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Autosomal recessive polycystic kidney disease: The prototype of the hepato-renal fibrocystic diseases

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Abstract. Autosomal recessive polycystic kidney disease (ARPKD) is a severe, typically early onset form of renal cystic disease. The care of ARPKD patients has traditionally been the purview of pediatric nephrologists for management of systemic hypertension and progressive renal insufficiency. However, the disease has multisystem manifestations and a comprehensive care strategy frequently requires a multidisciplinary team. In severely affected infants, the diagnosis often is first suspected by obstetricians when enlarged, echogenic kidneys and oligohydramnios are detected on prenatal ultrasounds. Neonatologists are central to the care of these infants, who may have respiratory compromise due to pulmonary hypoplasia and massively enlarged kidneys. Among neonatal survivors, a subset of ARPKD patients has clinically significant congenital hepatic fibrosis, which can lead to portal hypertension, requiring close monitoring by pediatric hepatologists. Surgical consultation may be sought to access pre-emptive nephrectomy to relieve mass effect, placement of dialysis access, surgical shunting procedures, and kidney and/or liver transplantation. Recent data suggest that children with ARPKD may be at risk of neurocognitive dysfunction, and may require neuropsychological referral. In addition to these morbidities, families of patients with ARPKD face decisions regarding genetic testing of affected children, testing of asymptomatic siblings, or consideration of preimplantation genetic diagnosis for future pregnancies. These issues require the input of genetic counselors, geneticists, and reproductive endocrinologists. As a result, the management of ARPKD requires the involvement of multiple subspecialists, as well as the general pediatrician, in a complex care network. In this review, we discuss the genetics of this disorder and provide an overview of the associated pathobiology; outline the spectrum of clinical manifestations of ARPKD and the management of organ-specific complications; discuss other disorders that involve genes encoding cilia-associated proteins that can clinically mimic ARPKD; review the animal models available for preclinical studies; and finally, consider future directions for potential targeted therapies.

Keywords: ARPKD, hepato-renal fibrocystic disease, primary cilium, *PKHD1* mouse models

1. Introduction

Autosomal recessive polycystic kidney disease (ARPKD) (MIM 263200) is an important inherited cause of chronic kidney disease, with an estimated incidence of 1 in 20,000 live births [1]. Mutations in a single gene, *PKHD1*, account for essentially all cases of ARPKD [2, 3]. The largest protein product of *PKHD1*, termed the FPC/polyductin complex (FPC), is a single-membrane spanning protein that is localized to the apical membrane, the primary apical cilium/basal body and the mitotic spindle [4].

Typically, ARPKD presents as an early onset disorder with a perinatal mortality rate of approximately 30–40% [5]. The majority of patients are identified

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either *in utero* or at birth with enlarged echogenic kidneys and oligohydramnios. At birth, the most severely affected neonates have a critical degree of pulmonary hypoplasia that is incompatible with survival. Renal function, though frequently compromised, is rarely a cause of neonatal death. In patients who survive the first month of life, 1-yr survival rates of 92–95% have been reported [6, 7]. Neonatal survivors have a spectrum of clinical manifestations that primarily involve the kidneys and biliary tract and depend in part on the age at presentation [6]. The basic structural defects observed in ARPKD suggest that the terminal differentiation of the renal collecting duct and intrahepatic biliary ducts is disordered (Fig. 1).

The major morbidities in neonatal survivors include severe systemic hypertension, renal impairment, and portal hypertension [6, 8, 9]. Hyponatremia occurs in a subset of neonates, presumably due to defects in free water excretion [6]. Systemic hypertension usually develops within the first 6 mo of life, often associated with a transient improvement in glomerular filtration rate (GFR) due to renal maturation. Subsequently, there is a progressive, but variable decline in renal function [10].

A subset of patients with late-onset ARPKD has a liver-predominant phenotype with few or no manifestations of kidney disease [9]. These patients present with portal hypertension, hepatosplenomegaly, esophageal or gastric varices, as well as hypersplenism with associated thrombocytopenia, anemia, and leukopenia. Hepatocellular function is usually preserved. Ascending suppurative cholangitis is a serious complication and can cause fulminant hepatic failure [11, 12].

Other associated features include an increased incidence of culture-confirmed urinary tract infections [6], (very rare) intracranial aneurysms [13], and growth retardation [6], although the mechanism for the latter is not defined. Recent data suggest that children with
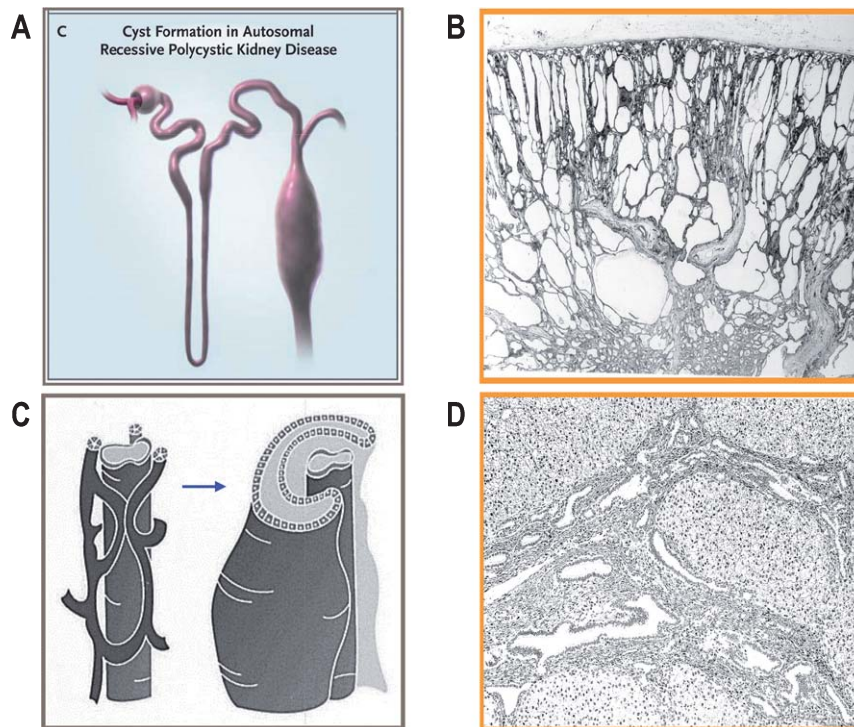

Fig. 1. Classic autosomal recessive polycystic kidney disease histopathology. The histopathology in autosomal recessive polycystic kidney disease primarily involves the kidney and liver. As schematically represented in panel A, the classic renal cystic lesion involves fusiform dilatation of the cortical and medullary collecting ducts. Therefore, the predominant histopathological finding is dilated collecting ducts arrayed perpendicular to the renal capsule. (B) The hepatobiliary lesion results from an architectural defect in the developing biliary tree. The normal ramifications of the portal venous system and the lattice-like network of associated biliary ducts (left side of panel C) are disrupted due to the ductal plate malformation (right side of panel C), likely due to a defect in terminal differentiation. The ductal plate malformation results in the histopathological lesion, congenital hepatic fibrosis (D). Panel A is derived from reference [73] and panel C used with permission of V.E. Torres (personal communication).

ARPKD may be at risk of neurocognitive dysfunction, but the specific defects and the underlying mechanisms have yet to be characterized [14].

In addition to child-centered morbidities, the families of ARPKD children are burdened with a number of challenges. With advances in genetic testing and imaging methodologies, families face decisions about genetic testing of a symptomatic child, as well as genetic testing and/or imaging evaluation of asymptomatic children. For future pregnancies, there are issues of prenatal diagnosis and consideration of new reproductive technologies such as pre-implantation genetic diagnosis (PGD). Disease progression prompts decisions about dialysis modalities and/or transplantation, e.g. kidney, liver, or sometimes both. Therefore, the multidisciplinary care team must be well-versed in the genetics of ARPKD, the pathobiology of the disease, clinical management strategies, and the psychosocial implications for affected families.

2. ARPKD genetics

All typical forms of ARPKD are caused by mutations in *PKHD1*, a large, ∼500 kb gene [2, 3]. The longest open reading frame comprises 67 exons that encodes FPC. There is evidence for extensive alternative splicing of this gene [15]. Whether all the predicted alternative *PKHD1* transcripts are translated into proteins and what their biological functions may be remains unknown. In general, it appears that a critical amount of full-length protein is required for normal biological functions (e.g. tubular differentiation and maintenance of tubular architecture).

2.1. Human mutations

ARPKD mutations have been identified along the entire length of the *PKHD1* gene, and multiple mutation types have been characterized as pathogenic. To date, almost 750 pathogenic mutations have been catalogued in the ARPKD mutation database [16], of which approximately half are missense changes. The most common mutation is a missense mutation in exon 3, c.107 C>T (p.Thr36Met), which accounts for approximately 20% of all mutant alleles [8]. This mutation has been observed in a large number of unrelated patients, but typically in the context compound heterozygosity, with a second distinct mutant allele [17]. In general, *PKHD1* does not appear to harbor muta-

tional hotspots and a large proportion of mutations are unique to a single pedigree [17, 18]. The first *PKHD1* founder mutation has recently been described in a cohort of Afrikaner ARPKD patients, involving a missense change in exon 20, i.e. c.1880T>A (p.M627K) substitution [19].

2.2. Genotype-phenotype correlations

Given the diversity of *PKHD1* mutations, most patients are compound heterozygotes, that is they carry two different mutant alleles. The functional effect of any particular mutant allele can be difficult to characterize. Nevertheless, several themes have emerged from genotype-phenotype studies. First, in a study of fetuses and neonates with ARPKD, Denamur et al. [20] determined that when adjusted for gestational age, the extent of collecting duct dilatation, but not portal fibrosis, was significantly correlated with the presence of two truncating mutations (severe genotype). Of note, in this study, the presence of at least one missense mutation did not guarantee survival to the neonatal period. In general, patients with two truncating mutations often, but not invariably, have a severe phenotype leading to perinatal demise [18]. However, there are notable exceptions, e.g. a child homozygous for a large *PKHD1* deletion who survived well past the neonatal period [21]. While most missense mutations are associated with milder disease, a number of missense mutations result in severe phenotypes when combined with a truncating mutation or occurring in the homozygous state [18].

In addition, significant phenotypic variability in a subset of affected siblings suggests that genetic modifiers modulate disease expression. For example, in one study of 126 unrelated families with more than one affected child, 20 sibships demonstrated widely discordant phenotypes (perinatal lethality in one sibling and survival into childhood in the other) [7].

3. ARPKD pathobiology

The largest protein product of *PKHD1*, termed FPC, is a single-membrane spanning protein with a long extracellular N-terminus and short cytoplasmic tail [22]. A subset of membrane-bound FPC appears to undergo notch-like proteolytic processing, with shedding of the extracellular domain into the tubular lumen and nuclear translocation of the C-terminus, where it may play a role in transcriptional regulation [23].

During fetal development, *PKHD1* is expressed widely and is found in the neural tube, bronchi, primordial gut, early ureteric bud, mesonephric tubules, adrenal cortex, and immature hepatocytes, suggesting a role in organ development and tubular morphogenesis. In adult tissues, FPC is expressed predominantly in the kidney (primarily in collecting ducts and thick ascending loops of Henle) and the ductal epithelia of the liver and the pancreas [2, 22, 24–26]. In renal tubular and biliary epithelial cells, FPC localizes to apical membranes, the primary cilia/basal body, and mitotic spindle [4].

The specific functions of FPC have yet to be fully characterized. However, numerous other proteins associated with other hepato-renal fibrocystic diseases (e.g. autosomal dominant polycystic kidney disease [ADPKD], nephronophthisis, Meckel-Gruber, Joubert, Bardet-Biedl and other ciliary chondrodysplasias syndromes) (Table 1) also localize to the primary cilia/basal body (Fig. 2) [27].

This suggests a central role for the primary cilium in the development and maintenance of renal tubular architecture, perhaps via mechanisms such as flow sensing and establishment of planar cell polarity. The ADPKD proteins, polycystin-1 and polycystin-2, interact physically and appear to function via a common signaling pathway [28]; in turn, FPC has been shown to interact with polycystin-2 and appears to regulate its expression and function [29]. In animal studies, mice harboring mutations in both *Pkhd1* and either of the ADPKD genes (*Pkd1* or *Pkd2*) display cystic phenotypes much more severe those seen with either mutation alone, suggesting genetic interaction *in vivo* [29].

4. Clinical diagnosis

4.1. Imaging

ARPKD is typically first detected on routine prenatal ultrasound, with the findings of symmetrically enlarged, echogenic kidneys (due to multiple microscopic cysts) and medullary hyperechogenicity due to loss of corticomedullary differentiation [30]. Discrete cysts can be observed, but are not common [31]. Oligohydramnios may be present due to poor fetal urine output [6, 30]. However, normal sonographic findings do not necessarily exclude the diagnosis of ARPKD in an *at risk* fetus, since abnormalities may not be seen until late in the second trimester (or beyond), even in fetuses who present with a severe phenotype at birth [6, 30, 32]. In addition, the presence or absence of oligohydramnios does not always correlate with disease severity or degree of pulmonary insufficiency [32].

Table 1
ARPKD and hepatorenal fibrocystic disease phenocopies

| Disease	Gene(s)	Renal disease	Hepatic disease	Systemic features	Prevalence
ARPKD	*PKHD1*	Collecting duct dilatation	CHF; Caroli syndrome	no	∼1 in 20,000
ADPKD	*PKD1; PKD2*	Cysts along entire nephron	Biliary cysts; CHF (rare)	yes - adults	∼1 in 1,000
Nephronophthisis	*NPHP1-18*	Cysts at the cortico-medullary junction	CHF	some	∼1 in 100,000
Joubert syndrome and related disorders	*JBTS1-22*	Cystic dysplasia; NPHP	CHF; Caroli syndrome	yes	∼1 in 100,000
Bardet-Biedel syndrome	*BBS1-19*	Cystic dysplasia; NPHP	CHF	yes	∼1 in 140,000
Meckel-Gruber syndrome	*MKS1-11*	Cystic dysplasia	CHF	yes	∼1 in 250,000
Oral-facial-digital syndrome type I	*OFD1*	Glomerular cysts	CHF (rare)	yes	rare
Glomerulocystic disease	*PKD1; HNF1B; UMOD*	Enlarged; normal or hypoplastic kidneys	CHF (with *PKD1* mutations)	some	rare
Short-Rib Thoracic Dysplasia	*SRTD1-12*	Cystic dysplasia; NPHP	CHF; Caroli syndrome	yes	rare
Renal-hepatic-pancreatic dysplasia (Ivemark II)	*NPHP3, NEK8*	Cystic dysplasia	Intrahepatic biliary dysgenesis	yes	rare
Zellweger syndrome	*PEX1-3;5-7;10-14;16;19;26*	Renal cortical microcysts	Intrahepatic biliary dysgenesis	yes	rare
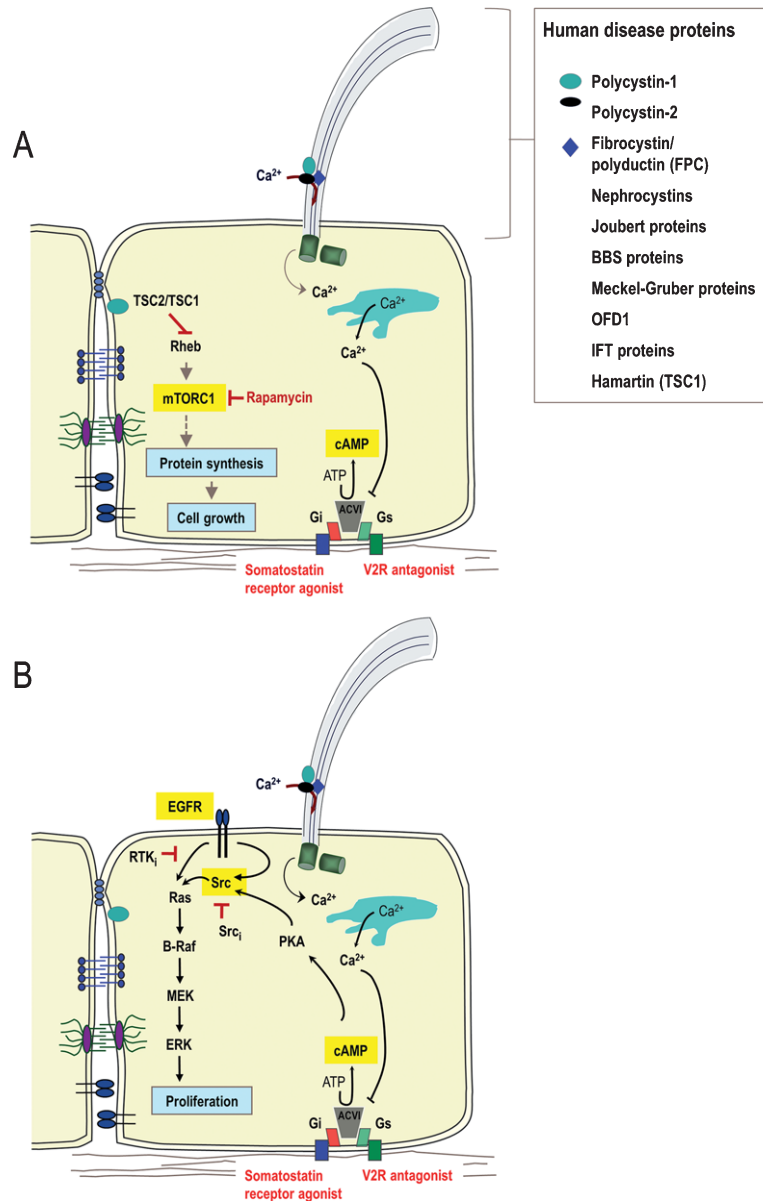
Fig. 2. The primary cilium with associated cystoproteins, and autosomal recessive polycystic kidney disease related pathways. The cilium concentrates and organizes a number of channels, receptors, and effectors, e.g. transcription factors and proteolytic fragments of cystoproteins (panel A). Almost all cystoproteins, including polycystins 1 and 2, FPC, the nephrocystins, the BBS proteins, OFD1, and TSC1 (or hamartin), all localize to the cilia/centrosome complex, providing compelling evidence that this complex is critical in the pathogenesis of renal cystic disease. Cilia appear to play a role in maintaining the balance between cell proliferation and differentiation through sensing the extracellular milieu, responding to mechanical cues, and modulating different signaling cascades. Ciliary dysfunction contributes to increased intracellular accumulation of cAMP and activation of mTOR, features common to cystic epithelia in human and rodent models of renal cystic disease (panel A). In addition, dysregulation of the epidermal growth factor receptor (EGFR) axis is a common feature of cystic epithelia (panel B). Each of these abnormal signaling pathways represents potential targets for therapeutic intervention. FPC = Fibrocystin-polyductin complex; BBS = Bardet-Biedl syndrome; cAMP = Cyclic adenosine monophosphate; mTORC1 = Mammalian target of rapamycin complex 1; OFD1 = Oral-facial-digital syndrome, type 1; TSC1 = Tuberous sclerosis type 1; V2 R=Vasopressin 2 receptor; RTKi = Receptor tyrosine kinase inhibitor; Srci = Src kinase inhibitor.

As discussed below, ARPKD belongs to a group of disorders described as hepato-renal fibrocystic diseases [33] (Table 1). While most of these disorders are characterized by large, echogenic kidneys in the fetus and neonate, they can sometimes be distinguished by ultrasonography [31]. With respect to the polycystic kidney diseases, ARPKD kidneys *in utero* are typically hyperechogenic and display decreased corticomedullary differentiation due to the hyperechogenic medulla. With high-resolution ultrasound, the radial array of dilated collecting ducts can be observed. In comparison, ADPKD kidneys *in utero* tend to be moderately enlarged with a hyperechogenic cortex and relatively hypoechogenic medulla causing increased corticomedullary differentiation [34].

Kidney size in children with ARPKD typically peaks at 1 to 2 yrs of age, then gradually declines relative to the child's body size, and stabilizes by 4 to 5 yrs [4]. As patients age, there is increased medullary echogenicity with scattered small cysts, measuring less than 2 cm in diameter. These cysts and progressive fibrosis can alter the usual kidney contour, causing ARPKD in some older children to be mistaken for ADPKD [35]. Contrast-enhanced computed tomography scanning can be useful in delineating the renal architecture in these children. Bilateral pelvicaliectasis and renal calcifications have been reported in 25% and 50% of ARPKD patients respectively [9, 36]. In adults with medullary ectasia alone, the cystic lesion may be confused with medullary sponge kidney.

The liver may be either normal in size or enlarged. It is usually less echogenic than the kidneys. Prominent intrahepatic bile duct dilatation suggests associated Caroli syndrome. With age, the portal fibrosis tends to progress and in older children, ultrasound typically shows hepatosplenomegaly and a patchy increase in hepatic echogenicity [37, 38].

4.2. Genetic testing in ARPKD

Mapping of the ARPKD locus in the mid-1990s led to haplotype (linkage-based) analysis for genetic diagnosis, provided DNA from a previously affected child and the parents was available.

In the last decade, the identification of the *PKHD1* gene has allowed genetic diagnosis by direct (Sanger method-based) DNA sequencing. Initially, a wide range of mutation detection rates were reported. More recent studies indicate that bi-allelic mutations are detected in 80–87% of tested alleles, and about 95% of ARPKD patients are found to have at least one *PKHD1* mutation. However, as discussed above, sequencing results have limited prognostic value. While the presence of two truncating mutations is generally incompatible with survival, clinical consequences of other mutation types can be difficult to predict. Of note, an estimated 44% of *PKHD1* mutations involve missense changes [16].

Clinical genetic testing laboratories (listed at GeneTests, www.genetests.org) offer direct sequencing of the entire coding region, with mutation detection rates of approximately 80%. Direct sequencing cannot detect all mutations, for example, those in non-coding exons, or in promoter or regulatory regions. Some laboratories also offer multiplex ligation-dependent probe amplification to detect large deletions or genomic rearrangements, although the frequency of such large genomic alterations appears to be quite low [21]. In families with more than one affected child, haplotype analysis remains a valuable tool when only one or no *PKHD1* mutations have been identified [39].

As discussed below, several other disorders mimic the clinical presentation of ARPKD, further compounding the molecular diagnosis of ARPKD. For example, patients with mutations in the ADPKD genes, *PKD1* and *PKD2*, can present with early onset renal cystic disease indistinguishable from ARPKD. In addition, a number of other hepato-renal fibrocystic diseases (Table 1) have clinical manifestations that overlap with ARPKD.

Thus, mutational analysis of *PKHD1* using current single-gene testing methodologies should not be considered a first-line diagnostic strategy for infants and children presenting with an ARPKD-like phenotype. It is expensive and potentially confounded by the existence of phenocopy disorders. Moreover, the high frequency of missense mutations makes pathogenicity predictions challenging, and particular caution is required when novel or rare missense changes are detected. The one clear exception to this guidance is in the context of planned PGD where putative *PKHD1* mutations transmitted from the mother and father, respectively, must be prospectively identified.

This testing conundrum may soon be resolved with advances in next-generation DNA sequencing, where massively-parallel sequencing technologies can simultaneously evaluate dozens of genes of interest in a single test. This diagnostic approach promises to be particularly powerful for patients with clinically

unclassified cystic kidneys in whom the differential diagnosis can be broad [40].

4.3. PGD

In families who have had a previous child with severe ARPKD, PGD offers an alternative to prenatal diagnosis for a subsequent pregnancy. The procedure requires prospective identification of the *PKHD1* mutations transmitted from each parent. The couple then must undergo *in vitro* fertilization. The resulting embryo is biopsied at the 8-cell stage, with removal of 1–2 embryonic cells for genetic testing [41]. There are at least two reported cases of PGD guiding the birth of unaffected infants in *at risk* families [42, 43].

5. Management and prognosis

5.1. Fetal monitoring

Once a presumptive diagnosis of ARPKD is made, ultrasonography should be performed every 2 to 3 wks for serial assessment of the renal size and amniotic fluid volume. The gestational age at onset of oligohydramnios is variable in ARPKD. Onset of oligohydramnios in the second trimester may be, but is not invariably, associated with pulmonary hypoplasia [44]. A study of 46 fetuses with severe genitourinary anomalies [45] demonstrated that after 26 wk gestational age, a total lung volume value of <0.90 by magnetic resonance imaging has a sensitivity of 77.8% and specificity of 95% for predicting non-survival.

5.2. Neonatal issues

The estimated rate of neonatal mortality in ARPKD patients is approximately 30–40%, primarily due to respiratory compromise. One-year survival rates of 92–95% have been reported in patients who survive the first month of life [6, 7]. Neonatal pulmonary hypoplasia, often complicated by pneumothoraces, is a major cause of neonatal mortality [46]. Aggressive interventions such as unilateral or bilateral nephrectomies and continuous hemofiltration have been advocated for neonatal respiratory management. However, these interventions are based on limited set of small case reports and case series. Evidence-based guidelines for clinical practice will require prospective, well-controlled studies.

5.3. Post-neonatal management

5.3.1. Systemic hypertension

For those children who survive the perinatal period, systemic hypertension is a major issue, with a prevalence of 55–75% and onset that typically precedes the decline in GFR. The pathogenic mechanism(s) remain elusive and the data, particularly regarding the role of renin-angiotensin-aldosterone system activation, is controversial. Interestingly, a recent study in the polycystic kidney (*PCK*) rat model reported a significant increase in intrarenal, but not systemic, renin-angiotensin-aldosterone system activation [47]. This finding may explain why previous human studies had not detected increased plasma renin levels.

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are widely used as therapeutic agents. However, combination angiotensin converting enzyme inhibitors and angiotensin receptor blockers therapy is not recommended, due to increased risk of side effects. Multi-agent therapy may be required and therapeutic strategies should be directed towards optimizing blood pressure control, while minimizing further reduction in GFR in the context of chronic kidney disease (CKD) [48]. The management of ARPKD children with declining GFR should follow the standard guidelines established for chronic CKD in pediatric patients [49].

5.3.2. Other renal issues

Hyponatremia occurs in up to 25% of neonates and may be due to an inability to maximally dilute the urine [6]. Children with ARPKD appear to be at higher risk for urinary tract infections, possibly due to urinary stasis within the cystic, dilated collecting ducts. Urinary tract infections have been reported at rates of around 20–50% in various cohorts, and are more common in females. Renal calcifications have also been reported to be common in older children with ARPKD, and may be related to hypocitraturia and a defect in urine acidification due to CKD [50]. Given their relative urinary concentrating defect, ARPKD children should be monitored for dehydration during intercurrent illnesses associated with fever, tachypnea, nausea, vomiting or diarrhea.

5.3.3. Chronic renal insufficiency

Most ARPKD patients progress to end-stage renal disease (ESRD), but the age at onset is highly variable and depends in part on the age at initial presentation,

e.g. 25% of patients diagnosed in the perinatal period require renal replacement therapy by 11 yrs, whereas only 25% of those who presented after 1 mo of age require renal replacement therapy by age 32 yr [10].

5.3.4. Hepatobiliary manifestations

ARPKD is invariably associated with congenital hepatic fibrosis, the result of a developmental defect in ductal plate development (Figs. 1C and D). In a subset of patients, the associated progressive portal tract fibrosis causes portal hypertension and associated complications of hypersplenism and varices [37]. Platelet counts, prothrombin time, splenic volume, and Doppler flow studies have been correlated with the severity of portal hypertension and should be serially monitored [38]. Liver transaminases are generally normal, with abnormalities in serum alkaline phosphatase and γ-glutamyltransferase evident in only a fraction of patients. Medical management includes sclerotherapy or variceal banding; whereas surgical approaches such as portocaval or splenorenal shunting may be indicated in some patients [37]. Ascending cholangitis is another important complication, and is a leading cause of morbidity and mortality in ARPKD patients, particularly after renal transplantation [51]. Meticulous evaluation is required for suspected bacterial cholangitis and if indicated, aggressive antibiotic therapy should be initiated.

5.3.5. Transplantation

Since ARPKD is a recessive disorder, either parent may be a suitable kidney donor. However, subtle renal and liver sonographic abnormalities have recently been described in ARPKD parents [52], warranting particular caution in the donor evaluation. Native nephrectomies may be indicated in patients with massively enlarged kidneys to allow allograft placement.

In one survey, about 7% of long-term survivors were reported to require liver transplantation, with primary indications being significant portal hypertension or recurrent cholangitis [6]. In some patients, combined kidney-liver transplantation may be appropriate [53]. Indications include the combination of renal failure and either recurrent cholangitis or significant complications of portal hypertension, e.g. recurrent variceal bleeding, refractory ascites, and the hepatopulmonary syndrome [37].

5.3.6. Prognosis

The relationship between renal and hepatic disease severity in ARPKD is unclear, with most studies demonstrating no significant correlation. A subset of patients with late-onset ARPKD can express a liver-predominant phenotype with few or no manifestations of kidney disease [9].

Effective management of neonatal morbidities, and systemic and portal hypertension, coupled with successful renal replacement therapy and transplantation options, has allowed for long-term patient survival. Therefore, the prognosis in ARPKD, particularly for those children who survive the first month of life, is far less bleak than previously thought and aggressive medical therapy is warranted.

5.4. Genetic counseling

Most ARPKD patients are compound heterozygotes and the functional effect of any particular mutant allele can be difficult to define. In general, patients with two truncating mutations have a severe phenotype, leading to perinatal demise [18]. However, there are notable exceptions, e.g. a child homozygous for a large *PKHD1* deletion who survived well past the neonatal period [21]. While most missense mutations are associated with milder disease, a number of missense mutations result in severe phenotypes when combined with a truncating mutation or occurring in the homozygous state [18]. In addition, significant phenotypic variability between and within families suggests that genetic modifiers modulate disease expression. These data can complicate genetic counseling and caution must be exercised in predicting the clinical outcome of future affected children [54].

6. Disorders mimicking ARPKD (non-*PKHD1* genes)

Studies over the past decade have demonstrated that an increasing number of single gene disorders that involve renal cystic disease and extra-renal phenotypes disrupt proteins involved in the structure/function of the primary cilium, a sensory organelle of the cell that extends from the apical plasma membrane. As a result, this very broad class of disorders is increasingly referred to the "ciliopathies" [55–57]. These data provide collective evidence that ciliary dysfunction is potentially a central mechanism in renal cystogenesis [22, 58, 59].

A subset of the ciliopathies is characterized by fibrocystic disease of the kidney and dysgenesis of the porto-biliary tract (congenital hepatic fibrosis and/or Caroli syndrome), prompting a redefinition of these disorders as hepato-renal fibrocystic diseases [33, 60]. While ARPKD is considered as the flagship disorder in this new phenotypic sub-classification, defects in the other hepato-renal fibrocystic diseases genes may mimic (phenocopy) ARPKD (Table 1). For example, 2% of all ADPKD patients express an early onset, severe phenotype that is clinically indistinguishable from ARPKD [61]. Rarer recessive disorders such as nephronophthisis, Joubert syndrome, Bardet-Biedl syndrome, Meckel-Gruber syndrome, and various ciliary chondrodysplasias also have variable degrees of renal and/or biliary involvement (Table 1). Finally, the renal phenotype of ARPKD can also be mimicked by mutations in the *HNF1B* gene, which encodes the transcription factor, hepatocyte nuclear factor-1 beta (HNF1B).

7. Animal models

At least eight mouse *Pkhd1* models have been described to date. The majority were generated by gene-targeting methods, while one model arose spontaneously as a truncating mutation in exon 48 (Table 2). In addition, the rat *PCK* model developed spontaneously in the Crj:CD/SD strain [62], due to an exon skipping event involving *Pkhd1* exon 36, leading to a frame shift mutation [2].

Of note, while an ARPKD-like liver phenotype is invariably present in all murine *Pkhd1* models, a renal phenotype is either absent or very mild in its expression, typically involving the proximal tubules and not the collecting duct. Interestingly, several models also express a severe pancreatic ductal phenotype, whereas clinically significant pancreatic disease in human ARPKD is quite rare.

The mechanism that underlies the limited renal phenotype remains unclear. However, genetic background appears to have a major impact on renal pathology, suggesting the genetic modifiers modulate renal disease expression. For example, in the *Pkhd1* del3-4 model, initial crosses of outbred heterozygotes resulted in a high rate of prenatal and perinatal lethality and a significant renal cystic lesion, but these phenotypes disappeared with subsequent inbreeding of viable ARPKD mice [63]. In the rat *PCK* model, transfer of the *Pkhd1* mutation from the original Sprague-Dawley background onto the Fawn-Hooded hypertensive genetic background resulted in significant attenuation of the renal cystic lesion, but had no effect on the hepatic phenotype [64].

While orthologous *Pkhd1* models in the mouse and rat do not phenocopy human ARPKD, there are at least two non-orthologous mouse models in which the renal and biliary lesions closely resemble the human ARPKD phenotype. The congenital polycystic kidney (*cpk*) model involves a truncating mutation in the *Cys1* gene that is predicted to completely disrupt the function of cystin, the encoded cilia-associated protein [65]. The BALB/c polycystic kidney (*bpk*) mouse model results from a splicing defect involving one of two isoforms encoded by *Bicc1*, thereby partially disrupting the function of bicaudal C, an RNA-binding protein [66]. While the common phenotype is sugges-

Table 2
Mouse *Pkhd1* models

Type	Symbol	Investigator	Mutation	*Pkhd1*$^{-/-}$	Kidney	Other
Targeted allele	*Pkhd1*^{tm1Rbu}	R. Buettner	Exon 40 skipping	viable	none	Liver*
Targeted allele	*Pkhd1*^{tm1Cjwa}	C.J. Ward	Exon 2 skipping	viable	PT dilatation	Liver*, Pancreas**
Targeted allele	*Pkhd1*^{tm1Ggg}	G.G. Germino	Exon 3-4 deletion	PL (29% survive)	TAL and CD	Liver*, Pancreas**
Targeted allele	*Pkhd1*^{tm1Gwu}	G. Wu	Exon 15-16 deletion	viable	PT and MCD dilatation	Liver*
Targeted allele	*Pkhd1*^{tm1Som}	S. Somlo	Exon 4 deletion	viable	none	Liver*, Pancreas**
Targeted allele	*Pkhd1*^{tm1Sswi}	S.S. Williams	Exon 1-3 deletion	viable	PT dilatation	Liver*
Targeted allele	*Pkhd1*^{tm2Cjwa}	C.J. Ward	Transcription termination intron 2	viable	PT dilatation	Liver*
Spontaneous allele	*Pkhd1*^{cyli}	L.M. Guay-Woodford	Exon 48 (c.7589delGGinsT)	viable	none	Liver*

Compiled from the Mouse Locus Catalogue. http://www.informatics.jax.org/allele/summary?markerId=MGI:2155808. PL = Partial perinatal lethality. PT = Proximal tubule; TAL = Thick ascending limb; CD = Collecting duct; MCD = Medullary collecting duct; Liver*=Intra-hepatic biliary ductal dysgenesis; Pancreas**=Intra-pancreatic ductal dysgenesis.

tive, it remains to be determined whether cystin and bicaudal C function in a common molecular pathway as FPC.

8. Perspectives on targeted therapies

Activation of the cyclic adenosine monophosphate (cAMP)-signaling and the mammalian target of rapamycin (mTOR) pathways, as well as dysregulation of the epidermal growth factor receptor (EGFR) axis have been well described in human ADPKD, ARPKD, and experimental PKD models [4] (Fig. 2).

Agents such as tolvaptan, that antagonize the vasopressin 2 receptor (V2R) and decrease intracellular cAMP, have been effective in attenuating cystic disease progression in the *PCK* rat [67] (Fig. 2A). The potential efficacy of V2R antagonists has been further demonstrated by genetic studies in which *PCK* rats were crossed with vasopressin knock-out rats to generate double mutant progeny with varying levels of circulating vasopressin. *PCK* rats lacking vasopressin showed lower intra-renal cAMP activity and almost complete inhibition of cystogenesis [68]. In addition, when treated with somatostatin analogs, which also reduce intracellular cAMP activation, *PCK* rats demonstrated reduced renal and hepatic cyst formation, with pasireotide showing greater benefit than octreotide [69].

Agents that inhibit the EGFR axis have been shown to significantly reduce the biliary and renal abnormalities in various murine models of ARPKD [70] (Fig. 2B). Furthermore, therapies directed at downstream targets of both the cAMP and EGFR pathways, such as Src, may prove efficacious, as demonstrated by one study of Src inhibition in ARPKD mice that led to improvement in both the biliary and renal abnormalities [71].

On the other hand, not all signaling defects readily translate into successful pre-clinical trials. For example; a trial with mTOR inhibition in *PCK* rat model failed to impact progression of kidney and liver disease [72]. The paradox between the tissue findings of mTOR activation and the lack of therapeutic efficacy in this one pre-clinical trial remains to be explained.

Despite the generally promising studies in experimental models, specific disease-targeting therapies to slow progression of human ARPKD remain elusive. Effective human clinical trial designs continue to be stymied by the lack of non-invasive predictive and prognostic markers to track disease progression and assess therapeutic impact on disease course. Current efforts are focused on optimizing pre-clinical studies with targeted therapeutics in experimental models and developing non-invasive markers for human clinical trials, which assess progression endpoints and are acceptable to regulatory agencies. Therefore, the goal of identifying targeted treatment that slows or arrests disease progression remains a work in progress.

9. Conclusion

In conclusion, ARPKD is a multifaceted genetic disorder, which requires expert, multi-disciplinary management. Investigations over the last decade have yielded new insights about the genetics and pathobiology of this disorder. Patient survival has been improved by advances in supportive therapy for neonates, treatment of systemic and portal hypertension, dialysis modalities, and transplantation. However, there are many remaining challenges to surmount in order to fully elucidate the mechanisms of disease expression and progression. Specifically, advances in understanding the function of the FPC protein, its putative isoforms, and the role of genetic modulators are key to defining pathogenetic mechanisms and identifying specific pathways for targeted therapeutics. In addition, improved technologies for non-invasive disease monitoring are essential for developing more precise predictive and prognostic markers. Newer study design methodologies, coupled with more robust predictive markers will set the stage for developing human clinical trials that can rigorously evaluate the efficacy of targeted therapeutic strategies (with single or multiple agents). The ultimate goal is to identify disease-specific markers that predict prognosis and validate targeted therapies to slow or even arrest the inexorable progression of ARPKD-related morbidities.

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