An approach to cystic kidney diseases: the clinician's view

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Abstract | Advances in molecular genetics have led to the identification of more than 70 different genes involved in the development of cystic kidney diseases. Most of these diseases are rare, and interpreting the resultant plethora of disease-causing mutations requires a methodical and meticulous approach to differential diagnosis. In this Review we discuss a clinical approach to the diagnosis of cystic kidney diseases in adults, for use by nephrologists. This approach is based upon a thorough clinical evaluation, which considers both kidney phenotype and extrarenal manifestations of the underlying disorder, in combination with genetic testing in selected patients. In our view, cystic kidney disease can (in the majority of patients) be reliably classified on the basis of clinical findings. We therefore propose that defining clinical situations to precipitate the initiation of genetic testing is mandatory and cost-effective. New techniques such as next-generation sequencing will facilitate the diagnosis of cystic kidney diseases in the future, increasing diagnostic safety in a subset of patients. In renal tumour syndromes, genetic testing is warranted.

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Introduction

Advances in molecular genetics have encouraged attempts to unify the diverse spectrum of cystic kidney diseases under the pathophysiological concept of the ciliopathies.[1–5] Cilia are small, hair-like cellular organelles present on almost all vertebrate cells. By sensing extracellular signals and transferring them to the interior of the cell, cilia regulate distinct functions such as cellular proliferation, differentiation, epithelial cell polarity, nerve growth and tissue maintenance.[6,7] The cilia-associated disorders include a variety of different entities, ranging from autosomal dominant and autosomal recessive forms of polycystic kidney disease (ADPKD and ARPKD, respectively) to nephronophthisis, Senior–Løken syndrome, Joubert syndrome, Meckel–Gruber syndrome, Bardet–Biedl syndrome, von Hippel–Lindau syndrome and tuberous sclerosis complex (Table 1).

Even though many of these disorders become symptomatic in childhood and adolescence, patients often still present to the adult nephrology clinic without a diagnosis or, in rare cases, experience onset of the first symptoms in adulthood. Understanding the various rare cystic kidney syndromes is, therefore, important for nephrologists who manage adult patients to enable adequate counselling of the patient and their families.

A large variety of gene mutations can lead to the development of cystic kidneys as part of different diseases and syndromes.[8–13] The list of novel and interesting disease-related loci is constantly growing, and now includes more than 70 different genes.[14–20] Distinct genetic cystic kidney disease syndromes vary with regard to their mode of inheritance, age of onset of disease, and severity of renal and extrarenal phenotypes. However, most cystic kidney diseases are rare, and nephrologists are confronted with an increasing number of different gene mutations involved in a large variety of diseases. In fact, this complexity is even greater than the absolute number suggests, since mutations in the same genes can cause different disorders, and different phenotypes are manifested as a result of mutations of one or more genes. For example, mutations in the gene *CEP290* (also known as *NPHP6, BBS14* and *KIAA0373)* can manifest as a variety of different disease phenotypes, such as nephronophthisis, Senior–Løken syndrome, Joubert syndrome, Bardet–Biedl syndrome and Meckel–Gruber syndrome. Approximately 90 of the known *CEP290* mutations result exclusively in only one phenotype, but 14 mutations can lead to either of two different phenotypes, and eight mutations to three or more different phenotypes.[8] The clinical presentation of *CEP290*-related disease is presumably also influenced by second-site modifier genes.[8] Thus, predicting the *CEP290*-related phenotype from a given mutation is almost impossible. Moreover, nephronophthisis (a classic cystic disease manifestation) can be caused by mutations in more than a dozen different genes (Table 2), and additional phenotypic overlaps will probably be described in the future. Mutations in genes that are not overtly cilia-related, such as *XPNPEP3* and *SLC41A1,* can also cause cystic kidney disease.[21,22] These examples stress the importance of a careful clinical evaluation of patients who present to the nephrologist with cystic kidneys, and illustrate that genetic testing alone is not always helpful for clinicians and their patients.

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Key points

- Cystic kidney diseases are multisystemic disorders that present with distinct extrarenal manifestations
- Cystic kidney diseases are regarded as ciliopathies, since almost all of the >70 different genes implicated in these diseases have products that have been linked to the biology and function of primary cilia
- The most prevalent cystic kidney disease in adulthood is autosomal dominant polycystic kidney disease
- Diagnosis of cystic kidney diseases requires a thorough clinical workup, taking into account not only kidney size and cyst localization, but also extrarenal manifestations
- The utility of genetic testing varies greatly between diseases; however, testing is generally warranted in cystic kidney diseases accompanied by renal tumours
- New techniques such as next-generation sequencing will facilitate the genetic diagnosis of cystic kidney diseases

In this Review, we describe a strategy for nephrologists and clinicians to improve the classification of adult patients presenting with cystic kidney disease. Classification is based on clinical findings and radiological criteria, which are tailored to correctly diagnose ADPKD or identify phenotypes that suggest other much less common disorders (Figure 1).

Kidney size and cyst localization

Clinical assessment of patients with cystic kidneys should always involve documentation of kidney size and the localization of cysts (Figure 1). In healthy individuals, sporadic renal cysts are quite common, although multiple cysts are rare. One cyst is present in 1.7% of healthy individuals aged 30–49 years, in 11.5% of individuals aged 50–70 years and in 22.1% of those older than 70 years.[23] Bilateral renal cysts can be visualized in 1%, 4% and 9% of the same age groups, respectively.[23]

ADPKD and ARPKD are always accompanied by renal cysts, and even in early stages of ADPKD, cysts can be found throughout the cortex and medulla (Figure 2). In other disease entities such as nephronophthisis, Senior–Løken syndrome, Joubert syndrome, Bardet–Biedl syndrome, Meckel–Gruber syndrome, von Hippel–Lindau syndrome or tuberous sclerosis complex, renal cysts are not an obligatory finding; moreover, in nephronophthisis and medullary cystic kidney disease (MCKD), cysts are found predominantly at the corticomedullary junction (Figure 3). In von Hippel-Lindau syndrome and tuberous sclerosis complex, kidney size is usually enlarged whereas in syndromes characterized by nephronophthisis, kidney size is normal or small.

ADPKD

Estimates of the prevalence of ADPKD vary from 1 in 400 to 1 in 1,000 of the population,[10] and 5% of patients with end-stage renal disease (ESRD) have ADPKD.[10,13] Thus, adult patients who present with polycystic kidney disease are most likely to have ADPKD, which is by far the most common renal cystic disorder worldwide.[9] ADPKD is characterized by enlarged kidneys containing multiple cysts throughout the kidney.[24] Cysts can also occur in other organs, including the liver and (less commonly) the pancreas, seminal vesicles and ovaries (Figure 2). APDKD has a more progressive disease course in men than in women, since affected women usually exhibit smaller kidney size and develop ESRD later in life than affected men.[11]

Genetic basis and pathophysiology

Two genes underlying ADPKD have been identified, *PKD1* on chromosome 16p13.3 (85% of cases) and *PKD2* on chromosome 4p21 (15% of cases), encoding two distinct proteins, polycystin-1 and polycystin-2 (~460 and ~110 kDa, respectively).[10,12] Polycystin-1 is a receptor for an as yet unidentified ligand, whereas polycystin-2 forms a nonselective calcium channel.[13] These proteins constitute a mechanosensory ion channel complex, and have an important function in tubular differentiation and maintenance.[13,14] Both proteins localize to primary cilia and are essential for their correct function.

ADPKD is inherited in an autosomal dominant manner. However, the resulting genetic defect is recessive, since it requires mutations in both alleles. Thus, final cyst formation in the kidney and liver is presumably triggered by an additional somatic mutation of the second allele in a limited number of cells (second-hit hypothesis)[25] leading to cellular proliferation and increased fluid secretion.[26–29] Moreover, research in mouse models suggests that additional mechanisms such as changes in the extracellular matrix and interstitial inflammation also contribute to the formation of cysts.[13,30] Polycystin-1 and polycystin-2 are not only expressed in kidney tissue, but also in bile duct epithelium, bronchial epithelium and vascular smooth muscle cells.[31–35] Patients with ADPKD might also develop liver and pancreatic cysts, and less commonly, intracranial aneurysms, arachnoid cysts, abdominal hernias, cardiac complications (valve abnormalities, left ventricular hypertrophy), male infertility, intestinal diverticulosis and bronchiectasis.[10,15] In a few patients, ADPKD is accompanied by congenital hepatic fibrosis.[36]

A defect in urine-concentrating capability with onset in childhood is common in patients with ADPKD,[13,16] many of whom also report polydipsia and polyuria at an early stage of disease. These symptoms have been linked to an altered osmolality–vasopressin regulatory axis.[17,18] Interestingly, kidney function is well preserved, despite continuous cyst growth and kidney enlargement.[13] By the time renal dysfunction is evident, both kidneys show little recognizable parenchyma. At this stage, glomerular filtration rate declines at a rate of 4.4–5.9 ml/min/1.73 m^2 per year on average.[19] Apart from renal insufficiency, adults with ADPKD might initially present with haematuria or hypertension (even before decline in kidney function), and occasionally these symptoms are detected in childhood. Children might also present with flank and back pain, as well as impaired urine-concentrating capacity.[37] Later in life, urinary tract infections or a palpable abdominal mass might occur. Glomerular filtration rate continues to decline gradually, eventually leading to ESRD by 55–75 years of age in patients with *PKD1* mutations and around 20 years later in patients with *PKD2* mutations who exhibit a milder course of disease.[20,38]

Table 1 | Characteristics of the ciliopathies

Syndrome	Renal manifestations	Extrarenal manifestations	Genetic basis
ADPKD	Urine-concentrating defects, enlarged kidneys with continuous growth of cysts throughout, haematuria, hypertension, decline in glomerular filtration rate with advancing age[9,16,19,37]	Liver and pancreatic cysts, intracranial aneurysms, arachnoid cysts, abdominal hernias, cardiac complications (valve abnormalities, left ventricular hypertrophy), male infertility, intestinal diverticulosis, bronchiectasis[10,15]	Mutations in *PKD1* and *PKD2* account for 91% of all cases[10,12]
ARPKD	Chronic renal insufficiency, multiple renal cysts[65–67]	Biliary dysgenesis, congenital hepatic fibrosis, hepatosplenomegaly, hepatic complications, cholangitis, cholangiocarcinomas[65–67]	Mutations in *PKHD1*[145,146]
NPHP	Polydipsia, polyuria, urine-concentrating defects and secondary enuresis in childhood;[74] tubulointerstitial nephropathy, corticomedullary cysts, tubular basement membrane thickening and disruption	Numerous possible extrarenal complications, largely depending upon the exact mutation[74] Many extrarenal complications of NPHP are described as separate syndromes	18 known subtypes (NPHP1–18), accounting for 40% of cases[72,76,77]
MCKD	Tubulointerstitial nephritis, renal cysts, hyperuricaemia, gout, small-sized kidneys[96–98]	None identified to date	*MUC1* mutations are associated with type 1 disease;[100–102] mutations in *UMOD1* account for 17.8% of type 2 disease
Senior–Løken syndrome	Similar to NPHP	Retinitis pigmentosa[73]	Always observed in NPHP5 and NPHP6, can also occur in most other subtypes of NPHP except NPHP7[74]
Joubert syndrome	Similar to NPHP	Cerebellar vermis hypoplasia or aplasia, liver fibrosis, retinitis pigmentosa, coloboma of the eye, altered neonatal respiration[73,86,87]	Mutations in 21 different genes[153]
Meckel–Gruber syndrome	Similar to NPHP	Bilateral postaxial hexadactyly, hepatobiliary ductal dysgenesis causing fibrocystic liver disease, CNS malformations, usually occipital encephalocele[82]	Mutations in 11 different genes[154]
Bardet–Biedl syndrome	Similar to NPHP	Polydactyly, juvenile obesity, mental retardation, retinal defects, anosmia, hypogonadism[93]	BBS1–19 account for 80% of cases[95]
VHL syndrome	Renal cell carcinoma, multiple renal cysts, resembling ADPKD[127]	Haemangioblastomas in the CNS (retina, brain and spinal cord); possible phaeochromocytomas, pancreatic cysts, pancreatic neuroendocrine tumours, endolymphatic sac tumours of the inner ear, cystadenomas of the epididymis and broad ligament[127]	Autosomal dominant mutations in *VHL*[128,129,131]
Tuberous sclerosis complex	Renal cell carcinoma, angiomyolipoma, sometimes multiple renal cysts	Hypomelanotic macules, epilepsy, cognitive dysfunction, behavioural disturbances, developmental disorders	Mainly sporadic *TSC1* or *TSC2* germ line mutations[125]

Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; BBS, Bardet–Biedl syndrome; CNS, central nervous system; MCKD, medullary cystic kidney disease; NPHP, nephronophthisis; VHL, von Hippel–Lindau syndrome.

Risk factors for disease progression include gross haematuria before 30 years of age, degree of proteinuria and early onset hypertension.[39,40] Potentially modifiable factors for disease progression are high urinary NaCl excretion, high 24 h urinary osmolarity, and low plasma HDL cholesterol levels.[41–43]

Diagnosis

In a patient with a positive family history, ADPKD is diagnosed by imaging techniques. According to established ultrasonography criteria published in 1993,[44] at least two (unilateral or bilateral) renal cysts are sufficient to diagnose ADPKD in patients younger than 30 years. For patients aged 30–59 years, at least two cysts in each kidney are required, whereas in patients ≥60 years, four cysts in each kidney are required to establish the diagnosis.[44] However, these criteria offered only 67% sensitivity for diagnosing ADPKD in patients with *PKD2* mutations who were below 30 years of age.[45] Thus, in 2009, the ultrasonography criteria for diagnosis of ADPKD were redefined to reflect the advances in this imaging technique.[46] In families of unknown genotype, three or more unilateral or bilateral cysts were reported to be sufficient for diagnosis of ADPKD in patients aged 15–39 years, two or more cysts in each kidney for patients aged 40–59 years, and four or more cysts in each kidney for patients ≥60 years of age.[46] These new criteria provide increased diagnostic certainty, especially for patients with *PKD2* mutations since the initial diagnostic criteria were only evaluated in patients with *PKD1* mutations. Patients with *PKD2* mutations usually have a milder phenotype and later onset of disease.

It is important to emphasize that these diagnostic criteria have been defined for ultrasonography only,

Table 2 | Genetic and phenotypic overlap between NPHP subtypes

NPHP subtype	OMIM entry	Gene	Chromosomal locus	Additional gene names
NPHP1	256,100	*NPHP1*	2q13	*SLSN1, JBTS4*
NPHP2	602,088	*INVS*	9q22-31.1	None
NPHP3	604,387	*NPHP3*	3q21.1	*SLSN3, MKS7*
NPHP4	606,966	*NPHP4*	1p36	*SLSN4*
NPHP5	609,237	*IQCB1*	3q13.33	*SLSN5*
NPHP6	610,188	*CEP290*	12q21.32	*SLSN6, BBS14, MKS4, JBTS5*
NPHP7	611,498	*GLIS2*	16p13	None
NPHP8	610,937	*RPGRIP1L*	16q12.2	*MKS5, JBTS7*
NPHP9	613,824	*NEK8*	17q11	None
NPHP10	613,524	*SDCCAG8*	1q43	*SLSN7*
NPHP11	613,550	*TMEM67*	8q22	*BBS14, MKS3, JBTS6*
NPHP12	613,820	*TTC21B*	2q24	*JBTS11, SRTD4*
NPHP13	614,377	*WDR19*	4p14	*SRTD5, CED4*
NPHP14	614,844	*ZNF423*	16	*JBTS19*
NPHP15	614,845	*CEP164*	11q23.3	*SLSN, MKS*
NPHP16	615,382	*ANKS6*	9q22	None
NPHP17	615,630	*IFT172*	2p23.3	*SRTD10*
NPHP18	615,862	*CEP83*	12q22	None

NPHP subtypes show considerable phenotypic and genetic overlap with other syndromes (as is also true of each of these syndromes, not shown). Abbreviations: BBS, Bardet–Biedl syndrome; CED, cranioectodermal dysplasia; JBTS, Joubert syndrome; MKS, Meckel–Gruber syndrome; NPHP, nephronophthisis; SLSN, Senior–Løken syndrome; SRTD, short-rib thoracic dysplasia with or without polydactyly.

and not for MRI or CT, since the latter techniques are more sensitive than ultrasonography for detecting cysts. T2-weighted MRI is much better than ultrasonography for detecting small cysts down to 2 mm diameter, but the number of cysts detected in histological samples is still 60 times higher than that detected by MRI.[47] Although ultrasonography might be of limited use for disease exclusion in patients younger than 30 years, it is not clear whether performing an additional MRI or CT evaluation would outperform modern, state-of-the-art ultrasonography in terms of diagnostic accuracy.

In the absence of a family history of cystic kidney disease, the presence of bilaterally enlarged kidneys with multiple cysts or bilateral renal cysts as well as hepatic cysts might suggest ADPKD—assuming that any additional renal or extrarenal manifestations do not point towards a different disease. Although patients with ADPKD develop renal cell carcinoma at a comparable rate to the normal population, detection of a renal mass might suggest a tumour syndrome independent of ADPKD, especially in the case of multiple lesions. Renal cell carcinomas and angiomyolipomas of the kidney strongly suggest non-ADPKD tumour syndromes, such as von Hippel–Lindau disease and tuberous sclerosis complex.[48–50] If renal involvement is asymmetrical and strictly or mostly unilateral cystic localization is present, then nonprogressive localized renal cystic disease, segmental multicystic dysplasia, or cystic tumours should be considered.[9] Rarely, medullary sponge kidney can have a similar presentation to ADPKD. In this cystic kidney disorder, the cysts originate from collecting ducts and are limited to the medullary pyramids, sparing the renal cortex.[51,52]

Extrarenal manifestations

It is important to stress that all genetic cystic kidney diseases are multiorgan and multisystem disorders. This characteristic is due to the fact that the pathophysiology of cystic renal diseases involves dysfunction of cilia. Almost all organs of the human body depend to some degree on cilia-controlled morphogenetic events during development and cilia-controlled physiology later in life, which explains the varied extrarenal phenotypes associated with cystic kidney diseases.

The most common extrarenal manifestation of ADPKD is polycystic liver disease, in which cysts originate from biliary ducts and peribiliary glands. Large hepatic cysts are more frequent in women than in men,[13,15] because oestrogens increase cell proliferation in hepatic cysts; thus, women with multiple pregnancies or taking oral contraceptives generally exhibit the most severe cystic liver disease.[53,54] Oestrogen-free contraception should, therefore, be recommended for female patients with ADPKD. Usually, hepatic cysts become clinically apparent late in the course of the disease, when they induce mechanical impairment of adjacent structures. Although liver function is typically unaffected, hepatic complications might occur that require specific treatment.[13] Cysts are also present in the pancreas and seminal vesicles. However, whether female patients with ADPKD have an increased rate of ovarian cyst formation is currently unclear.[55]

The prevalence of intracranial aneurysms is approximately five times higher in patients with ADPKD than in the general population. Screening for intracranial aneurysms by MRI is, therefore, recommended in patients with ADPKD who fulfil one or more of the following criteria: a positive family history for intracranial aneurysms, symptoms such as severe or atypical headaches, cranial nerve palsy or transient ischaemic attack and patients who are scheduled for major surgery, receiving long-term anticoagulation therapy or in high-risk professions such as pilots or bus drivers.[15,56] Asymptomatic intracranial aneurysms are detected by screening in 6–12% of patients with ADPKD without a family history of stroke or intracranial aneurysms, and in 16–21% of patients with a positive family history of these conditions.[57–59] Current ADPKD management guidelines do not suggest general screening. However, if the results of screening are negative, re-screening of patients at 5-year intervals is advisable. For patients with small untreated intracranial aneurysms, annual MRI screening is suggested in the beginning, but the screening intervals can be increased in patients whose aneurysm size remains stable.[59]

Cardiac manifestations of ADPKD include mitral valve prolapse in 25% of patients, aortic insufficiency, tricuspid insufficiency and tricuspid valve prolapse.[60] Echocardiography is recommended if a heart murmur is detected. Colonic diverticula as well as diverticulitis are more frequent in patients with ESRD owing to ADPKD, although autopsy studies revealed that the

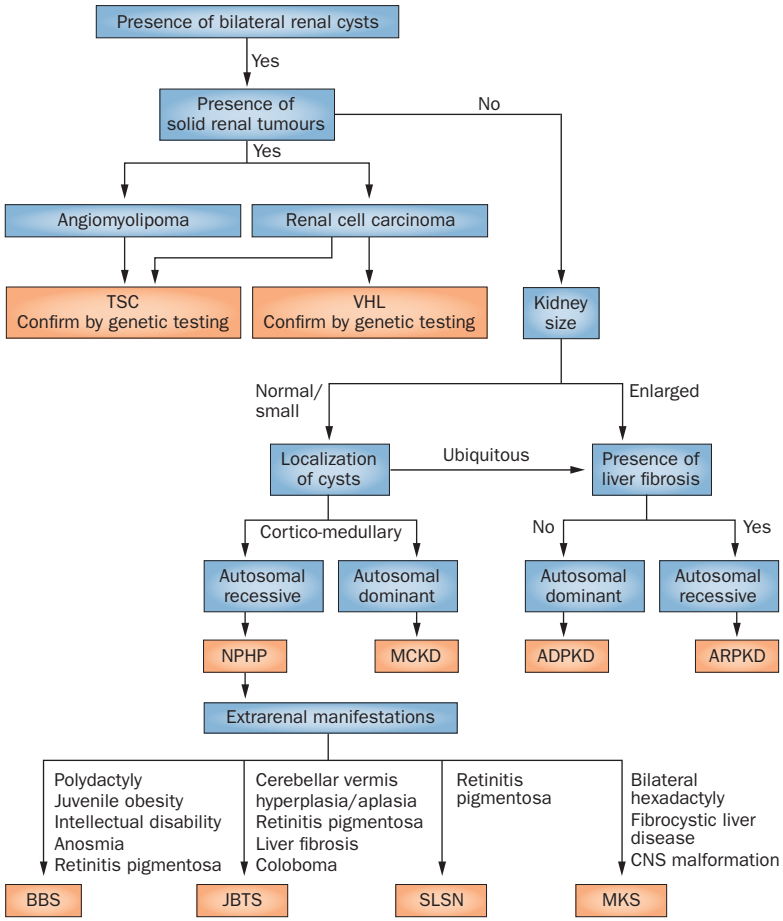

Figure 1 | Diagnostic work-up of cystic kidney disease. There is significant overlap between syndromes. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease; BBS, Bardet–Biedl syndrome; CNS, central nervous system; JBTS, Joubert syndrome; MCKD, medullary cystic kidney disease; MKS, Meckel–Gruber syndrome; NPHP, nephronophthisis; SLSN, Senior–Løken syndrome; TSC, tuberous sclerosis complex; VHL, von Hippel–Lindau syndrome.

prevalence of diverticula in this group is no higher than in the general population.[61,62]

Non-ADPKD renal cystic diseases

Several extrarenal features that might be a hallmark of specific non-ADPKD renal cystic diseases should be considered during the diagnostic work-up of patients who present with cystic kidney disease.

ARPKD

The incidence of ARPKD varies from 1:20,000 to 1:40,000 in white people of European origin, but members of all ethnic groups are affected.[63,64] ARPKD is a rare disorder that can manifest as classic Caroli syndrome in combination with renal cysts (Figure 2). ARPKD is caused by mutations in the *PKHD1* gene on chromosome 6p12, which encodes a multidomain integral membrane protein called fibrocystin (also known as polycystic kidney and hepatic disease 1 protein or polyductin).

The presence of enlarged polycystic kidneys can sometimes lead nephrologists to mistake ARPKD for the more common ADPKD if extrarenal manifestations are not taken into account. However, the first-time finding of large polycystic kidneys in an adult patient without hepatic fibrosis makes ARPKD a highly unlikely diagnosis, as the predominant characteristics in adult patients presenting with ARPKD and fairly well-preserved kidney function are hepatosplenomegaly and hepatic fibrosis.[65–67] Although chronic renal insufficiency is also present in adult patients, complications of liver disease (such as portal hypertension) are the most frequent reasons for seeking medical attention.[66] Recurrent cholangitis is not uncommon, and adults with ARPKD are at increased risk of cholangiocarcinomas.[65] Complications of liver disease can also impair the long-term outcome of patients with ARPKD after renal transplantation.[68]

Ultrasound scans of kidneys in children with ARPKD show increased echogenicity of both cortex and medulla, caused by increased reflection of ultrasound waves by microcystic dilated collecting ducts.[69] At later stages, multiple renal cysts develop that are ubiquitously localized throughout the kidney, thereby mimicking the ultrasonographic appearance of ADPKD. In adults with well-preserved renal function, the kidneys might be normal in size or are only slightly enlarged, with a few cysts.[65,70] Furthermore 71% of patients with ARPKD present with nephrocalcinosis and/or small medullary or papillary stones.[66]

ARPKD is always associated with biliary dysgenesis, some degree of congenital hepatic fibrosis and dilatation of the intrahepatic bile ducts. Thus, ARPKD is normally diagnosed *in utero* or shortly after birth,[63,67,71] although a minority of patients are diagnosed as adolescents or even adults.[66] The characteristic histological features of ARPKD are fusiform dilatation of the renal collecting ducts and distal tubuli combined with defects in the ductal plate and hyperplasia of biliary ducts.[71] Biliary dysgenesis leads to both congenital hepatic fibrosis and Caroli disease (dilatation of the intrahepatic bile ducts). Mortality is 25–30% in newborn babies affected by ARPKD, and most of these deaths are caused by respiratory insufficiency. Almost 50% of children with ARPKD progress to ESRD by the age of 10 years. The 15-year survival of infants with ARPKD surviving the first year of age is 67–79%.[67]

The diagnosis of ARPKD can be established by the detection of enlarged, echogenic kidneys showing reduced corticomedullary differentiation at ultrasonography, plus at least one of the following criteria: no renal cysts detected by ultrasound scanning in both parents, particularly if the parents are more than 40 years of age; radiographic, clinical or laboratory evidence of hepatic fibrosis; hepatic pathology that indicates ductal plate abnormalities; existence of a sibling with confirmed ARPKD; and parental consanguinity or a family history of autosomal recessive disease.[67]

Nephronophthisis and related disorders

Nephronophthisis, an autosomal recessive cystic kidney disease, is clinically characterized by normal or slightly reduced kidney size (Figure 3), except for the rare infantile nephronophthisis type 2, in which kidneys are moderately

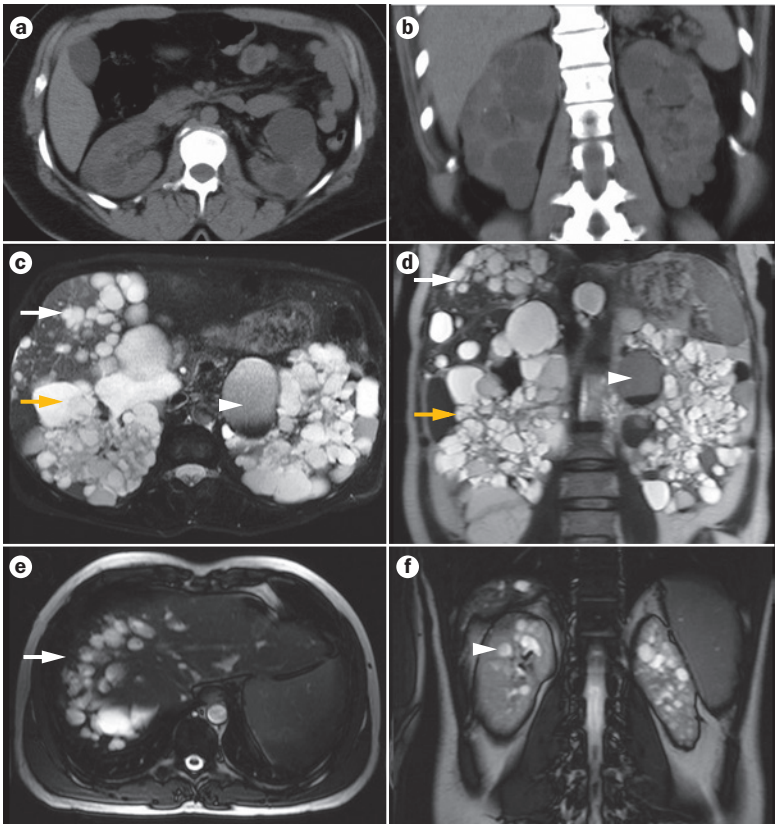

Figure 2 | Imaging findings from patients with ADPKD and ARPKD. **a** | Axial and **b** | coronal CT images of a patient with ADPKD and multiple bilateral renal cysts. **c** | Axial and **d** | coronal T2-weighted MRI scans of a patient with advanced ADPKD with renal (yellow arrow) and hepatic (white arrow) cysts. One renal cyst is haemorrhagic (white arrowhead). **e** | Axial and **f** | coronal T2-weighted MRI scans show liver Caroli syndrome (white arrow) and enlarged polycystic kidneys (white arrowhead) in a patient with ARPKD. Abbreviations: ADPKD, autosomal dominant polycystic kidney disease; ARPKD, autosomal recessive polycystic kidney disease.

enlarged.[72,73] By contrast the kidneys are greatly enlarged in both ADPKD and ARPKD. Moreover, renal cysts in patients with nephronophthisis are primarily localized to the corticomedullary junction and not distributed randomly as they are in ADPKD (Figure 3). On ultrasonography, kidneys in patients with nephronophthisis are echogenic and loss of corticomedullary differentiation is often observed. Over time, multiple renal cysts might develop (Figure 3). Characteristic nephronophthisis-associated alterations in renal histology include tubulointerstitial nephropathy, corticomedullary cysts and tubular basement membrane thickening and disruption.[74]

The earliest clinical symptoms of nephronophthisis are polydipsia, polyuria, urine-concentrating defects and secondary enuresis, usually occurring at the age of 4–6 years.[74] Later in the course of the disease, growth retardation and anaemia might develop. Patients with nephronophthisis do not usually present with hypertension, oedema or frequent urinary tract infections. Consequently, diagnosis of the disease is often delayed. Nephronophthisis is a leading genetic cause of ESRD in children, adolescents and young adults;[73,75,76] typically, ESRD develops in the first three decades of life. Retinitis pigmentosa seems to be always present in patients with mutations in *IQCB1* (NPHP5) and *CEP290* (NPHP6), but can be seen in most subtypes of nephronophthisis, except patients with *GLIS2* mutations (NPHP7).[74]

Mutations in a growing list of genes are involved in the development of nephronophthisis, and to date, 18 different subtypes of nephronophthisis have been identified (Table 2).[77] The products of the genes associated with these disorders localize to primary cilia, basal bodies or centrosomes of renal epithelial cells.[72–75] Cilia are also involved in determining left-right asymmetry in embryonic development.[78–80] Thus, *situs inversus* might be seen in patients presenting with nephronophthisis (Figure 4). Congenital oculomotor apraxia resulting in defective voluntary horizontal eye movement has been described in combination with nephronophthisis, and is referred to as Cogan syndrome.[81] Nephronophthisis-like kidney diseases are also observed in a range of complex developmental disorders. In Meckel–Gruber syndrome, a perinatally lethal ciliopathy, nephronophthisis is present together with bilateral postaxial hexadactyly, hepatobiliary ductal plate malformation presenting as fibrocystic liver disease and central nervous system malformations (typically occipital encephalocele).[82] Cone-shaped epiphyses associated with nephronophthisis are characteristic for Mainzer–Saldino syndrome,[83] and defects in the ciliary protein IFT172 (resulting in NPHP17) have been described in affected patients.[84] Short-rib dysplasia, with or without polydactyly also is associated with cortico-medullary renal cysts. Patients present with a narrow thorax, short ribs, shortened tubular bones, an abnormal acetabulum and extraskeletal malformations such as cardiac, liver and brain anomalies. The affected children die in the perinatal period.[85] Mutations in *IFT80*, *DYNC2H1* and *WDR34* have been described.[86] In cranioectodermal dysplasia (Sensenbrenner syndrome), a rare disease with skeletal, ectodermal, craniofacial, connective tissue, renal and liver anomalies, kidneys can be echogenic, normal in size or enlarged,[87] and patients may present with renal insufficiency.

Known mutations account for approximately 40% of cases of nephronophthisis, and more genes will certainly be identified in the future. The large number of genes associated with nephronophthisis might be the basis of the many extrarenal manifestations associated with this disease, since the protein products of these genes are broadly expressed in kidney, liver, retina and brain, and mutations in the corresponding genes have a profound effect on highly conserved cellular signal transduction pathways.

Senior–Løken syndrome

The most common extrarenal manifestation in nephronophthisis is tapetoretinal degeneration (retinitis pigmentosa), and the combination of these two conditions is defined as Senior–Løken syndrome, which is seen in approximately 10–15% of patients with nephronophthisis.[73]

Joubert syndrome

Joubert syndrome can present as nephronophthisis with liver fibrosis, retinitis pigmentosa, coloboma of the eye, an altered respiratory pattern in the neonatal period and

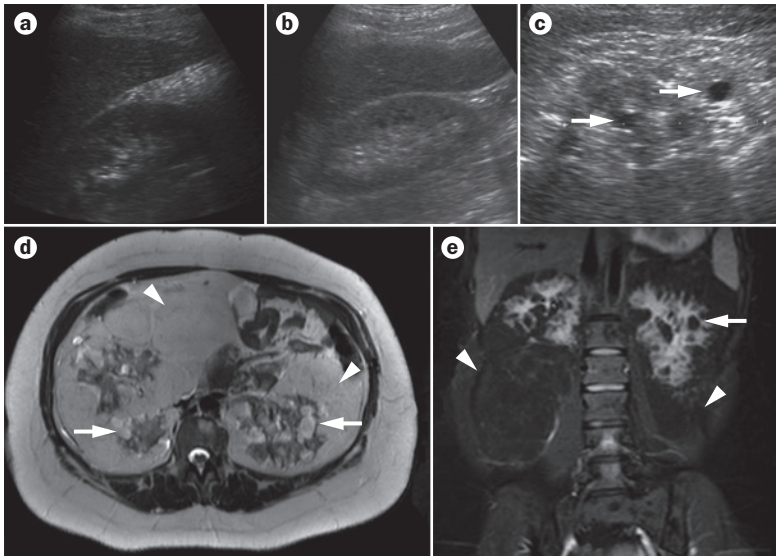

Figure 3 | Renal manifestations of rare cystic kidney diseases. **a** | Ultrasound scans showing nephronophthisis in an adult patient with Senior–Løken syndrome and multiple small renal cysts. **b** | Ultrasound scan showing nephronophthisis in an adult patient with medullary cystic kidney disease. **c** | Ultrasound image from a patient with Bardet–Biedl syndrome, showing small kidneys with multiple renal cysts (white arrows) and increased echogenicity. **d** | Axial T2-weighted MRI scan and **e** | coronal fat-suppressed MRI scan of a patient with tuberous sclerosis complex, showing cystic kidney disease (white arrows) and huge bilateral renal angiomyolipoma (white arrowheads).

cerebellar vermis hypoplasia or aplasia.[72,88,89] Vermis aplasia is apparent on cranial MRI as a malformed brain stem, termed molar tooth sign (Figure 4). Various neurological symptoms are variably associated with vermis aplasia, including intellectual disability, developmental delay, ataxia, oculomotor apraxia, nystagmus, muscle hypotonia and respiratory distress. Genetically, Joubert syndrome is heterogeneous, and mutations in more than 21 different genes (including *NPHP1)* that have a role in the formation and function of sensory cilia have been described (Tables 1 and 2).[90] 35% of the subset of patients with Joubert syndrome and retinal dystrophy develop renal cysts.[82]

Bardet–Biedl syndrome

Bardet–Biedl syndrome is an autosomal recessive multisystem disorder. Renal dysfunction constitutes a major cause of mortality in affected patients.[89] Renal abnormalities are detected in 82% of patients[92] and tubulointerstitial disease is common (Figure 3). One-third of patients develop urine-concentrating defects and subsequent polydipsia and polyuria. Urinary tract infections are also frequently seen. In a few patients, Bardet–Biedl syndrome is associated with renal tubular acidosis, glucosuria, hyperaminoaciduria or tubular proteinuria.

Kidneys in affected fetuses and newborn babies are enlarged, hyperechogenic on ultrasonography, lack corticomedullary differentiation and exhibit multiple corticomedullary cysts.[93] By the age of 1–2 years, kidney size returns to normal. In adulthood, the renal phenotype is very heterogeneous. Most patients with Bardet–Biedl syndrome develop a nephronophthisis-like phenotype with tubular dilatation, interstitial fibrosis and secondary focal glomerulosclerosis. However, in some patients, the renal phenotype includes multiple cysts and resembles ADPKD or ARPKD.[92,94]

The extrarenal manifestations of Bardet–Biedl syndrome include polydactyly, juvenile obesity, mental retardation, retinal defects, anosmia and hypogonadism.[93] Hypertension and diabetes might also be present in some patients.[92] To date, 19 genes associated with Bardet–Biedl syndrome have been identified, all encoding proteins that are involved in ciliary function. Approximately 80% of patients with Bardet–Biedl syndrome carry mutations in these genes.[95] Polydactyly is present in about 70% of patients with Bardet–Biedl syndrome (Figure 4).

Medullary cystic kidney disease

MCKD presents as a nephronophthisis-like kidney morphology, with a lack of extrarenal manifestations. Renal dysfunction secondary to tubulointerstitial nephritis, with development of renal cysts, hyperuricaemia and gout are characteristic findings in patients with MCKD, although neither hyperuricaemia nor renal cysts are required for its diagnosis. Kidneys are normal or small in size, and corticomedullary cysts are present in less than 50% of patients (Figure 3).[96–98] ESRD usually develops after the fourth decade of life, but renal function is maintained in a subset of patients into the eighth decade.[99] No extrarenal organ involvement in MCKD patients has been described so far.

Although MCKD is an autosomal dominant disease, 10% of patients have no family history of MCKD.[96] MCKD type 1 is associated with mutations in the *MUC1* gene (encoding mucin 1), whereas MCKD type 2 is caused by mutations in the *UMOD* gene.[100–102] *UMOD* encodes uromodulin, also known as Tamm–Horsfall protein, which is the most abundant urinary protein. Mutations in UMOD were detected in 17.8% of 109 patients with MCKD type 1, which suggests that additional MCKD-related genes are yet to be identified.[96] In 2009, mutations in *REN* (encoding renin) that result in a single amino acid change—a deletion or substitution of Leu16 in the renin signal sequence—were reported as an additional cause of MCKD.[103]

The renal cystic tumour syndromes

Tuberous sclerosis complex

Tuberous sclerosis complex is characterized by renal, dermatological and/or neurological manifestations. The birth incidence of this autosomal dominant disorder is estimated to be 1:5,800 and its overall population prevalence is 1:34,000.[104] The symptoms of tuberous sclerosis complex comprise features used as major and minor diagnostic criteria.[105] Renal lesions, including angiomyolipomas, are present in approximately 50–85% of patients, renal cysts in 30–45%, and clear cell, papillary and chromophobe renal cell carcinoma as well as oncocytoma in 4% of patients.[49,105–107]

Angiomyolipoma is a classic manifestation of tuberous sclerosis complex and is strongly suggestive of the disease.[49,106] Angiomyolipomas are usually bilateral and

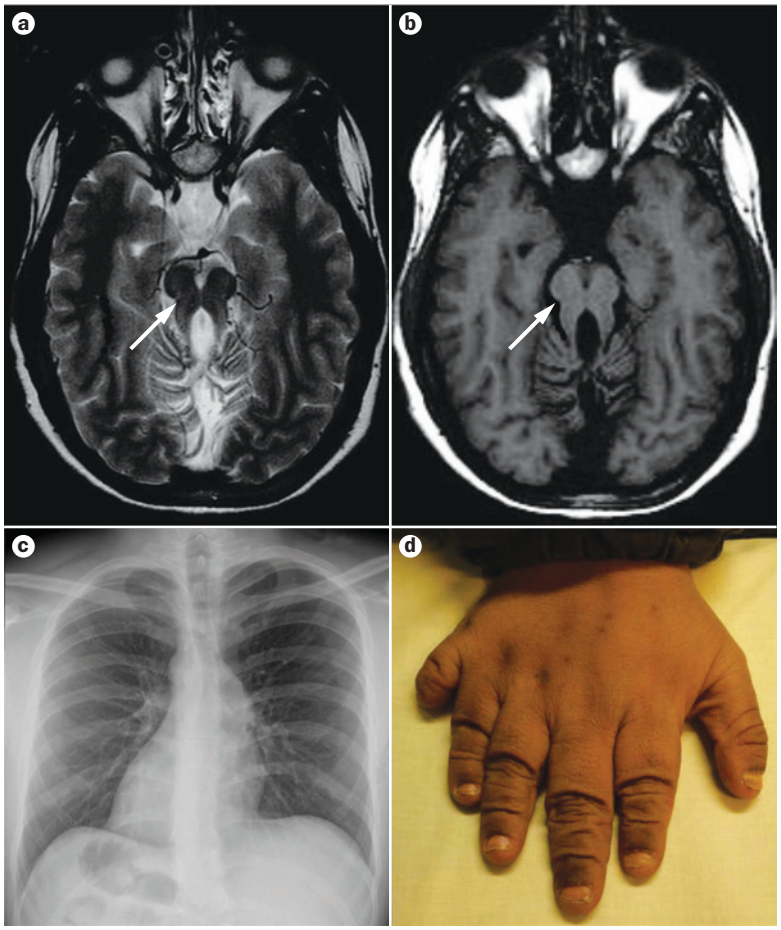

Figure 4 | Extrarenal manifestations of rare cystic kidney diseases. **a** | T2-weighted and **b** | T1-weighted brain MRI scans from a patient with Joubert syndrome, showing cerebellar vermis aplasia and a malformed brain stem (molar tooth sign, white arrows). **c** | X-ray image showing *situs inversus* in an adult patient with nephronophthisis and Senior–Løken syndrome. **d** | Hexadactyly in an adult patient with Bardet–Biedl syndrome.

multilocular; these benign tumours consist of abnormal blood vessels, immature smooth muscle cells, and adipose cells (Figure 3). Angiomyolipomas pose a significant risk of haemorrhagic complications and renal disease—including renal cell carcinoma, which is a common cause of death in patients with tuberous sclerosis complex.[108] However, considering their benign nature, surgery for angiomyolipomas is avoided whenever possible, to preserve renal function.[105] The lifetime risk of renal cell carcinoma in patients with tuberous sclerosis complex (2–3%) is higher than that in the general population (0.01%);[105,109,110] renal cell carcinoma in patients with tuberous sclerosis complex is also often bilateral and develops significantly earlier than in the general population, at an average age of 28 years.[109] Angiofibromas are present in 75% of patients with tuberous sclerosis complex, and develop in adolescence and adulthood. Developmental disorders and neurological symptoms, such as epilepsy, cognitive dysfunction and behavioural disturbances are common and challenging to treat.[111,112] Structural brain alterations, such as subependymal giant cell astrocytomas or cerebral tubers, are thought to strongly contribute to the underlying pathology.[113,114] Lymphangioleiomyomatosis—abnormal proliferation of smooth muscle cells of the lung—exclusively affects female patients.[115] Dermatological manifestations of tuberous sclerosis complex are very common; in childhood, hypomelanotic macules are found in more than 90% of affected patients.[114,116]

Tuberous sclerosis complex is caused by mutations in either *TSC1* on chromosome 9q34 (encoding hamartin) or *TSC2* on chromosome 16p13.3 (encoding tuberin).[117,118] Hamartin and tuberin interact through their coiled-coil domains to form a complex. This complex acts as a tumour suppressor by inhibiting mammalian target of rapamycin (mTOR) signalling, which is implicated in a number of cellular processes, including proliferation, cell cycle control and regulation of cell size.[119–121] Thus, mTOR inhibitors might be a promising therapeutic strategy in patients with tuberous sclerosis complex. For example, beneficial effects of sirolimus on controlling the growth of angiomyolipomas were demonstrated in a non-randomised, open-label trial.[122] In the USA, mTOR inhibitors have gained FDA approval for treatment of subependymal giant cell astrocytomas.[123,124]

In the majority of patients, tuberous sclerosis complex results from sporadic germ line mutations in *TSC1* or *TSC2*.[125] Furthermore, 2–3% of patients with tuberous sclerosis carry a contiguous germ line deletion affecting both the *TSC2* gene and the *PKD1* gene, which are located in close proximity on chromosome 16p13.[126] This deletion results in a polycystic renal phenotype that is already detectable in infancy or early childhood and leads to renal insufficiency in adolescence and early adulthood.

Von Hippel–Lindau syndrome

Von Hippel–Lindau syndrome is typically present in 1 of 36,000 individuals and was the first hereditary renal cancer syndrome to be described.[127] Mutations in the *VHL* gene cause autosomal dominant von Hippel–Lindau syndrome.[128,129] The VHL protein functions as a tumour suppressor that regulates the activity of hypoxia-inducible transcription factors. In the absence of VHL protein, high levels of vascular endothelial growth factor stimulate angiogenesis and hypervascularization.[130] The mean age at diagnosis of von Hippel–Lindau syndrome is 26 years; however, in some patients, haemangioblastomas of the retina develop in childhood.[127] Haemangioblastomas also occur in the spinal cord and brain. Phaeochromocytomas, pancreatic cysts, pancreatic neuroendocrine tumours, endolymphatic sac tumours of the inner ear and cystadenomas of the epididymis and broad ligament might also be present.[131] About 70% of patients with von Hippel–Lindau syndrome who survive to the age of 60 years develop renal cell carcinoma; the mean age at diagnosis of renal cell carcinoma is approximately 40 years.[132] By contrast, sporadic renal cell carcinoma usually develops significantly later in life; the median age of diagnosis is 65 years.[133]

Alterations in renal morphology affect approximately 70% of patients with von Hippel–Lindau syndrome.[132,134] Hundreds of renal cysts might be present, mimicking an ADPKD phenotype and complicating the diagnosis of

renal cell carcinoma, albeit generally without significantly compromising renal function. The renal parenchyma in patients affected by von Hippel–Lindau syndrome contains multiple foci of dysplastic epithelium as well as carcinoma *in situ,* accounting for the high incidence of renal cell carcinoma.[131] Complex renal cysts might develop, and the risk of renal cell carcinoma increases with age, ranging from 25% to 70%.[127] Although diagnostic techniques have markedly improved over the past decades, the average life expectancy of patients with von Hippel–Lindau syndrome is currently less than 50 years,[132,135] and renal cell carcinoma is still the leading cause of death in this setting.

MRI is the gold standard for diagnosis of renal cell carcinoma in patients with von Hippel–Lindau syndrome. For adult carriers of *VHL* mutations, annual ultrasound scans of the abdomen and MRI at least every 2 years are recommended to detect early stage renal cell carcinoma.[132,134] Many patients require repeated surgery for control of renal cell carcinoma. Nephron-sparing surgery is the therapy of choice, and total nephrectomy should be avoided if possible, to prevent the need for early dialysis.[127] For MRI lesions suspected of harbouring RCC smaller than 3 cm, a monitoring strategy is recommended.[132,134]

The role of genetic testing

ADPKD

Although in the vast majority of patients, diagnosis of ADPKD on the basis of clinical criteria is straightforward, genetic testing might be useful in selected patients.[136] It is advisable to offer counselling before genetic testing since receiving a diagnosis of ADPKD could influence family planning decisions, insurability and/or emotional stability. Individuals with a clinical presentation of ADPKD and no known family history of this disease, inconclusive ultrasonography, CT or MRI findings, or below 30 years of age with no detectable cysts (especially if they are being evaluated as potential kidney donors) could also potentially benefit from genetic testing.[137]

Mutations in *PKD1* and *PKD2* are found in 91% of patients with ADPKD; however, these mutations are not clustered at any particular sites.[9,137] The remaining 9% of patients with ADPKD usually have a negative family history and mild disease.[137] Most patients with a family history of ADPKD exhibit only one mutation. Thus, for accurate diagnosis, all *PKD1* and *PKD2* exons and exon–intron boundaries must be sequenced. Genetic testing for ADPKD is, therefore, costly and technically difficult, as *PKD1* contains 46 exons, of which exons 1–33 are encoded by a duplicated region, whereas *PKD2* comprises 15 exons.[137] To date, changes deep within introns, gene promoter alterations, or changes in splice sites have not been captured by regular sequencing techniques, although they might account for some of the 9% of patients with ADPKD who do not have *PKD1* or *PKD2* mutations.[137] Recently, epigenetic alterations have come into focus. *PKD1* was found to be hypermethylated in ADPKD patients, suggesting a mechanism of epigenetic silencing underlying cyst formation.[138] Moreover, mutations in various additional genes have been postulated to be involved in the pathogenesis of ADPKD, but are unconfirmed to date.[139,140] Furthermore, a germ line mutation in *PKD1* or *PKD2* resulting in mosaicism cannot be ruled out in individuals who are apparently negative for *PKD1* or *PKD2* mutations.[10]

In patients who lack detectable *PKD1* or *PKD2* mutations several differential diagnoses might be taken into consideration. For example, ARPKD might manifest in adulthood, mimicking an ADPKD phenotype. As discussed in detail above, liver fibrosis is present in all patients with ARPKD, and should be assessed if ARPKD is suspected.[136] Phenotypic overlap with ADPKD is also seen in patients with *HNF1B* mutations,[136] which cause renal cysts and a diabetes syndrome, also known as maturity-onset diabetes of the young type 5 (MODY5). Although a rare disease, MODY5 can present with cystic kidney disease even before the onset of diabetes mellitus, and is associated with early onset of gout and/or urogenital tract abnormalities.[141,142] Patients with autosomal dominant polycystic liver disease caused by mutations in *SEC63* or *PRKCSH* can also have multiple renal cysts.[143,144]

ARPKD

PKHD1, the gene mutated in ARPKD, has 86 exons that can be alternatively spliced, resulting in several isoforms.[145,146] Polymorphisms in *PKHD1* are very common, although so far, only mutations in the 66 exons encoding the longest open reading frame have been described in association with ARPKD. Previous studies established genotype–phenotype correlations in a subset of patients with ARPKD and *PKHD1* polymorphisms.[147–149] The presence of two truncated alleles leads to a severe renal phenotype that can result in neonatal death.[150,151] However, given that most patients with ARPKD are compound heterozygotes,[152] genotype–phenotype correlation is difficult.

Genetic testing for *PKHD1* mutations has particular utility for prenatal diagnosis in families in which one child is severely affected by ARPKD, although the large size of the gene, its alternative splicing and substantial allelic heterogeneity pose a diagnostic challenge. As for ADPKD, genetic testing is currently not recommended for patients in whom the diagnosis can be established by imaging and clinical parameters, since genotyping is still expensive and does not always yield conclusive results.[67] However, in families with a known ARPKD-causing mutation, asymptomatic family members can easily and inexpensively be screened for the mutation, and such screening is especially important in individuals being evaluated as potential living kidney donors.

Nephronophthisis and related disorders

At present, mutations are only detected in 30–40% of patients with nephronophthisis; in the remaining 60–70%, the underlying gene is still unknown.[72,76,77] Thus, routine screening for nephronophthisis-related mutations is not performed owing to the low frequency of detected mutations and the huge variety of genes involved.

Since *NPHP1* deletions account for approximately 20–40% of cases of nephronophthisis, screening for *NPHP1* mutations in a child presenting with normal-sized

kidneys, polyuria, urinary sodium loss and renal insufficiency without haematuria, proteinuria or hypertension might, however, have some diagnostic utility. If *NPHP1* mutations are ruled out, kidney biopsy is currently the best option to diagnose nephronophthisis.[74]

Renal cystic tumour syndromes

Tuberous sclerosis complex is diagnosed on the basis of clinical features, but genetic testing of *TSC1* and *TSC2* can be used to confirm the diagnosis.[105] The phenotype of VHL syndrome, even within the same family, is highly heterogeneous. Five classic VHL phenotypes have been described on the basis of the relative frequency of haemangioblastomas and renal cell carcinoma.[127] In type 1 von Hippel–Lindau syndrome, haemangioblastoma of the retina, brain and spinal cord are present, and the risk of renal cell carcinoma is high but the risk of phaeochromocytoma is low. In type 1B von Hippel–Lindau syndrome, which is associated with large deletions of the *VHL* gene, the risk of both renal cell carcinoma and phaeochromocytoma is low. Type 2A von Hippel–Lindau syndrome is associated with a high risk of phaeochromocytoma and a low incidence of renal cell carcinoma, whereas type 2B von Hippel–Lindau syndrome has a high risk of both tumour types. Patients with type 2C von Hippel–Lindau syndrome show no associated haemangioblastomas but do have a high risk of phaeochromocytoma.[127] Knowing the type of *VHL* mutation carried by an individual patient can, therefore, be used to estimate the risk of renal cell carcinoma. Genetic testing is consequently recommended in patients with von Hippel–Lindau syndrome.[124]

Conclusions

The past decade has witnessed tremendous progress in our understanding of renal cystic diseases. Landmark genetic studies have identified numerous genes involved in cystic kidney diseases and the number of mutations identified as associated with ciliopathies is constantly increasing. Thus, nephrologists deal with an increasing complexity of diseases caused by a large variety of different gene mutations. Cystic kidney diseases are even more complex, as mutations in the same genes can cause different disorders, and similar phenotypes can be caused by mutations in many genes. Thorough clinical examination and radiological imaging is, therefore, mandatory in the differential diagnosis of cystic kidney diseases. In our view, such clinical phenotyping is essential to improve understanding of the pathophysiology and molecular genetics of cystic kidney diseases and ultimately to develop tailored treatment strategies for the different disease entities.

The introduction of next-generation sequencing (NGS), which potentially enables the entire human genome to be sequenced within a few days, should change the diagnosis of ciliopathies in the near future.[136] Using targeted approaches of NGS, the search for mutations can focus on the specific genes involved in the development of ciliopathies (a 'ciliary panel'). This approach, which is already available at a reasonable price, could facilitate routine genetic diagnosis of ciliopathies. In the coming years a variety of novel genes involved in the development of polycystic kidney disease are likely to be identified. These new sequencing techniques will help to correctly diagnose rare ciliopathies and will be valuable for evaluating disease risk in family members of affected patients for living-donor renal transplantation.

Review criteria

A PubMed search was performed using the search terms "polycystic OR cystic kidney disease", "autosomal dominant polycystic kidney disease", "autosomal recessive polycystic kidney disease", "nephronophthisis", "Senior–Løken syndrome", "Cogan syndrome", "Joubert syndrome", "Meckel–Gruber syndrome", "Mainzer–Saldino syndrome", "medullary cystic kidney disease", "Bardet–Biedl syndrome", "von Hippel–Lindau syndrome", "tuberous sclerosis". Articles in English were selected. No restrictions on dates or article type were employed for the search.

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