, birth incidence, and penetrance of von Hippel-Lindau disease (vHL) in Denmark. Eur J Hum Genet 2017;25:301-7.
75. Sahney S, Weiss L, Levin NW. Genetic counseling in adult polycystic kidney disease. Am J Med Genet 1982;11:461-8.
76. Gimpel C, Avni FE, Bergmann C, Cetiner M, Habbig S, Haffner D, *et al*. Perinatal diagnosis, management, and follow-up of cystic renal diseases: A clinical practice recommendation with systematic literature reviews. JAMA Pediatr 2018;172:74-86.

Supplement A: Genes associated with cystic kidney diseases[10]

Cystic diseases	Associated Gene (s)
ADPKD	GANAB
	PKD1
	PKD2
	MUC1
	UMOD
Alport syndrome	COL4A3
	COL4A4
	COL4A5
ARPKD	PKHD1
Branchio-oto-renal dysplasia syndrome	EYA1
Cilia-associated cystic genes	CYS1
	DYNC2H1
	IFT140
	IFT172
	IFT80
	WDR34
	WDR35
	WDR60
Cilia-associated cystic genes, phenotype resembling ADPKD	IFT88
ER candidate gene (polycystic liver)	ATF6B
	ATXN3
	CAPN2
	EDEM3
	HSP90AA1
	HSPA6
	HYOU1
	NGLY1
	PARK2
	SEC24B
	SEC24C
	SEC24D
	SEC31A
	SEC31B
	SEC61A1
	SEC61A2
	SEC62
	TXNDC5
	UBE4B
	UGGT1
	UGGT2
	WFS1
Familial hyperproteinemia, high blood pressure	REN
Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps	COL4A1
Joubert syndrome	INPP5E
	KIAA0586
	AHI1
	ARL13B
	C5ORF42
	CC2D2A

Contd...

Supplement A: Contd...

Cystic diseases	Associated Gene (s)
	CEP120
	CSPP1
	TCTN2
	TMEM216
Joubert syndrome/MKS	MKS1
	RPGRIP1L
Karyomegalic interstitial nephritis	FAN1
Neonatal diabetes, hypothyroid, and cystic kidney disease	GLIS3
NPHP	CEP164
	GLIS2
	INVS
	IQCB1
	NEK8
	NPHP3
	NPHP4
	SDCCAG8
	TTC21B
	WDR19
NPHP/Joubert syndrome/MKS	TMEM67
NPHP/MKS	CEP290
OFD	OFD1
Optic nerve coloboma, renal hypoplasia	PAX2
Polycystic kidney and liver diseases	XBP1
Polycystic kidney disease	AVP
	AVPR2
	NEK1
Polycystic kidney disease with hyperinsulinemic, hypoglycemia	PMM2
Polycystic liver disease	ALG8
	LRP5
	PRKCSH
	SEC61B
	SEC63
Renal cysts and diabetes syndrome	HNF1B
Tuberous sclerosis complex	TSC1
	TSC2
Von Hippel-Lindau syndrome	VHL