Chapter 2

Childhood Polycystic Kidney Disease

Ameya Patil[1,3], William E. Sweeney Jr.[1,3], Ellis D. Avner[1,2,3], Cynthia Pan[1,3]

Department of [1]Pediatrics, and [2]Physiology, Medical College of Wisconsin
[3]Children's Research Institute, Children's Hospital Health System of Wisconsin, USA

Author for Correspondence: Ellis D Avner, M.D, Emeritus Professor of Pediatrics and Physiology, Founding Director, Children's Research Institute; Children's' Hospital Health System of Wisconsin; Founding Associate Dean for Pediatric Research, Medical College of Wisconsin; Children's Corporate Center, Suite C-510, Mailstop CCC C510, 999 North 92nd Street, Wauwatosa, WI 53226, USA. Email: eavner33@gmail.com

Doi: http://dx.doi.org/10.15586/codon.pkd.2015.ch2

Abstract

Autosomal recessive polycystic kidney disease (ARPKD), historically called infantile PKD, is a major cause of morbidity and mortality in neonates, infants and young adults. Autosomal dominant polycystic kidney disease (ADPKD), historically referred to as adult PKD, is increasingly recognized as a significant cause of morbidity and mortality in children and young adults. ARPKD, a dual-organ disease with hepatic and renal

In: *Polycystic Kidney Disease.* Xiaogang Li (Editor)
ISBN: 978-0-9944381-0-2; Doi: http://dx.doi.org/10.15586/codon.pkd.2015
Codon Publications, Brisbane, Australia

involvement has an incidence of 1: 20,000 to 1: 40,000. All ARPKD patients are invariably afflicted with congenital hepatic fibrosis (CHF) of varying degrees of severity. Improved survival of ARPKD patients has led to recognition of significant clinical complications of CHF and the highly variable age at which it presents, ranging from early childhood to young adulthood. ADPKD, with an incidence as high as 1:400, affects more than 13 million individuals worldwide, and accounts for 7-10% of end stage kidney disease (ESKD) in adults. However, asymptomatic disease is increasingly recognized in infants and children and nearly equivalent numbers of ADPKD and ARPKD patients may be seen in academic pediatric nephrology clinics. The delineation of the basic molecular and cellular pathophysiology of ADPKD and ARPKD has seen remarkable progress in the last decade. This progress has led to the development of promising therapies currently being evaluated in clinical trials. Early diagnosis of ADPKD and ARPKD allows for optimal anticipatory care (for example, early blood pressure control). Given the predicted benefit of early intervention with new disease-specific therapeutics, screening at-risk youth, a previously-discouraged strategy, may now be warranted. This chapter will discuss central clinical characteristics essential for diagnosis and the care of children with ARPKD or ADPKD. We will also highlight recent insights in the molecular and cellular pathophysiology of PKD and the clinical translation into new therapies that promise to alter the natural history of disease for children with genetic PKD.

Key words: BP control; CHF; Combination therapy; c-Src; EGFR; Fibrosis; Preemptive care

Introduction

Cystic kidney diseases (CKDs) are a clinically and genetically diverse group of renal cystic diseases that have tubular cysts or renal dysplasia as a phenotypic element of their disease phenotype (1). These "phenocopies" and differentiating features are covered in detail in different Chapters in this text. Traditionally, the term polycystic kidney disease (PKD) refers to one of two genetically-distinct disorders: autosomal recessive polycystic kidney disease (ARPKD-OMIM 263200); and autosomal dominant polycystic kidney disease (ADPKD-OMIM 173900 and OMIM 173910).

ARPKD is the result of mutations in a single gene, the polycystic kidney and hepatic disease 1 (PKHD1) gene which encodes the fibrocystin/polyductin protein complex (FPC). ARPKD is typically diagnosed in the latter half of the trimester of pregnancy at birth or shortly thereafter with massive bilaterally enlarged kidneys that may complicate delivery. This disease was traditionally called infantile PKD, a name that no longer applies.

ADPKD is a heterogenic disease caused by mutations in two genes, PKD1 encoding polycystin 1 (PC1) and PKD2 encoding polycystin 2 (PC2). ADPKD, usually asymptomatic well into adulthood, is characterized by bilateral, progressive growth of renal cysts that most likely began *in utero*. It is now recognized that that both ARPKD and ADPKD can be clinically symptomatic in infants, children and adolescents and causing substantial degrees of morbidity and mortality in these age groups (2-8). The manifestations of childhood PKD can have considerable significant overlap in clinical and radiographic features making differential diagnosis between the two diseases difficult. This chapter will highlight the central clinical characteristics essential for the diagnosis and care of children with ARPKD or ADPKD, followed by a discussion regarding the existing knowledge of the molecular and cellular pathophysiology of these two genetic diseases, and how this information is informing development of current and future PKD-specific therapies.

Although ADPKD is typically an adult-onset, systemic disease, when presenting in the neonatal period, ADPKD may be clinically indistinguishable from ARPKD (9-11). In such instances, a detailed history, complete physical, imaging, and rarely, genetic testing and/or biopsy are usually sufficient to distinguish the two (7, 11, 12). Although no single finding is diagnostic (4, 6, 11) certain clinical features can help differentiate between ARPKD and ADPKD and these differentiating features are discussed in detail in different Chapters. Early diagnosis of asymptomatic individuals with either ARPKD or ADPKD currently offers the opportunity for maximal preemptive care such as tight blood pressure control, close surveillance of extrarenal manifestations (CHF, cardiovascular disease), avoidance of potential dietary and lifestyle progression factors and targeted disease-specific therapies that are on the horizon (6-8, 11, 13,14).

Autosomal recessive polycystic kidney disease (ARPKD)

ARPKD (OMIM 263200) is a rare, hepatorenal fibrocystic disease, characterized by non-obstructive, fusiform, cystic distension of renal collecting ducts with unpredictable degrees of congenital hepatic fibrosis (CHF), as a result of a biliary ductal plate malformation. Progressive biliary disease leads to periportal fibrosis or CHF, and may progress to Caroli disease, a cystic widening of the intrahepatic bile ducts; and the common bile duct (4, 6 , 12, 15, 16). ARPKD has an incidence rate of 1/20,000, is commonly diagnosed in utero or at birth, and despite a wide variability in phenotype, occurs due to mutations in a single gene, the PKHD1 gene (17-19). Despite the characteristic neonatal presentation of ARPKD, there is a significant variability in both age and presentation of initial clinical symptoms including the comparative level of renal and biliary abnormalities (15, 20, 21). The variability in the degree of organ involvement in ARPKD is not well understood but it is

generally recognized (7, 22-24). This phenotypic variability is regulated by the influence of other disease modifying genes, the combination of the two different parental PKHD1 mutations, epigenetic factors, hormonal effects, and environmental influences (23, 25).

Epidemiology and genetics

ARPKD is caused by mutations of PKHD1 gene that encodes the FPC. PKHD1 was cloned by two independent research groups in 2002 (18, 19). PKHD1 is an exceptionally large gene that spans approximately 470 kb of genomic DNA and consists of 86 exons, with 67 exons included in the longest open-reading frame transcript (18). A number of alternatively spliced transcripts have been identified; however, the exact function and clinical significance of these isoforms are unknown (26). Nearly 750 PKHD1 mutations have been identified to date (http://www.humgen.rwth-aachen.de).

With the cloning and identification of PKHD1 as the causative gene in ARPKD, attempts to define genotype-phenotype correlations have been attempted but to date only general correlations can be made. Recent discoveries regarding transcriptional complexities have only complicated any tenuous correlations and must be considered for appropriate genetic counseling.

A series of published ARPKD kinships demonstrate that mutations in PKHD1 are dispersed across the gene, without obvious clustering at mutational hotspots, and most families have distinctive ("private") mutations (19, 27-29). Additionally, nearly all patients are compound heterozygotes (23, 30), that is, each allele carries a different mutation. Missense, nonsense, frame shift and truncating mutations have all been described (31).

Patients with truncating mutations on both alleles typically displayed a severe phenotype, with a high rate of perinatal or neonatal demise (23, 27, 30). Patients with a least one missense mutation (amino acid substitutions) are more likely to, survive the neonatal period and beyond.(32, 33). Boddu et al. found 22 novel renal transcripts derived through numerous methods of alternative splicing. These include the use of alternate acceptor/donor splice sites, exon skipping and in a specific animal model of Pkhd1, inclusion of novel exons (26). These studies suggest that unconventional PKHD1 splicing occurs frequently and these splicing events may represent another pathogenic mechanism leading to ARPKD (26). The functional activity of these transcripts is unknown but these observations add a level of complexity for genetic counseling.

As the term autosomal recessive inheritance indicates, parents are heterozygotes (carriers), and are clinically-unaffected. The risk of any pregnancy producing an affected offspring is

25% and there is a 50% chance that unaffected offspring will carry a mutation in PKHD1 (4, 12). There appears to be no gender preference for ARPKD and all ethnic and racial groups are equally affected.

Diagnosis

With the advent of modern obstetrical ultrasonography (US), many patients with ARPKD are identified in the prenatal period. The diagnosis of ARPKD is based on clinical observations and our current understanding of the disease process. The diagnostic criteria proposed by Zerres et al. with modifications (11, 12, 34), are generally used and include:

1. US features typical of ARPKD, including enlarged, echogenic kidneys, with poor corticomedullary differentiation; and
2. One or more of the following:
    a. Absence of renal cysts in both parents, particularly if they are at least 30 years old,
    b. Clinical, laboratory or radiographic evidence of hepatic fibrosis,
    c. Hepatic pathology demonstrating characteristic ductal plate abnormalities,
    d. Previous affected sibling with pathologically or genetically confirmed disease,
    e. Parental consanguinity suggestive of autosomal recessive inheritance.

ARPKD is typically diagnosed in utero or at birth and manifests as progressive renal insufficiency and portal hypertension (PH) (34-36). The most severely affected fetuses display a classic "Potter" phenotype (oligohydramnios sequence) with massively enlarged echogenic kidneys with poor corticomedullary differentiation due to fusiform dilatation of the collecting ducts, respiratory insufficiency, cranial abnormalities and club feet (36). Oligohydramnios is detectable in utero, but may not develop in ARPKD until the third trimester (37).

Pulmonary insufficiency, a serious complication that generally occurs as the result of oligohydramnios, results in respiratory failure and subsequently neonatal death in approximately one third of neonates presenting with large, echogenic kidneys (4, 7, 11, 38). Patients that survive the neonatal period have a 1 year survival rate of 85% and a 10 year survival rate of 82% (25, 36). A smaller, though increasingly recognized subset of patients with ARPKD are diagnosed as older children or adults with abdominal enlargement secondary to enlarged kidneys or hepatosplenomegaly (21, 35, 39). These patients typically present with signs and symptoms related to congenital hepatic fibrosis including PH and esophageal bleeding (20, 25, 40). Other associated comorbidities including systemic hypertension, progressive renal insufficiency, and less commonly,

chronic lung disease in older children (35), especially in children who had respiratory insufficiency at birth. Improvements in neonatal critical care have allowed neonatal survival rates to improve, and with more patients with ARPKD surviving to adulthood, liver and other complications are likely to become more prevalent (20).

Pre-implantation genetic diagnosis through linkage analysis or mutational analysis is possible in families with at least one pathologically or genetically confirmed affected child when the mutation on both the maternal and paternal allele can be identified. Linkage analysis can also be used to identify the carrier status of an unaffected child. In "genetically informative" families, the accuracy of prenatal diagnosis using linkage analysis is >95% (41). Successful preimplantation genetic diagnosis has been reported for ARPKD (42). A list of laboratories that offer genetic testing including pre-implantation genetic diagnosis for ARPKD is available at www.geneclinics.org.

Pathology

The typical kidney phenotype consists of enlarged echogenic kidneys with loss of corticomedullary differentiation due to fusiform dilatation of the collecting ducts. Renal ultrasound of infants and young children, reveal bilaterally enlarged echogenic kidneys with poor corticomedullary differentiation (Figure 1a). The kidneys retained a reniform contour (Figure 1b), and multiple tiny cysts are confined to collecting ducts (Figure 1c) (11, 12, 36, 43). Macroscopically, the cut surface reveals a radial pattern of the spindle-shaped collecting duct cysts that extend into the renal cortex (Figure 1c). Microscopically (Figure 1d) the cysts are usually less than 2 mm in diameter and microdissection and immunohistological studies have demonstrated these "microcysts" to be dilated collecting ducts (36, 43-45). The glomeruli and other tubular segments appear to be decreased in number due to collecting duct ectasia and interstitial changes that squeeze and atrophy the renal parenchyma. Proximal tubular cysts have been identified in fetal kidneys, (46), but are generally t not seen after birth. The calyces, renal pelvis and renal vessels appear normal.

In contrast to renal cysts in ADPKD, where the tubular cysts detach from the tubule of origin, the fusiform cystic tubules in ARPKD remain in contact with the urinary stream. This has two important implications: 1) obstruction is not a component of cyst formation in ARPKD (44, 47); and 2) the afferent and efferent opening of an ARPKD collecting duct cyst remains in continuity with the urinary stream, and thus the urine is more likely to reflect changes that occur with cystic formation and growth. In ADPKD, where cysts pinch off from the tubular segment of origin, changes occurring in the cystic lesion are unlikely to be reflected in the urine. With increased patient survival and disease progression, hyperplasia results in larger renal cysts and interstitial fibrosis begins to develop which produces a pattern more like ADPKD (see Figure 3) (11, 12, 48).

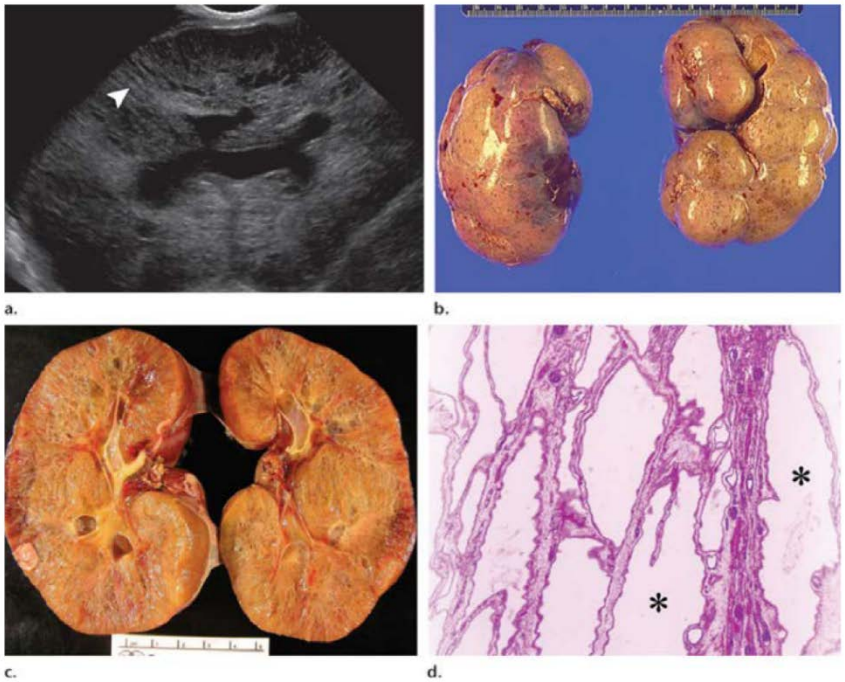

Figure 1. ARPKD in a 2-month-old boy. (a) Longitudinal high-spatial-resolution (8-MHz) ultrasonographic (US) image of the right kidney shows diffuse tubular ectasia involving the medulla and extending to the cortical surface (arrowhead). Note that the tubular nature of these cysts can be resolved by using a high-frequency transducer. The left kidney demonstrated a similar appearance (not shown). (b) Photograph of the gross specimen of the kidneys reveals a spongy appearance of the surface due to underlying cysts involving the cortex. (Scale is in centimeters.) (c) Photograph of the bivalved kidney shows a streaky appearance due to dilated tubules extending to the cortical surface with obscuration of the corticomedullary junction. (d) Photomicrograph (original magnification, ×4; hematoxylin-eosin stain) of the kidney shows the radially-oriented, ectatic collecting ducts (*) with glomeruli and normal tubules between the cysts, perpendicular to the connective tissue capsule.Reprinted, with permission, from Chung, et al. RadioGraphics 2014; 34:155-178 (43).

Biliary ectasia and the consequential hepatic fibrosis are invariably present in ARPKD. These biliary abnormalities are the result of a ductal plate malformation resulting in congenital hepatic fibrosis and biliary ductal ectasia (Figure 2) (7, 12, 16, 20). Although hepatic involvement is invariably present at the microscopic level at birth, it is symptomatic in only 40-50% of neonates (34). As the CHF advances, hepatomegaly and PH develop in a number of patients.

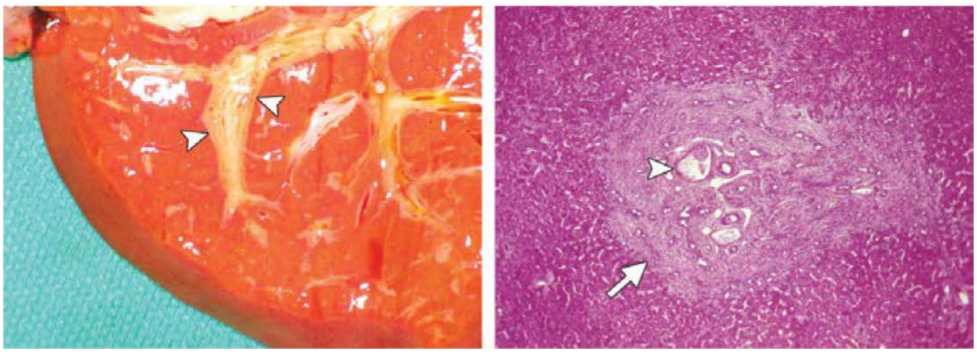

Figure 2. Pathologic findings of the liver in ARPKD-CHF. (a) Photograph of a liver section shows periportal fibrosis (arrowheads). (b) Photomicrograph (original magnification, ×10; hematoxylin-eosin stain) of the liver shows the portal vein and hepatic artery (arrowhead) in a portal area expanded by fibroblastic proliferation (arrow). Reprinted, with permission, from Chung, et al. RadioGraphics 2014; 34:155-178 (43).

PH is an increase in the blood pressure within the portal venous system and is clinically defined by the presence of splenomegaly, thrombocytopenia, low platelets counts, hypersplenism, enlarged hemorrhoids, and esophageal and gastric varices (20). In ARPKD, intrahepatic dilatation of both the central bile ducts and both large and small peripheral bile ducts in the setting of CHF (Caroli's syndrome) can occasionally progress to macrocysts and dilation of the extrahepatic bile duct (12, 20, 49). The combination of renal collecting duct and biliary ectasia with periportal fibrosis is unique to ARPKD (16, 40, 50-52).

Clinical

Lung development requires amniotic fluid to distend the developing fetal lung and adequate physical space for diaphragmatic movement is required (38). In ARPKD, oligohydramnios and restriction of diaphragmatic movement due to large cystic kidneys results in pulmonary hypoplasia. Pulmonary insufficiency is the major cause of morbidity and mortality in neonates with ARPKD. Infants with true pulmonary hypoplasia remain hypoxemic despite neonatal interventions and rarely survive (4, 11, 12).

At birth, patients usually have large, palpable flank masses that may be large enough to complicate delivery. Most newborns with ARPKD (70-80%) have some degree of impaired renal function which is often followed by a brief improvement as respiratory issues are alleviated, and renal development continues (7, 10, 34). Hyponatremia which may exist initially, usually resolves quickly, unless the patient has acute renal failure (34, 53). Most patients have a urinary concentrating defect and symptoms of polyuria and polydipsia (7,

10, 12, 48, 53, 54). Although kidneys may be markedly enlarged at birth, over time, the majority show stable to decreased renal size (12, 55, 56).

Although all ARPKD patients demonstrate some degree of microscopic evidence of CHF at birth, the consequence of these findings is unpredictable. Complications of CHF may develop at any time between birth and adulthood or they can remain asymptomatic even into adulthood (57). The renal and hepatobiliary disease components of ARPKD advance at varying rates for reasons that are unclear. However, the progressive biliary ductal ectasia and CHF must be closely monitored because the hepatobiliary disease can lead to the development of PH which can be severe (12, 16, 20).

PH is the main complication of CHF. Manifestations of PH can include hepatosplenomegaly, hypersplenism with low platelet counts, variceal and hemorrhoid bleeding and most importantly an increased risk of developing bacteremic infections from ascending cholangitis (7, 11, 16, 57). Recent studies of PH in ARPKD reveal that this progression starts early in life, and can initially be identified by hepatomegaly that starts in the left lobe of the liver (20, 34).

The clinical significance of severe hepatobiliary disease has become an increasingly important as ARPKD survival rates improve. Recent studies into the hepatobiliary component of ARPKD estimate that 40% of ARPKD survivors will demonstrate severe renal and severe hepatobiliary disease. The remaining 60% of ARPKD survivors will exhibit degrees of dual-organ disease that can be generally grouped into either severe kidney/mild hepatobiliary disease, mild kidney/severe hepatobiliary disease, or mild kidney/mild hepatobiliary disease (20, 58). Platelet count was identified as an accurate measure of the severity of PH in patients with ARPKD and correlates well with spleen size (20).

Hypertension, a common presenting feature in both infants and children, is often severe, can be difficult to control and frequently requires multidrug treatment (6, 11, 12, 39, 48, 59). Hypertension is often found in patients with normal renal function and it will eventually affect nearly all children with ARPKD (11, 24, 35). The pathophysiology of hypertension in ARPKD multi-factorial but activation of the intrarenal renin-angiotensin system is thought to be an important component (15).

Treatment and complications

Advances in neonatal critical care have led to increased survival rates of neonates with ARPKD. Predicting which neonates with ARPKD who require immediate artificial

ventilation will have life-threatening degrees of pulmonary hypoplasia is currently not possible (4, 7, 10). This is due to the fact that, severe pulmonary distress may be caused by a potentially-reversible fluid overload, true neonatal pulmonary hypoplasia, or restricted motion of the diaphragm due to massively enlarged kidneys. In selected cases, a more accurate assessment of the long-term pulmonary prognosis of the patient can be achieved through continuous venovenous hemofiltration, or a unilateral or bilateral nephrectomy to allow diaphragmatic movement, coupled with peritoneal dialysis (60, 61).

Young patients with ARPKD, including those without significant renal insufficiency, should be closely monitored. The loss of concentrating ability in these patients creates a significant risk of dehydration with intercurrent illnesses. Hyponatremia due to impaired urinary dilution (rather than sodium wasting) is common in ARPKD. When present, fluid intake should be curtailed without compromising nutrition (24). In patients with severe polyuria, thiazide diuretics may be used to decrease distal nephron solute and water delivery. Patients with metabolic acidosis will require supplemental bicarbonate therapy.

Urinary tract infection (UTI) rates as high as 50% have been reported with in patients with ARPKD, with girls having a greater frequency than boys (12). Any child with an abnormal urinalysis, antibody therapy should be guided by clinical features and appropriately obtained urine cultures. If a UTI is diagnosed, an evaluation to rule out vesico-ureteral reflux, obstruction, or bladder dysfunction is recommended (4, 7, 62). Infants and children with ARPKD are at risk of the consequences of progressive CKD (e.g. growth failure, anemia, renal osteodystrophy and cognitive deficits) and this risk increases as renal function declines (7, 11, 12).

In patients with symptomatic end stage kidney disease (ESKD), peritoneal dialysis is preferred modality and is shown to work well even with intra-abdominal organomegalies including liver, spleen and kidneys [9, 40]. Renal transplant should be appropriately considered (7, 24). If transplantation is necessary, a nephrectomy may be necessary to permit room for transplant placement in patients with enormous kidneys and may be indicated to control hypertension. Patients suffering from severe renal and severe biliary disease should be evaluated for a combined liver and kidney transplant (58). A decision tree that guides appropriate choices has been developed and can be found in Telega et al. (58).

Difficulties in feeding and poor growth, even in patients without renal insufficiency, are often noted. In such cases, regular nutritional evaluation, can help guide appropriate therapy, and feeding specialists should be part of the multidisciplinary care team. Data from the NIH-supported Natural History Study of ARPKD indicate that normal growth curves can be achieved with appropriate support measures (51). Improvements in neonatal

critical care and advances in renal replacement therapy have improved patient survival and as a result hepatic complications become the dominant clinical issue of many patients with ARPKD (20, 34, 35, 63-65). PH, an increase in the portal venous pressure occurs in 37-65% of ARPKD neonatal survivors (20, 25, 35). Despite the development of PH, hepatocellular function frequently remains normal (11, 16, 20).

The most serious complications of PH are bacterial cholangitis and bleeding varices. ARPKD patients with extensive dilatations of intrahepatic and extrahepatic bile ducts are at increased risk of ascending bacterial cholangitis. Development of fever or rarely a sudden elevation of liver function tests at any time should raise the suspicion of cholangitis and appropriate evaluation and antimicrobial therapy should be initiated.

From the time of initial diagnosis, all patients with ARPKD should be evaluated by a gastroenterologist and undergo regular evaluations for hepatobiliary complications (58). Recommended evaluations should include periodic imaging by either magnetic resonance cholangiopancreatography (MRCP), magnetic resonance imaging (MRI) or ultrasound on an annual basis for increased liver echogenicity, hepatobiliary abnormalities, and splenomegaly. Platelet counts have been reported to be a surrogate marker of the severity of PH and should be checked immediately (20). Endoscopy is routinely required to find varices early and treat them by endoscopic bind ligation (EBL) to prevent potentially lethal bleeding. Platelet count (as a surrogate marker of the severity of PH) (20) and hemoglobin/hematocrit are routinely monitored as a sign of hypersplenism, splenic sequestration and GI hemorrhage with varices. Porto-systemic shunting may be indicated in cases where variceal sclerotherapy is inappropriate or has failed (53, 66), but Telega et al. recommend this should be done in consultation with a transplant surgeon (58). Patients with severe PH and moderate to severe renal disease should be evaluated for dual liver and kidney transplant (58).

ARPKD patients are potentially at risk for neurocognitive and behavioral dysfunction due to early onset severe hypertension and CKD (67) although little data exist to guide clinical practice (24). In addition to the significant medical problems, the psychosocial stresses of ARPKD on the patient and family can be formidable (4, 7) and should be kept in mind. Social support measures may be required for exhaustion because of due to the demands of new roles, depleted finances, and other aspects of a changed lifestyle (4).

A multi-disciplinary team that includes a pediatric nephrologist, and pediatric gastroenterologists in concert with, dietitians, social workers, and if needed psychiatrists and other support staff may be necessary to provide optimal comprehensive care for patients with ARPKD.

Autosomal dominant polycystic kidney disease (ADPKD)

ADPKD, more common than ARPKD, has a incidence rate of 1:400-1:1000 with 13 million people affected worldwide, and accounts for 7 to 10% of ESKD in adults. ADPKD was historically termed "adult" polycystic kidney disease due to the classic presentation of clinical symptoms that typically do not arise until adulthood. ADPKD is a systemic disease with early-onset hypertension and extrarenal manifestations that include, cystic lesions in the liver, spleen, and pancreas and vascular abnormalities that may including mitral valve prolapse and less frequently, intracranial aneurysms (ICAs).

Despite the classic textbook description of ADPKD as an adult disease, significant clinical manifestations of ADPKD can be seen in children and in some cases, in utero (2, 3, 5, 8). Pediatric patients who do present in childhood have similar renal findings to those of affected adults. In contrast, the extrarenal manifestations of ADPKD commonly seen in adults (for example, cysts in the liver and pancreas and ICAs) are infrequently or rarely observed in pediatric patients. A detailed discussion of these extrarenal manifestations of ADPKD can be found in other Chapters of this volume and therefore only pediatric specific topics stemming from childhood ADPKD will be discussed below.

It is increasingly being recognized that pediatric ADPKD patients, with early manifestations of disease, are most likely to benefit from early therapeutic interventions (7, 8, 11, 68). It is important therefore that clinicians be aware of these ADPKD-related manifestations when caring for children with, or at risk of, ADPKD.

Renal cysts in ADPKD kidneys form in utero and bilateral enlarged cystic kidneys, left ventricular hypertrophy with or without systemic hypertension, proteinuria, gross hematuria, nephrolithiasis, flank pain, and impaired renal function can be seen in infants, children and adolescences (2, 3, 7, 8, 11). The most clinically-significant, potential lethal extrarenal manifestation of ADPKD, ICAs rarely occurs in children. In patients with ADPKD there is a significant degree of phenotypic variability in the rate of progression even among family members, implying factors other than the primary mutation, influence the clinical course of ADPKD. These include modifying genes, epigenetics, dietary and environmental factors.

Diagnosis

As previously noted, the clinical spectrum of pediatric or early-onset ADPKD is especially broad and on rare occasions may be difficult to distinguish ADPKD from ARPKD especially in newborns. However, ADPKD in early childhood generally presents as

unilateral or bilateral renal cysts in a normal or in mildly enlarged kidneys. Unfortunately, it is still difficult to predict how ADPKD will progress in children with this presentation. The disease may become more clinically symptomatic or the disease may remain asymptomatic well into adulthood (9, 36, 54, 59, 69-72). The differential diagnosis of ADPKD is further discussed in Chapter 1 of this text.

Pathology

The typical appearance of ADPKD in children by US is one or more renal cysts within enlarged kidneys (see Figure 3a). In ADPKD children, kidney cysts form in glomeruli and all tubular segments (see Figures 3b, 3c, 3d, and 3e). The cyst formation is commonly asymmetric and may occasionally present as unilateral (7, 73). In general, the finding of even a single solidary renal cyst in an at-risk pediatric or adolescent patient should prompt further evaluation as simple cysts are extremely rare in children (7). Glomerular cysts may be a component of ADPKD or can occur as a separate, autosomal dominant disease entity. Unlike ARPKD, in which the cystic lesions are ectatic and remain in continuity with the nephron of origin, in ADPKD enlarging cysts "pinch off' or detached from the tubule and do not remain connected to the urinary stream.

Clinical features

As previously noted the clinical spectrum of pediatric or early-onset ADPKD is particularly broad and there is still little evidence to allow accurate prediction of those patients that will rapidly progress. It may present infrequently as severe disease as noted above may be indistinguishable from ARPKD. More frequently, pediatric ADPKD will presents as unilateral or bilateral renal cysts in near normal or mildly enlarged kidneys. Children with this presentation may be symptomatic or may they may remain asymptomatic into adulthood (9, 36, 54, 59, 69-72). Additional renal manifestations of childhood ADPKD include micro and gross hematuria, hypertension, proteinuria, and rarely abdominal, flank or back pain (7, 8). Overt proteinuria is ordinarily a feature of more advanced structural kidney disease and is rare in children with ADPKD (74) but little to no correlation between microalbuminuria and either kidney volume or function in children with ADPKD has been reported (75, 76).

As with ARPKD, hypertension as early as the newborn periods can be a presenting feature in children with ADPKD. Hypertension often precedes biochemical and clinical manifestations of ADPKD and is an important screening measure for at risk children (2, 54, 68, 69, 77). A strong correlation between hypertension and larger kidneys has been observed in multiple cohorts of ADPKD children (74-76, 78). If the affected parent has hypertension, it is more likely to develop at a greater frequency and at an earlier age in their offspring with ADPKD (79).

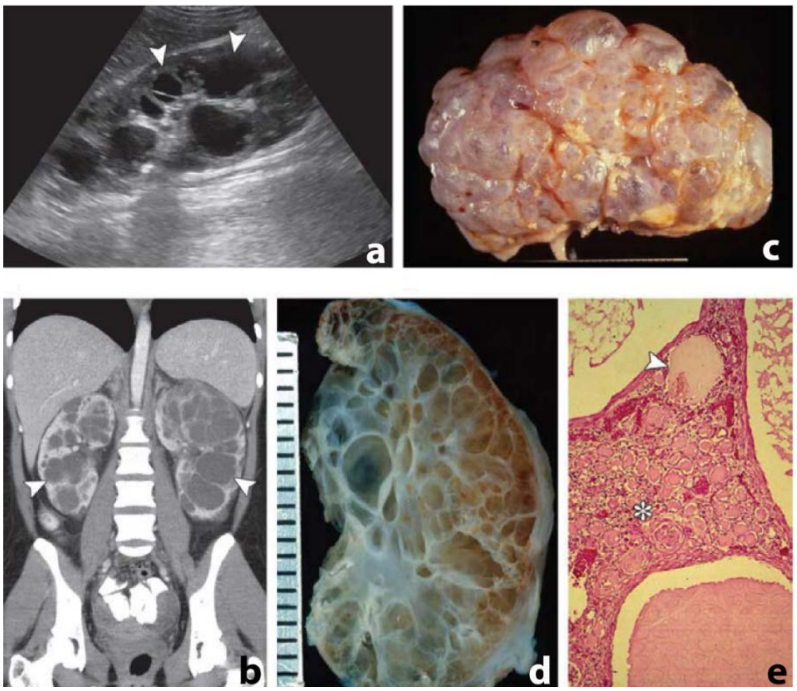

Figure 3. Renal cysts in ADPKD. (a) Longitudinal ultrasound (US) image of the right kidney in a 14-year-old girl reveals multiple round renal cysts (arrowheads). (b) Coronal computed tomography (CT) image in the same patient after administration of intravenous contrast material shows multiple cysts in both kidneys (arrowheads). (c) Photograph of the gross specimen from another patient shows the bosselated surface of the kidney due to many underlying cysts. (d) Photograph of the sectioned gross specimen from another patient shows innumerable round medullary and cortical cysts replacing much of the parenchyma. (Scale is in centimeters.) (e) Photomicrograph (original magnification, ×4; hematoxylin-eosin stain) demonstrates multiple cysts crowding the intervening renal parenchyma with distention of tubules by proteinaceous material (*). Multiple smaller cysts are seen interspersed in the parenchyma as well (arrowhead). Reprinted, with permission, from Chung, et al. RadioGraphics 2014; 34:155-178 (43), and the Radiological Society of North America (RSNA).

The use of ambulatory blood pressure monitoring (ABPM) to assess blood pressure (BP) in ADPKD patients has permitted greater precision and revealed abnormalities of BP in ADPKD patients. Nearly 33% of children with ADPKD demonstrate exclusively nocturnal hypertension (80, 81). A significant proportion of normotensive young adults with ADPKD have "prehypertension" by ABPM (68, 82). Blunted "nocturnal dipping" on ABPM has also been reported to be associated with endothelial dysfunction in this population (83). The pathogenesis of hypertension in ADPKD is multifactorial and beyond the scope of this chapter. Excellent reviews are available (68).

Childhood PKD

Cardiovascular disease is a major feature of ADPKD, and children with ADPKD demonstrate a substantial correlation between left ventricular mass index (LVMI) and systolic blood pressure (68, 84). Hypertensive and pre-hypertensive (blood pressure in the upper range of normal (75–95th percentile for age, sex, and height) children with ADPKD have a statistically significantly higher LVMI than normotensive ADPKD children (8, 78, 84).

Adult ADPKD patients have an increased incidence of cardiac valvular abnormalities such as mitral valve prolapse, and these abnormalities have also been reported in children with ADPKD (36 , 84, 85). In addition to hypertension, other presenting symptoms can include abdominal pain, palpable abdominal masses, gross or microscopic hematuria, UTIs, and abdominal or inguinal hernias. The occurrence of gross hematuria after minor trauma to the side or back should raise the possibility of ADPKD in at risk children. Renal insufficiency in children with ADPKD has been reported but it is generally rare (4, 12, 69, 71). A renal concentrating defect was found in 58% of children with ADPKD in a cohort of children with ADPKD (10, 86). The finding of a renal concentrating defect was shown to correlate with the presence of hypertension by ABPM (87). These findings suggest that impaired renal concentrating ability may be a rough measure of disease severity in children with ADPKD. Renal infections can be a presenting feature in an infant or child with ADPKD (54). Pain from renal stones or a ruptured cyst rupture can also occur in children with ADPKD.

The extrarenal cysts seen in adults with ADPKD (85, 88) occur infrequently in pediatric patients. However, can they provide clinical criteria for a differential diagnosis if found in a child with ADPKD (11). Liver cysts (detected by US) were thought to be a rare finding in children with ADPKD, but a recent MRI study found liver cysts in 55% of adolescents and young adults with ADPKD (89). Liver cysts in children, when present, are not generally associated with pain, infection, and hepatomegaly.

Treatment and complications

Currently treatment options for ADPKD patients is limited to management of renal and extra-renal complications. Asymptomatic children at risk for ADPKD should be closely monitored especially for the development of hypertension and pre-hypertension, hematuria, polyuria, proteinuria or palpable abdominal masses. Any of these findings should prompt further evaluation.

Identification and treatment of hypertension in children is vital in order to slow progression to ESKD in ADPKD. In adults with ADPKD, more intensive blood pressure control (<120/80)

was reported to have a greater impact on LVH reduction than standard control (<140/90) (90). Recent report from the HALT/PKD study failed to demonstrate any benefit gained by adding an angiotensin receptor blocker (ARB) telmisartin to an angiotensin converting enzyme inhibitor (ACEi) lisinopril on ADPKD progression in adult patients with early or moderately-advanced kidney disease. However, a second arm of the HALT/PKD study in younger patients with moderately-preserved renal function, a beneficial effect on total kidney volume (TKV), decreased urinary albumin excretion and LVH was observed when the blood pressure was reduced to a lower target level with an ACEi (91, 92). These data may be particularly applicable to children especially earlier in the disease process. In a randomized double-blind placebo-controlled phase III clinical trial of pravastatin on height-corrected total kidney volume (HtTKV) and LVMI by MRI, pravastatin was effective in slowing the progression of structural kidney disease in older children and young adults with ADPKD (76).

These considerations notwithstanding, well-established international guidelines for staged therapy of hypertension in pediatric patients should be followed.(93). There is little data regarding specific features of UTIs or renal cyst infections in children with ADPKD but the clinical course and certainly the treatment would likely be similar to that for adult ADPKD patients (94, 95).

Flank pain in pediatric ADPKD patients is unusual most likely due to fewer cysts. However, as the disease progresses, particularly in adolescents, flank pain may require intervention. A recent review summarizes the multifactorial pathogenesis and management of chronic pain in ADPKD (96).

Cerebral aneurysms and bleeding occurs in approximately 10% of ADPKD patients and this trait seems to cluster within families (97-99). However, since this rarely occurs before 20 years of age routine screening of pediatric ADPKD patients is not recommended until they reach the age of 20 years old, (100). Screening by magnetic resonance angiography (MRA) may be recommended for patients with symptoms or a positive family history once they reach 20 years of age (97).

Prognosis

The prognosis of early-onset ADPKD presenting in utero or in the neonate was once thought poor. However, recent studies of "very early onset" ADPKD suggest that the prognosis is not as dire as generally presumed. (4, 101, 102).

Given the findings that aggressive treatment of hypertension reduces LVH and the use of pravastatin slows progression of structural kidney disease as well as reduces LVH,

screening of at risk patients to identify those at risk for rapid progression has become increasingly important (8, 76). New therapies that effectively and safely reduces the number and/or size of renal cysts will most likely provide maximum benefit when started early in the disease course. A recent systematic review of factors that predict progression in ADPKD can be found in (103) .

Pathophysiology of cyst formation in childhood PKD

Delineation of our understanding of molecular mechanisms that drive pathophysiology of cyst formation in PKD is advancing rapidly. However, abnormal cell-signaling networks ultimately produce disease burden. Therefore, therapeutic interventions are largely based on targeting the complex aberrant cellular signaling which defines the cystic cellular phenotype noted below.

Molecular pathogenesis [See chapters 7 to 16, this text]

It is clear that standard Mendelian genetics are inadequate to predict the severity or the rate of progression of the renal disease nor the severity of extrarenal manifestations in childhood PKD. Complex transcriptional events are clearly major disease modifiers in childhood PKD. Recent findings including: the discovery of hypomorphic or incompletely penetrant alleles (104); homozygosity involving either PKD1 or PKD2 (105); compound heterozygosity (23); digenic inheritance or trans-heterozygosity (106); somatic and germline mosaicism (107); genetic modifiers (108) and epigenetic regulators (109, 110) co-inheritance of mutations in either PKD1 or PKD2 with other PKD-causing genes such as HNF1B (36, 111) or the tuberous sclerosis 2 (TSC2) gene (112), all demonstrate that complex inheritance patterns contribute to disease severity and progression in ADPKD and ARPKD.

Cellular pathophysiology of cyst formation in PKD

Cyst development and growth is a complex, multi-factorial process and no single element acts independently. The exact mechanisms that lead to the PKD phenotype is still unclear; however, multiple cellular defects have been identified. Molecular factors that have been shown to influence the extent or severity of cyst formation include: the developmental timing of PKD1 inactivation (113, 114); reduction in functional PC1 dosage (105, 115, 116); cellular and nephron differences in sensitivity to PC1 dosage (115) and the influence of one cyst on neighboring nephrons creating a "snowball effect" leading to cyst development in adjacent tubules (117).

The defining features of a PKD cystic epithelial cell include: a changeover from a mature differentiated, nonproliferative, absorptive cell to a partially dedifferentiated; secretory cell characterized by specific polarization defects; and increased rates of proliferation as well as apoptosis. These changes leading to a proliferating secretory cell is a fundamental and critical change because mathematical modeling of renal cystic epithelia establish proliferation and secretion as necessary and sufficient to account for cyst growth in PKD (118).

Cyst formation in PKD

ADPKD and ARPKD cells share phenotypic abnormalities regardless of when they become clinically-evident. Mutated PKD genes result in abnormal multiprotein complexes whose abnormal function leads to aberrant signaling events resulting in the unique phenotype of the cystic epithelial cell. The precise mechanisms by which these abnormal complexes disrupt normal signaling and cause renal cyst formation are not fully elucidated, significant progress in understanding the cellular events surrounding cyst formation has been made. Key pathogenic features of the unique cystic phenotype have been identified (6, 13, 116, 19-24). These phenotypic abnormalities provide therapeutic targets for the development of PKD therapies, and include:

- abnormalities of in expression of one or more members of the epidermal growth factor (EGF) family of receptors and/or ligands, the (EGFR –axis), leading to an autocrine-paracrine cycle of proliferation through activation of the Ras-Raf-MEK-ERK pathway
- increased cAMP in concert with decreased intracellular calcium levels leads to aberrant intracellular cAMP signaling resulting in activation of the β-Raf /MEK-ERK pathway and stimulates both proliferation and tubular fluid secretion.
- abnormal activity of C-terminal Src kinase or cellular Src (c-Src). A critical molecule that mediates cross-talkbetween the EGFR axis and G-protein-cAMP pathways
- abnormal function of the primary cilia;
- changes in cell-cell, and cell-matrix interactions, and
- alternative activation of renal interstitial macrophages that contribute to the development of progressive fibrosis.

The pathogenic processes listed above all likely contribute at some point to the central characteristic features of renal cyst formation and progressive enlargement, namely: (a) tubular epithelial proliferation; (b) abnormal tubular secretion; and (c) alterations in extracellular matrix, structure, and/or function; and (d) recruitment of macrophages and inflammatory mediators (6, 118, 121, 122, 124-128). Crucial insights into the cellular events

leading to renal cyst formation in PKD have been discovered by orthologous and non-orthologous models of ARPKD and ADPKD. Due to rapid advances in molecular techniques allowing for rapid creation of genetically-manipulated or conditionally targeted models of disease, a comprehensive listing of these models would not be feasible. The interested reader is referred to the following, which review the most significant of these models produced to date (104, 105, 113, 124, 129-131).

The cystic phenotype and targeted future therapy

As discussed in a number of chapters in this text, studies designed to delineate the molecular and cellular biology of ADPKD and ARPKD have defined a unique "cystic phenotype." This phenotype provides a number of potential targets for the current and future pharmacological therapy (see Figure 4 and Table 1).

Targeted therapeutic strategies can be divided into three categories based upon insights into the pathogenesis of cyst formation in PKD and the aberrant integration of signaling pathways identified to date. These include therapies to: (a) reduce cell proliferation; (b) reduce cAMP levels, and (c) reduce fluid secretion.

Proliferation is an essential process that must be targeted and controlled for any therapy to be effective. There are two main signaling pathways that lead to unchecked proliferation: a) the EGFR family of receptors and ligands; and b) a G-protein regulated axis that leads to increased cAMP and a phenotypic shift in renal epithelia's response to cAMP. c-Src is a key intermediate that connects both pathways and plays a role in perpetuating the activity of the two pathways. A theoretical sequence of events could follow this step-by-step description: A mutation in PKD1 lead to increased production of amphiregulin, which activates the EGFR axis resulting in: reciprocal phosphorylation (activation) of Src that interacts with the cAMP pathways by altering the response of renal epithelia to cAMP levels, from a normally anti-mitotic to a pro-proliferative response and, in the presence of the terminal tail of PC1, Src dependent activation of STAT3 leads to a persistence of the proliferative signal.. The most promising therapies will most likely target key signaling intermediates that integrate multiple pathways, such as Src, and/or a combination therapy approach where multiple compounds are used to target multiple pathways simultaneously or a single compound that targets multiple pathways such as a multi-kinase inhibitors (MKI) like tesevatinib (132, 133) ("Tesevatinib Ameliorates Progression of ARPKD in Rodent Models" manuscript submitted 9, 2015), currently in clinical trial for ADPKD (ClinicalTrials.gov Identifier NCT01559363).

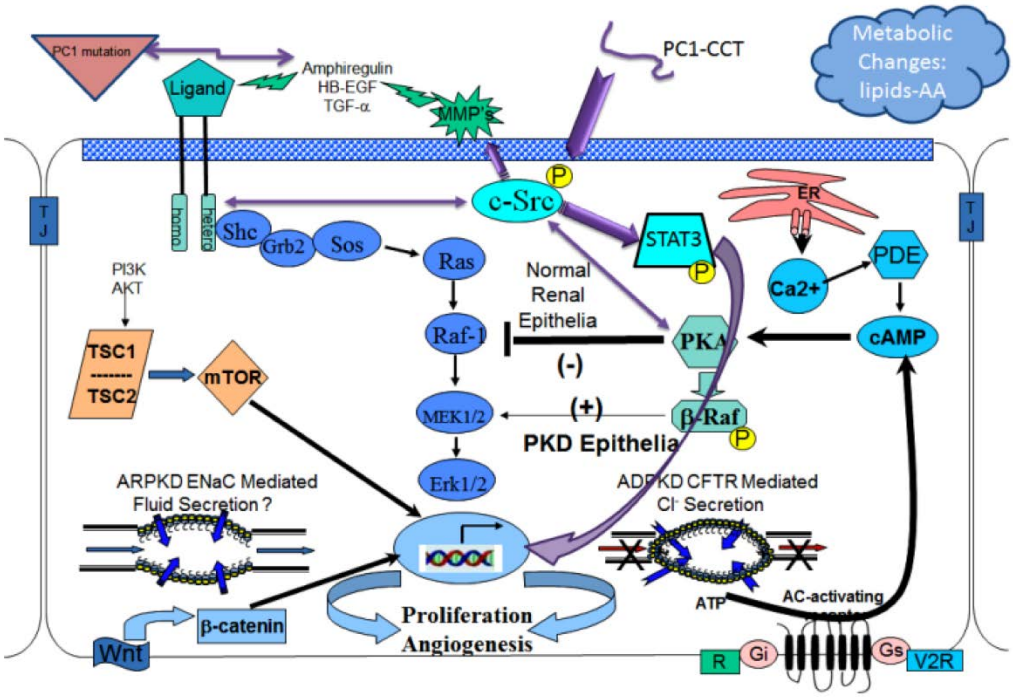

Figure 4. An abridged composite of the abnormally active signal transduction pathways in PKD. This figure represents our approach to the discovery and testing of potential therapeutic interventions. We view proliferation as the critical factor that must be targeted for any therapy to be effective. There are two main conduits that lead to unchecked proliferation: 1) the EGFR axis; and 2) a G-protein axis that leads to increased cAMP and a switch in phenotypic response of renal epithelia to cAMP. Using therapies that inhibit both pathways, a smaller dose will be necessary to achieve maximum cyst reduction and any toxicity associated with the therapy will be minimized. We view c-Src as a critical intermediate that connects both conduits and plays a critical role in integrating the signaling from both conduits. Mutations in PKD1 lead to increased production of amphiregulin, an EGFR ligand which activates the EGFR axis resulting in: reciprocal phosphorylation (activation) of Src that alters the response of renal epithelia to cAMP, from a normally anti-mitotic to a pro-proliferative response. In the presence of the cleaved terminal tail of PC1, Src-dependent activation of STAT3 leads to increased proliferation. Src activation of STAT 3 is amplified by the increased activity of both the EGFR axis and cAMP axis thereby further driving the proliferation of tubular epithelium.

Table 1. The future: potential therapies for childhood PKD

CLASS	ADPKD	ARPKD	EVIDENCE Clinical trials (www.clinicaltrials.gov) Preclinical Studies (PCS) (ref#)
VPV2R antagonist	+/-	+/- (renal only)	multiple CTs ongoing
Src-i	+/?	+/?	CT- Phase II-III
mTOR-i	-/?	-/?	CTs (poor results to date)
Multikinase-i	+/?	+/?	CT for ADPKD in progress
Somastatin and/or analogues	+/?	+/?	CTs for ADPKD in progress
ACEi and ARB	+/? (early disease)	?/?	HALT-PKD (91)
	--/? (late disease)	?/?	HALT-PKD (92)
Statins	?/?	?/?	CT (small cohort) (76)
Triptolide	?/?	?/?	CT (China only) PCS (135)
EGFR axis inhibitors	+/?	+/?	PCS (136)
Angiogenesis-i (+ other therapy)	+/?	+/?	PCS (137)
MMP-i	+/?	+/?	PCS (138)
SMAC Mimetics	+/?	+/?	PCS (139)
HDAC-I	+/?	?/?	PCS (140-142)
Bromodomain Protein-i	+/?	?/?	PCS-(143)
MIF-i	+/?	?/?	PCS-(144)
TNF-α-i	-/?	+/?	PCS (145)
20-HETE-i	+/?	+/?	PCS (146)
ROS-i	+/?	+/?	PCS (147)
CDK inhibitors	+/?	+/?	PCS (148)
HSP90-i	??	??	PCS (149)
Manipulation genetic modifiers	??	??	PCS (150)

The table lists potential therapies based upon pre-clinical trial studies (PCS) or (CT= clinical trials). Updated listing of clinical trials can be found at (www.clinicaltrials.gov).

A number of agents in advanced states of pre-clinical development or Phase 2-3 clinical trials are discussed in Chapter 6. Current listings of ongoing clinical trials for ADPKD and ARPKD can be found at (www.pkdcure.org; and http://clinicaltrials.gov/).

Conclusion

The diagnosis of childhood PKD is no longer the terminal diagnosis it once was. For children with ARPKD advances in neonatal critical care and renal replacement therapy have allowed many to survive much longer than what was possible just a few decades ago. Insights into the development and treatment of PH is preventing lethal complications of hepatobiliary disease and provides for a better quality of life. Renal transplantation and dual organ transplantation provides an opportunity for these children to live a near normal life. Pre-implantation genetic diagnosis holds the possibility of eliminating this ARPKD from families who can afford the procedure and who aren't ethically opposed.

For families afflicted with ADPKD, screening of non-symptomatic at-risk offspring, once almost universally discouraged, may change given the evidence that tight control of hypertension can dramatically reduce development of LVH and that pravastatin can dramatically slow structural renal damage from ADPKD. The development of targeted therapies for PKD, and the fact that early intervention should provide the greatest benefit may also increase the number of at-risk offspring being screened.

Despite the extraordinary progress made to date in understanding the molecular and cellular mechanisms of cyst formation in PKD much remains to be done. As our understanding of the molecular mechanisms improves, we must couple this knowledge with new techniques that allow for the rapid creation of animal models that more accurately represent the human disease state. These models will provide increased understanding and new insights into the molecular and cellular mechanisms of PKD that will generate new therapeutic targets as well as provide the basis for the development of even better pre-clinical models of PKD.

Therapies will become increasingly focused on treating PKD in early childhood where they are likely to provide the maximal benefit. The strict control of hypertension will remain an absolute essential component of PKD therapies in the future. Therapies that currently target abnormal signaling pathways will be carefully balanced so that pathway activity is reduced to "normal" or wildtype levels rather than eliminated completely. Modifications to promising compounds will be developed to guide the molecule to the site of need, making these therapies highly specific with very low levels of toxicity (134). This specificity will speed the development of protocols for the ethical treatment of children with PKD where early intervention may allow a lifetime free from the deleterious effects of PKD. Epigenetic and dietary factors that slow or hasten the progression of PKD will be uncovered and adherence or avoidance of such factors may slow the progression of PKD and eliminate the need for pharmacological intervention or renal replacement therapy for some.

As clinical trials to date have shown, targeting a single molecule of pathway has not brought the promising reduction of disease burden as originally hoped for. It is unlikely that any single therapy or compound will be effective especially at all stages of disease. Rational therapies will require knowledge of the extent of disease, the rate of progression, and how this is best assessed. In the near term, therapeutic intervention will likely involve multiple compounds, and the choice of compounds or targets will be stage specific and change as disease progresses.

Conflict of interest

The authors declare that they have no conflicts of interest with respect to research, authorship and/or publication of this book chapter.

Acknowledgements

This work was supported, in part, by the Lillian Goldman Charitable Trust; the Ellsworth Family Fund; and the Children's Research Institute at the Children's Hospital of Wisconsin.

References

1. Fliegauf M, Benzing T, Omran H. When cilia go bad: cilia defects and ciliopathies. Nat Rev Mol Cell Biol. 2007;8(11):880-93.
http://dx.doi.org/10.1038/nrm2278
PMid:17955020
2. MacDermot KD, Saggar-Malik AK, Economides DL, Jeffery S. Prenatal diagnosis of autosomal dominant polycystic kidney disease (PKD1) presenting in utero and prognosis for very early onset disease. J Med Genet. 1998;35(1):13-6.
http://dx.doi.org/10.1136/jmg.35.1.13
PMid:9475088 PMCid:PMC1051180
3. Pretorius DH, Lee ME, Manco-Johnson ML, Weingast GR, Sedman AB, Gabow PA. Diagnosis of autosomal dominant polycystic kidney disease in utero and in the young infant. J Ultrasound Med. 1987;6:249-55.
PMid:3295293
4. Dell KM. The spectrum of polycystic kidney disease in children. Adv Chronic Kidney Dis. 2011;18(5):339-47.

http://dx.doi.org/10.1053/j.ackd.2011.05.001
PMid:21896375 PMCid:PMC3168776

5. Orskov B, Christensen KB, Feldt-Rasmussen B, Strandgaard S. Low birth weight is associated with earlier onset of end-stage renal disease in Danish patients with autosomal dominant polycystic kidney disease. Kidney Int. 2012;81(9):919-24.
http://dx.doi.org/10.1038/ki.2011.459
PMid:22297678

6. Sweeney WE, Jr., Avner ED. Pathophysiology of childhood polycystic kidney diseases: new insights into disease-specific therapy. Pediatr Res. 2014;75(1-2): 148-57.
http://dx.doi.org/10.1038/pr.2013.191
PMid:24336431 PMCid:PMC3953890

7. Sweeney W, Jr., Gunay-Aygun M, Patil A, Avner ED. Childhood Polycystic Kidney Disease. In: Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein S, editors. Pediatric Nephrology: Springer Berlin Heidelberg; 2015. p. 1-58.
http://dx.doi.org/10.1007/978-3-642-27843-3_32-1

8. Cadnapaphornchai MA. Autosomal dominant polycystic kidney disease in children. Curr Opin Pediatr. 2015;27(2):193-200.
http://dx.doi.org/10.1097/MOP.0000000000000195
PMid:25635587

9. Guay-Woodford LM, Galliani CA, Musulman-Mroczek E, Spear GS, Guillot AP, Bernstein J. Diffuse renal cystic disease in children: morphologic and genetic correlations. Pediatr Nephrol (Berlin, Germany). 1998;12(3):173-82.
http://dx.doi.org/10.1007/s004670050431

10. Kaariainen H, Koskimies O, Norio R. Dominant and recessive polycystic kidney disease in children: evaluation of clinical features and laboratory data. Pediatr Nephrol (Berlin, Germany). 1988;2:296-302.
http://dx.doi.org/10.1007/BF00858681

11. Sweeney WE, Jr., Avner ED. Diagnosis and management of childhood polycystic kidney disease. Pediatr Nephrol (Berlin, Germany). 2011;26(5):675-92.
http://dx.doi.org/10.1007/s00467-010-1656-1
PMid:21046169

12. Sweeney W, Avner ED. Polycystic Kidney Disease, Autosomal Recessive. Seattle (WA), University of Washington; 2001 [updated 2014 Mar 6].
http://www.ncbi.nih.gov/books/NBK1326].

13. Avner ED, Sweeney WE, Jr. Renal cystic disease: new insights for the clinician. Pediatr Clin North Am. 2006;53(5):889-909, ix.
http://dx.doi.org/10.1016/j.pcl.2006.08.012
PMid:17027616

14. Grantham JJ. Rationale for early treatment of polycystic kidney disease. Pediatr Nephrol (Berlin, Germany). 2014.
15. Gunay-Aygun M, Avner ED, Bacallao RL, Choyke PL, Flynn JT, Germino GG, et al. Autosomal recessive polycystic kidney disease and congenital hepatic fibrosis: summary statement of a first National Institutes of Health/Office of Rare Diseases conference. J Pediatr. 2006;149(2):159-64.
http://dx.doi.org/10.1016/j.jpeds.2006.03.014
PMid:16887426 PMCid:PMC2918414
16. Gunay-Aygun M, Gahl WA, Heller T. Congenital Hepatic Fibrosis Overview Seattle (WA): University of Washington; 2008 (updated 2014 Apr 24).
http://www.ncbi.nlm.gov/books/NBK2701].
17. Guay-Woodford LM, Muecher G, Hopkins SD, Avner ED, Germino GG, Guillot AP, et al. The severe perinatal form of autosomal recessive polycystic kidney disease maps to chromosome 6p21.1-p12: Implications for genetic counseling. Am J Hum Genet. 1995;56:1101-7.
PMid:7726165 PMCid:PMC1801440
18. Onuchic LF, Furu L, Nagasawa Y, Hou X, Eggermann T, Ren Z, et al. PKHD1, the polycystic kidney and hepatic disease 1 gene, encodes a novel large protein containing multiple immunoglobulin-like plexin-transcription-factor domains and parallel beta-helix 1 repeats. Am J Hum Genet. 2002;70(5):1305-17.
http://dx.doi.org/10.1086/340448
PMid:11898128 PMCid:PMC447605
19. Ward CJ, Hogan MC, Rossetti S, Walker D, Sneddon T, Wang X, et al. The gene mutated in autosomal recessive polycystic kidney disease encodes a large, receptor-like protein. Nat Genet. 2002;30(3):259-69.
http://dx.doi.org/10.1038/ng833
PMid:11919560
20. Gunay-Aygun M, Font-Montgomery E, Lukose L, Tuchman Gerstein M, Piwnica-Worms K, Choyke P, et al. Characteristics of Congenital Hepatic Fibrosis in a Large Cohort of Patients With Autosomal Recessive Polycystic Kidney Disease. Gastroenterology. 2013;144(1):112-21.
http://dx.doi.org/10.1053/j.gastro.2012.09.056
PMid:23041322 PMCid:PMC4162098
21. Adeva M, El-Youssef M, Rossetti S, Kamath PS, Kubly V, Consugar MB, et al. Clinical and molecular characterization defines a broadened spectrum of autosomal recessive polycystic kidney disease (ARPKD). Medicine (Baltimore). 2006;85(1):1-21.
http://dx.doi.org/10.1097/01.md.0000200165.90373.9a
PMid:16523049

22. Bergmann C, Zerres K. Early manifestations of polycystic kidney disease. Lancet. 2007;369(9580):2157.
http://dx.doi.org/10.1016/S0140-6736(07)61005-8
23. Rossetti S, Harris PC. Genotype-phenotype correlations in autosomal dominant and autosomal recessive polycystic kidney disease. J Am Soc Nephrol. 2007;18(5): 1374-80.
http://dx.doi.org/10.1681/ASN.2007010125
PMid:17429049
24. Guay-Woodford LM, Bissler JJ, Braun MC, Bockenhauer D, Cadnapaphornchai MA, Dell KM, et al. Consensus expert recommendations for the diagnosis and management of autosomal recessive polycystic kidney disease: report of an international conference. J Pediatr. 2014;165(3):611-7.
http://dx.doi.org/10.1016/j.jpeds.2014.06.015
PMid:25015577
25. Bergmann C, Senderek J, Windelen E, Kupper F, Middeldorf I, Schneider F, et al. Clinical consequences of PKHD1 mutations in 164 patients with autosomal-recessive polycystic kidney disease (ARPKD). Kidney Int. 2005;67(3):829-48.
http://dx.doi.org/10.1111/j.1523-1755.2005.00148.x
PMid:15698423
26. Boddu R, Yang C, O'Connor AK, Hendrickson RC, Boone B, Cui X, et al. Intragenic motifs regulate the transcriptional complexity of Pkhd1/PKHD1. J Mol Med (Berlin, Germany). 2014;92(10):1045-56.
http://dx.doi.org/10.1007/s00109-014-1185-7
PMid:24984783 PMCid:PMC4197071
27. Bergmann C, Senderek J, Sedlacek B, Pegiazoglou I, Puglia P, Eggermann T, et al. Spectrum of mutations in the gene for autosomal recessive polycystic kidney disease (ARPKD/PKHD1). J Am Soc Nephrol. 2003;14(1):76-89.
http://dx.doi.org/10.1097/01.ASN.0000039578.55705.6E
PMid:12506140
28. Rossetti S, Torra R, Coto E, Consugar M, Kubly V, Malaga S, et al. A complete mutation screen of PKHD1 in autosomal-recessive polycystic kidney disease (ARPKD) pedigrees. Kidney Int. 2003;64(2):391-403.
http://dx.doi.org/10.1046/j.1523-1755.2003.00111.x
PMid:12846734
29. Bergmann C, Senderek J, Kupper F, Schneider F, Dornia C, Windelen E, et al. PKHD1 mutations in autosomal recessive polycystic kidney disease (ARPKD). Hum Mutat. 2004;23(5):453-63.
http://dx.doi.org/10.1002/humu.20029
PMid:15108277

30. Sharp AM, Messiaen LM, Page G, Antignac C, Gubler MC, Onuchic LF, et al. Comprehensive genomic analysis of PKHD1 mutations in ARPKD cohorts. J Med Genet. 2005;42(4):336-49.
http://dx.doi.org/10.1136/jmg.2004.024489
PMid:15805161 PMCid:PMC1736033
31. Bergmann C, Zerres K. Polycystic Kidney Disease:ADPKD and ARPKD. In: Geary DF, Schaefer F, editors. Comprehensive Pediatric Nephrology. Philadelphia: Mosby (Elsevier); 2008. p. 155-78.
http://dx.doi.org/10.1016/B978-0-323-04883-5.50015-5
32. Furu L, Onuchic LF, Gharavi A, Hou X, Esquivel EL, Nagasawa Y, et al. Milder presentation of recessive polycystic kidney disease requires presence of amino acid substitution mutations. J Am Soc Nephrol. 2003;14(8):2004-14.
http://dx.doi.org/10.1097/01.ASN.0000078805.87038.05
PMid:12874454
33. Gunay-Aygun M, Tuchman M, Font-Montgomery E, Lukose L, Edwards H, Garcia A, et al. PKHD1 sequence variations in 78 children and adults with autosomal recessive polycystic kidney disease and congenital hepatic fibrosis. Mol Genet Metab. 2010;99:160-73.
http://dx.doi.org/10.1016/j.ymgme.2009.10.010
PMid:19914852 PMCid:PMC2818513
34. Zerres K, Rudnik-Schoneborn S, Deget F, Holtkamp U, Brodehl J, Geisert J, et al. Autosomal recessive polycystic kidney disease in 115 children: clinical presentation, course and influence of gender. Arbeitsgemeinschaft fur Padiatrische, Nephrologie. Acta Paediatr. 1996;85(4):437-45.
http://dx.doi.org/10.1111/j.1651-2227.1996.tb14056.x
PMid:8740301
35. Guay-Woodford LM, Desmond RA. Autosomal recessive polycystic kidney disease: the clinical experience in North America. Pediatrics. 2003;111(5 Pt 1):1072-80.
http://dx.doi.org/10.1542/peds.111.5.1072
PMid:12728091
36. Bergmann C. ARPKD and early manifestations of ADPKD: the original polycystic kidney disease and phenocopies. Pediatr Nephrol (Berlin, Germany). 2014.
37. Zerres K, Hansmann M, Knopfle G, Stephan M. Prenatal diagnosis of genetically determined early manifestation of autosomal dominant polycystic kidney disease? Hum Genet. 1985;71(4):368-9.
http://dx.doi.org/10.1007/BF00388467
PMid:3908289
38. McDonald RA, Avner ED. Inherited polycystic kidney disease in children. Semin Nephrol. 1991;11:632-42.

PMid:1767136

39. Gunay-Aygun M, Font-Montgomery E, Lukose L, Tuchman M, Graf J, Bryant JC, et al. Correlation of kidney function, volume and imaging findings, and PKHD1 mutations in 73 patients with autosomal recessive polycystic kidney disease. Clin J Am Soc Nephrol. 2010;5(6):972-84.
http://dx.doi.org/10.2215/CJN.07141009
PMid:20413436 PMCid:PMC2879301
40. Srinath A, Shneider BL. Congenital hepatic fibrosis and autosomal recessive polycystic kidney disease. J Pediatr Gastroenterol Nutr. 2012;54(5):580-7.
http://dx.doi.org/10.1097/MPG.0b013e31824711b7
PMid:22197937 PMCid:PMC4369775
41. Zerres K, Mucher G, Becker J, Steinkamm C, Rudnik-Schoneborn S, Heikkila P, et al. Prenatal diagnosis of autosomal recessive polycystic kidney disease (ARPKD): molecular genetics, clinical experience, and fetal morphology. Am J Med Genet. 1998;76(2):137-44.
http://dx.doi.org/10.1002/(SICI)1096-8628(19980305)76:2<137::AID-AJMG6>3.0.CO;2-Q
42. Lau EC, Janson MM, Roesler MR, Avner ED, Strawn EY, Bick DP. Birth of a healthy infant following preimplantation PKHD1 haplotyping for autosomal recessive polycystic kidney disease using multiple displacement amplification. J Assist Reprod Genet. 2010;27:397-407.
http://dx.doi.org/10.1007/s10815-010-9432-5
PMid:20490649 PMCid:PMC2922704
43. Chung EM, Conran RM, Schroeder JW, Rohena-Quinquilla IR, Rooks VJ. From the radiologic pathology archives: pediatric polycystic kidney disease and other ciliopathies: radiologic-pathologic correlation. Radiographics. 2014;34(1):155-78.
http://dx.doi.org/10.1148/rg.341135179
PMid:24428289
44. Osathanondh V, Potter EL. Pathogenesis Of Polycystic Kidneys. Type 1 Due To Hyperplasia Of Interstitial Portions Of Collecting Tubules. Arch Pathol. 1964;77:466-73.
PMid:14120682
45. Dalgaard OZ. Bilateral polycystic diseases of kidneys: a follow-up of two hundred and eighty-four patients and their families. Acta Med Scand. 1957;328 (Suppl):1-255.
46. Nakanishi K, Sweeney WE, Jr, Zerres K, Guay-Woodford LM, Avner ED. Proximal tubular cysts in fetal human autosomal recessive polycystic kidney disease. J Am Soc Nephrol. 2000;11(4):760-3.
PMid:10752536
47. Kissane JM. Renal cysts in pediatric patients. A classification and overview. Pediatr Nephrol(Berlin, Germany). 1990;4(1):69-77.

http://dx.doi.org/10.1007/BF00858446
PMid:2206887

48. Lieberman E, Salinas-Madrigal L, Gwinn JL, Brennan LP, Fine RN, Landing BH. Infantile polycystic disease of the kidneys and liver: clinical, pathological and radiological correlations and comparison with congenital hepatic fibrosis. Medicine. 1971;50:277-318.
http://dx.doi.org/10.1097/00005792-197107000-00003
PMid:5143572

49. Kerr DN, Harrison CV, Sherlock S, Walker RM. Congenital hepatic fibrosis. QJ Med. 1961;30:91-117.
PMid:13752660

50. Lipschitz B, Berdon WE, Defelice AR, Levy J. Association of congenital hepatic fibrosis with autosomal dominant polycystic kidney disease. Report of a family with review of literature. Pediatr Radiol. 1993;23(2):131-3.
http://dx.doi.org/10.1007/BF02012406
PMid:8516038

51. Gunay-Aygun M. Liver and kidney disease in ciliopathies. Am J Med Genet C Semin Med Genet. 2009;151C(4):296-306.
http://dx.doi.org/10.1002/ajmg.c.30225
PMid:19876928 PMCid:PMC2919058

52. O'Brien K, Font-Montgomery E, Lukose L, Bryant J, Piwnica-Worms K, Edwards H, et al. Congenital Hepatic Fibrosis And Portal Hypertension In Autosomal Dominant Polycystic Kidney Disease. J Pediatr Gastroenterol Nutr. 2012;54:83-9.
http://dx.doi.org/10.1097/MPG.0b013e318228330c
PMid:21694639

53. Kaplan BS, Fay J, Shah V, Dillon MJ, Barratt TM. Autosomal recessive polycystic kidney disease. Pediatr Nephrol (Berlin, Germany). 1989;3(1):43-9.
http://dx.doi.org/10.1007/BF00859625

54. Gagnadoux MF, Habib R, Levy M, Brunelle F, Broyer M. Cystic renal diseases in children. Adv Nephrol Necker Hosp. 1989;18:33-57.
PMid:2493722

55. Blickman JG, Bramson RT, Herrin JT. Autosomal recessive polycystic kidney disease: long-term sonographic findings in patients surviving the neonatal period. AJR Am J Roentgenol. 1995;164(5):1247-50.
http://dx.doi.org/10.2214/ajr.164.5.7717240
PMid:7717240

56. Avni FE, Guissard G, Hall M, Janssen F, DeMaertelaer V, Rypens F. Hereditary polycystic kidney diseases in children: changing sonographic patterns through childhood. Pediatr Radiol. 2002;32(3):169-74.

http://dx.doi.org/10.1007/s00247-001-0624-0
PMid:12164348

57. Turkbey B, Ocak I, Daryanani K, Font-Montgomery E, Lukose L, Bryant J, et al. Autosomal recessive polycystic kidney disease and congenital hepatic fibrosis (ARPKD/CHF). Pediatr Radiol. 2009;39(2):100-11.
http://dx.doi.org/10.1007/s00247-008-1064-x
PMid:19089418 PMCid:PMC2918426

58. Telega G, Cronin D, Avner ED. New approaches to the autosomal recessive polycystic kidney disease patient with dual kidney-liver complications. Pediatr Transplant.. 2013;17:328-35.
http://dx.doi.org/10.1111/petr.12076
PMid:23593929 PMCid:PMC3663883

59. Cole BR, Conley SB, Stapleton FB. Polycystic kidney disease in the first year of life. J Pediatr. 1987;111(5):693-9.
http://dx.doi.org/10.1016/S0022-3476(87)80244-5

60. Spechtenhauser B, Hochleitner BW, Ellemunter H, Simma B, Hormann C, Konigsrainer A, et al. Bilateral nephrectomy, peritoneal dialysis and subsequent cadaveric renal transplantation for treatment of Ren Fail due to polycystic kidney disease requiring continuous ventilation. Pediatr Transplant.. 1999;3(3):246-8.
http://dx.doi.org/10.1034/j.1399-3046.1999.00030.x
PMid:10487288

61. Shukla AR, Kiddoo DA, Canning DA. Unilateral nephrectomy as palliative therapy in an infant with autosomal recessive polycystic kidney disease. J Urol. 2004;172(5 Pt 1):2000-1.
http://dx.doi.org/10.1097/01.ju.0000142025.80132.2f
PMid:15540776

62. Gang DL, Herrin JT. Infantile polycystic disease of the liver and kidneys. Clin Nephrol. 1986;25:28-36.
PMid:3955906

63. Fonck C, Chauveau D, Gagnadoux MF, Pirson Y, Grunfeld JP. Autosomal recessive polycystic kidney disease in adulthood. Nephrol Dial Transplant. 2001;16(8):1648-52.
http://dx.doi.org/10.1093/ndt/16.8.1648
PMid:11477168

64. Roy S, Dillon MJ, Trompeter RS, Barratt TM. Autosomal recessive polycystic kidney disease: long-term outcome of neonatal survivors. Pediatr Nephrol (Berlin, Germany). 1997;11(3):302-6.
http://dx.doi.org/10.1007/s004670050281

65. Shneider BL, Magid MS. Liver disease in autosomal recessive polycystic kidney disease. Pediatr Transplant. 2005;9(5):634-9.

http://dx.doi.org/10.1111/j.1399-3046.2005.00342.x
PMid:16176423

66. Benador N, Grimm P, Lavine J, Rosenthal P, Reznik V, Lemire J. Transjugular intrahepatic portosystemic shunt prior to renal transplantation in a child with autosomal-recessive polycystic kidney disease and portal hypertension: A case report. Pediatr Transplant. 2001;5(3):210-4.
http://dx.doi.org/10.1034/j.1399-3046.2001.00061.x
PMid:11422825

67. Hartung EA, Guay-Woodford LM. Autosomal recessive polycystic kidney disease: a hepatorenal fibrocystic disorder with pleiotropic effects. Pediatrics. 2014;134(3):e833-45.
http://dx.doi.org/10.1542/peds.2013-3646
PMid:25113295 PMCid:PMC4143997

68. Cadnapaphornchai MA. Hypertension in children with autosomal dominant polycystic kidney disease (ADPKD). Curr Hypertens Rev. 2013;9(1):21-6.
http://dx.doi.org/10.2174/1573402111309010004
PMid:23971640

69. Sedman A, Bell P, Manco-Johnson M, Schrier R, Warady BA, Heard ED, et al. Autosomal dominant polycystic kidney disease in childhood: a longitudinal study. Kidney Int. 1987;31:1000-5.
http://dx.doi.org/10.1038/ki.1987.98
PMid:3295357

70. Tee JB, Acott PD, McLellan DH, Crocker JF. Phenotypic heterogeneity in pediatric autosomal dominant polycystic kidney disease at first presentation: a single-center, 20-year review. Am J Kidney Dis. 2004;43(2):296-303.
http://dx.doi.org/10.1053/j.ajkd.2003.10.017
PMid:14750095

71. Fick GM, Duley IT, Johnson AM, Strain JD, Manco-Johnson ML, Gabow PA. The spectrum of autosomal dominant polycystic kidney disease in children. J Am Soc Nephrol. 1994;4(9):1654-60.
PMid:8011974

72. Selistre L, de Souza V, Ranchin B, Hadj-Aissa A, Cochat P, Dubourg L. Early renal abnormalities in children with postnatally diagnosed autosomal dominant polycystic kidney disease. Pediatr Nephrol (Berlin, Germany). 2012;27(9):1589-93.
http://dx.doi.org/10.1007/s00467-012-2192-y
PMid:22689086

73. Fick-Brosnahan G, Johnson AM, Strain JD, Gabow PA. Renal asymmetry in children with autosomal dominant polycystic kidney disease. Am J Kidney Dis. 1999;34(4):639-45.
http://dx.doi.org/10.1016/S0272-6386(99)70387-2

74. Fick-Brosnahan GM, Tran ZV, Johnson AM, Strain JD, Gabow PA. Progression of autosomal-dominant polycystic kidney disease in children. Kidney Int. 2001;59(5):1654-62.
http://dx.doi.org/10.1046/j.1523-1755.2001.0590051654.x
PMid:11318935

75. Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW. Prospective change in renal volume and function in children with ADPKD. Clin J Am Soc Nephrol. 2009;4(4):820-9.
http://dx.doi.org/10.2215/CJN.02810608
PMid:19346430 PMCid:PMC2666428

76. Cadnapaphornchai MA, George DM, McFann K, Wang W, Gitomer B, Strain JD, et al. Effect of pravastatin on total kidney volume, left ventricular mass index, and microalbuminuria in pediatric autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2014;9(5):889-96.
http://dx.doi.org/10.2215/CJN.08350813
PMid:24721893 PMCid:PMC4011448

77. Kelleher CL, McFann KK, Johnson AM, Schrier RW. Characteristics of hypertension in young adults with autosomal dominant polycystic kidney disease compared with the general U.S. population. Am J Hypertens. 2004;17(11 Pt 1):1029-34.
http://dx.doi.org/10.1016/j.amjhyper.2004.06.020
PMid:15533729

78. Cadnapaphornchai MA, McFann K, Strain JD, Masoumi A, Schrier RW. Increased left ventricular mass in children with autosomal dominant polycystic kidney disease and borderline hypertension. Kidney Int. 2008;74(9):1192-6.
http://dx.doi.org/10.1038/ki.2008.397
PMid:18716604 PMCid:PMC2574635

79. Schrier RW. Hypertension and autosomal dominant polycystic kidney disease. Am J Kidney Dis. 2011;57(6):811-3.
http://dx.doi.org/10.1053/j.ajkd.2011.02.379
PMid:21601126

80. Seeman T, Dusek J, Vondrichova H, Kyncl M, John U, Misselwitz J, et al. Ambulatory blood pressure correlates with renal volume and number of renal cysts in children with autosomal dominant polycystic kidney disease. Blood Press Monit. 2003;8(3):107-10.
http://dx.doi.org/10.1097/00126097-200306000-00003
PMid:12900587

81. Chapman AB, Stepniakowski K, Rahbari-Oskoui F. Hypertension in autosomal dominant polycystic kidney disease. Adv Chronic Kidney Dis. 2010;17(2):153-63.

http://dx.doi.org/10.1053/j.ackd.2010.01.001
PMid:20219618 PMCid:PMC2845913

82. de Almeida EA, de Oliveira EI, Lopes JA, Almeida AG, Lopes MG, Prata MM. Ambulatory blood pressure measurement in young normotensive patients with autosomal dominant polycystic kidney disease. Rev Port Cardiol. 2007;26(3):235-43.
PMid:17549981

83. Turgut F, Oflaz H, Namli S, Alisir S, Tufan F, Temiz S, et al. Ambulatory blood pressure and endothelial dysfunction in patients with autosomal dominant polycystic kidney disease. Ren Fail. 2007;29(8):979-84.
http://dx.doi.org/10.1080/08860220701641728
PMid:18067044

84. Ivy DD, Shaffer EM, Johnson AM, Kimberling WJ, Dobin A, Gabow PA. Cardiovascular abnormalities in children with autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1995;5(12):2032-6.
PMid:7579051

85. Gabow P. Autosomal dominant polycystic kidney disease. New Engl J Med. 1993;329:332-42.
http://dx.doi.org/10.1056/NEJM199307293290508
PMid:8321262

86. Fick GM, Johnson AM, Strain JD, Kimberling WJ, Kumar S, Manco-Johnson ML, et al. Characteristics of very early onset autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 1993;3(12):1863-70.
http://dx.doi.org/10.1007/bf01213346

87. Seeman T, Dusek J, Vondrak K, Blahova K, Simkova E, Kreisinger J, et al. Renal concentrating capacity is linked to blood pressure in children with autosomal dominant polycystic kidney disease. Physiol Res. 2004;53(6):629-34.
PMid:15588131

88. Kaehny WD, Everson GT. Extrarenal manifestations of autosomal dominant polycystic kidney disease. Semin Nephrol. 1991;11(661-670).
PMid:1767139

89. Bae KT, Zhu F, Chapman AB, Torres VE, Grantham JJ, Guay-Woodford LM, et al. Magnetic resonance imaging evaluation of hepatic cysts in early autosomal-dominant polycystic kidney disease: the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease cohort. Clin J Am Soc Nephrol. 2006;1(1):64-9.
http://dx.doi.org/10.2215/CJN.00080605
PMid:17699192

90. Schrier R, McFann K, Johnson A, Chapman A, Edelstein C, Brosnahan G, et al. Cardiac and renal effects of standard versus rigorous blood pressure control in

autosomal-dominant polycystic kidney disease: results of a seven-year prospective randomized study. J Am Soc Nephrol. 2002;13(7):1733-9.
http://dx.doi.org/10.1097/01.ASN.0000018407.60002.B9
PMid:12089368

91. Schrier RW, Abebe KZ, Perrone RD, Torres VE, Braun WE, Steinman TI, et al. Blood Pressure in Early Autosomal Dominant Polycystic Kidney Disease. N Engl J Med. 2014.
http://dx.doi.org/10.1056/NEJMoa1402685

92. Torres VE, Abebe KZ, Chapman AB, Schrier RW, Braun WE, Steinman TI, et al. Angiotensin Blockade in Late Autosomal Dominant Polycystic Kidney Disease. N Engl J Med. 2014.
http://dx.doi.org/10.1056/NEJMoa1402686

93. Ferguson MA, Flynn JT. Rational use of antihypertensive medications in children. Pediatr Nephrol (Berlin, Germany). 2014;29(6):979-88.
http://dx.doi.org/10.1007/s00467-013-2510-z
PMid:23715784

94. Gabow P. Autosomal dominant polycystic kidney disease. In: Gardner KD, editor. The Cystic Kidney. Dordrecht, Netherlands: Kluwer; 1990. p. 295-326.
http://dx.doi.org/10.1007/978-94-009-0457-6_12

95. Sallee M, Rafat C, Zahar JR, Paulmier B, Grunfeld JP, Knebelmann B, et al. Cyst infections in patients with autosomal dominant polycystic kidney disease. Clin J Am Soc Nephrol. 2009;4(7):1183-9.
http://dx.doi.org/10.2215/CJN.01870309
PMid:19470662 PMCid:PMC2709515

96. Hogan MC, Norby SM. Evaluation and management of pain in autosomal dominant polycystic kidney disease. Adv Chronic Kidney Dis. 2010;17(3):e1-e16.
http://dx.doi.org/10.1053/j.ackd.2010.01.005
PMid:20439087 PMCid:PMC4144785

97. Belz MM, Hughes RL, Kaehny WD, Johnson AM, Fick-Brosnahan GM, Earnest MP, et al. Familial clustering of ruptured intracranial aneurysms in autosomal dominant polycystic kidney disease. Am J Kidney Dis. 2001;38(4):770-6.
http://dx.doi.org/10.1053/ajkd.2001.27694
PMid:11576880

98. Chapman AB, Rubinstein D, Hughes R, Stears JC, Earnest MP, Johnson AM, et al. Intracranial aneurysms in autosomal dominant polycystic kidney disease. N Engl J Med. 1992;327(13):916-20.
http://dx.doi.org/10.1056/NEJM199209243271303
PMid:1513348

99. Ring T, Spiegelhalter D. Risk of intracranial aneurysm bleeding in autosomal-dominant polycystic kidney disease. Kidney Int. 2007;72(11):1400-2.
http://dx.doi.org/10.1038/sj.ki.5002488
PMid:17882153

100. Gibbs GF, Huston J, 3rd, Qian Q, Kubly V, Harris PC, Brown RD, Jr., et al. Follow-up of intracranial aneurysms in autosomal-dominant polycystic kidney disease. Kidney Int. 2004;65(5):1621-7.
http://dx.doi.org/10.1111/j.1523-1755.2004.00572.x
PMid:15086900

101. Abdollah Shamshirsaz A, Reza Bekheirnia M, Kamgar M, Johnson AM, McFann K, Cadnapaphornchai M, et al. Autosomal-dominant polycystic kidney disease in infancy and childhood: progression and outcome. Kidney Int. 2005;68(5):2218-24.
http://dx.doi.org/10.1111/j.1523-1755.2005.00678.x
PMid:16221221

102. Boyer O, Gagnadoux MF, Guest G, Biebuyck N, Charbit M, Salomon R, et al. Prognosis of autosomal dominant polycystic kidney disease diagnosed in utero or at birth. Pediatr Nephrol (Berlin, Germany). 2007;22(3):380-8.
http://dx.doi.org/10.1007/s00467-006-0327-8
PMid:17124604

103. Schrier RW, Brosnahan G, Cadnapaphornchai MA, Chonchol M, Friend K, Gitomer B, et al. Predictors of autosomal dominant polycystic kidney disease progression. J Am Soc Nephrol. 2014;25(11):2399-418.
http://dx.doi.org/10.1681/ASN.2013111184
PMid:24925719

104. Lantinga-van Leeuwen IS, Dauwerse JG, Baelde HJ, Leonhard WN, van de Wal A, Ward CJ, et al. Lowering of Pkd1 expression is sufficient to cause polycystic kidney disease. Hum Mol Genet. 2004;13(24):3069-77.
http://dx.doi.org/10.1093/hmg/ddh336
PMid:15496422

105. Hopp K, Ward CJ, Hommerding CJ, Nasr SH, Tuan HF, Gainullin VG, et al. Functional polycystin-1 dosage governs autosomal dominant polycystic kidney disease severity. J Clin Invest. 2012;122(11):4257-73.
http://dx.doi.org/10.1172/JCI64313
PMid:23064367 PMCid:PMC3484456

106. Pei Y, Lan Z, Wang K, Garcia-Gonzalez M, He N, Dicks E, et al. A missense mutation in PKD1 attenuates the severity of renal disease. Kidney Int. 2012;81(4):412-7.
http://dx.doi.org/10.1038/ki.2011.370
PMid:22031115 PMCid:PMC4105019

107. Tan AY, Blumenfeld J, Michaeel A, Donahue S, Bobb W, Parker T, et al. Autosomal dominant polycystic kidney disease caused by somatic and germline mosaicism. Clin Genet. 2014.

108. Menezes LF, Zhou F, Patterson AD, Piontek KB, Krausz KW, Gonzalez FJ, et al. Network Analysis of a Pkd1-Mouse Model of Autosomal Dominant Polycystic Kidney Disease Identifies HNF4alpha as a Disease Modifier. PLoS genetics. 2012;8(11):e1003053.
http://dx.doi.org/10.1371/journal.pgen.1003053
PMid:23209428 PMCid:PMC3510057

109. Li X. Epigenetics and autosomal dominant polycystic kidney disease. Biochim Biophys Acta. 2011;1812(10):1213-8.
http://dx.doi.org/10.1016/j.bbadis.2010.10.008
PMid:20970496 PMCid:PMC3413450

110. Cao Y, Semanchik N, Lee SH, Somlo S, Barbano PE, Coifman R, et al. Chemical modifier screen identifies HDAC inhibitors as suppressors of PKD models. Proc Natl Acad Sci U S A. 2009;106(51):21819-24.
http://dx.doi.org/10.1073/pnas.0911987106
PMid:19966229 PMCid:PMC2799791

111. Bergmann C, von Bothmer J, Ortiz Bruchle N, Venghaus A, Frank V, Fehrenbach H, et al. Mutations in multiple PKD genes may explain early and severe polycystic kidney disease. J Am Soc Nephrol. 2011;22(11):2047-56.
http://dx.doi.org/10.1681/ASN.2010101080
PMid:22034641 PMCid:PMC3279997

112. Brook-Carter PT, Peral B, Ward CJ, Thompson P, Hughes J, Maheshwar MM, et al. Deletion of the TSC2 and PKD1 genes associated with severe infantile polycystic kidney disease--a contiguous gene syndrome. Nat Genet. 1994;8(4):328-32.
http://dx.doi.org/10.1038/ng1294-328
PMid:7894481

113. Shibazaki S, Yu Z, Nishio S, Tian X, Thomson RB, Mitobe M, et al. Cyst formation and activation of the extracellular regulated kinase pathway after kidney specific inactivation of Pkd1. Hum Mol Genet. 2008.
http://dx.doi.org/10.1093/hmg/ddn039
PMid:18263604 PMCid:PMC2902289

114. Gallagher AR, Germino GG, Somlo S. Molecular advances in autosomal dominant polycystic kidney disease. Adv Chronic Kidney Dis. 2010;17(2):118-30.
http://dx.doi.org/10.1053/j.ackd.2010.01.002
PMid:20219615 PMCid:PMC2837604

115. Fedeles SV, Tian X, Gallagher AR, Mitobe M, Nishio S, Lee SH, et al. A genetic interaction network of five genes for human polycystic kidney and liver diseases defines polycystin-1 as the central determinant of cyst formation. Nat Genet. 2011;43(7):639-47.
http://dx.doi.org/10.1038/ng.860
PMid:21685914 PMCid:PMC3547075

116. Fedeles SV, Gallagher AR, Somlo S. Polycystin-1: a master regulator of intersecting cystic pathways. Trends Mol Med. 2014;20:251-60.
http://dx.doi.org/10.1016/j.molmed.2014.01.004
PMid:24491980 PMCid:PMC4008641

117. Leonhard WN, Zandbergen M, Veraar K, van den Berg S, van der Weerd L, Breuning M, et al. Scattered Deletion of PKD1 in Kidneys Causes a Cystic Snowball Effect and Recapitulates Polycystic Kidney Disease. J Am Soc Nephrol. 2014. PMid:25361818

118. Welling LW, Grantham JJ. Cystic and development diseases of the kidney. In: Brenner BM, Rector FC, editors. The Kidney. 4th ed. Philadelphia: WB Saunders; 1991. p. 1657-94.

119. Wilson PD. Polycystic kidney disease. N Engl J Med. 2004;350(2):151-64.
http://dx.doi.org/10.1056/NEJMra022161
PMid:14711914

120. Wilson PD. Polycystic kidney disease: new understanding in the pathogenesis. Int J Biochem Cell Biol. 2004;36(10):1868-73.
http://dx.doi.org/10.1016/j.biocel.2004.03.012
PMid:15203099

121. Sweeney WE, Jr., Avner ED. Molecular and cellular pathophysiology of autosomal recessive polycystic kidney disease (ARPKD). Cell Tissue Res. 2006;326(3):671-85.
http://dx.doi.org/10.1007/s00441-006-0226-0
PMid:16767405

122. Sweeney WE, Jr., von Vigier RO, Frost P, Avner ED. Src Inhibition Ameliorates Polycystic Kidney Disease. J Am Soc Nephrol. 2008;19(7):1331-41.
http://dx.doi.org/10.1681/ASN.2007060665
PMid:18385429 PMCid:PMC2440293

123. Weimbs T, Olsan EE, Talbot JJ. Regulation of STATs by polycystin-1 and their role in polycystic kidney disease. Jak-Stat. 2013;2(2):e23650.
http://dx.doi.org/10.4161/jkst.23650
PMid:24058808 PMCid:PMC3710321

124. Harris PC, Torres VE. Genetic mechanisms and signaling pathways in autosomal dominant polycystic kidney disease. J Clin Invest. 2014;124(6):2315-24.
http://dx.doi.org/10.1172/JCI72272
PMid:24892705 PMCid:PMC4089452

125. Calvet JP. Polycystic kidney disease: primary extracellular matrix abnormality or defective cellular differentiation? Kidney Int. 1993;43(1):101-8.
http://dx.doi.org/10.1038/ki.1993.17
PMid:8433548

126. Orellana SA, Avner ED. Cystic maldevelopment in the kidney. Semin Nephrol. 1995;15:341-52.
PMid:7569413

127. Murcia NS, Sweeney WE, Jr., Avner ED. New insights into the molecular pathophysiology of polycystic kidney disease. Kidney Int. 1999;55(4):1187-97.
http://dx.doi.org/10.1046/j.1523-1755.1999.00370.x
PMid:10200981

128. Harris PC, Torres VE. Polycystic kidney disease. Annu Rev Med. 2009;60:321-37.
http://dx.doi.org/10.1146/annurev.med.60.101707.125712
PMid:18947299 PMCid:PMC2834200

129. Qian Q, Hunter LW, Li M, Marin-Padilla M, Prakash YS, Somlo S, et al. Pkd2 haploinsufficiency alters intracellular calcium regulation in vascular smooth muscle cells. Hum Mol Genet. 2003;12(15):1875-80.
http://dx.doi.org/10.1093/hmg/ddg190
PMid:12874107

130. Starremans PG, Li X, Finnerty PE, Guo L, Takakura A, Neilson EG, et al. A mouse model for polycystic kidney disease through a somatic in-frame deletion in the 5' end of Pkd1. Kidney Int. 2008.
http://dx.doi.org/10.1038/ki.2008.111
PMid:18385665

131. Menezes LF, Germino GG. Murine Models of Polycystic Kidney Disease. Drug Discov Today Dis Mech. 2013;10(3-4):e153-e8.
http://dx.doi.org/10.1016/j.ddmec.2013.10.002
PMid:25013443 PMCid:PMC4085131

132. Gendreau SB, Ventura R, Keast P, Laird AD, Yakes FM, Zhang W, et al. Inhibition of the T790M gatekeeper mutant of the epidermal growth factor receptor by EXEL-7647. Clin Cancer Res. 2007;13(12):3713-23.
http://dx.doi.org/10.1158/1078-0432.CCR-06-2590
PMid:17575237

133. Trowe T, Boukouvala S, Calkins K, Cutler RE, Jr., Fong R, Funke R, et al. EXEL-7647 inhibits mutant forms of ErbB2 associated with lapatinib resistance and neoplastic transformation. Clin Cancer Res. 2008;14(8):2465-75.
http://dx.doi.org/10.1158/1078-0432.CCR-07-4367
PMid:18413839

134. Shillingford JM, Leamon CP, Vlahov IR, Weimbs T. Folate-conjugated rapamycin slows progression of polycystic kidney disease. J Am Soc Nephrol. 2012;23(10):1674-81. http://dx.doi.org/10.1681/ASN.2012040367 PMid:22859856 PMCid:PMC3458469

135. Leuenroth SJ, Bencivenga N, Igarashi P, Somlo S, Crews CM. Triptolide reduces cystogenesis in a model of ADPKD. J Am Soc Nephrol. 2008;19(9):1659-62. http://dx.doi.org/10.1681/ASN.2008030259 PMid:18650476 PMCid:PMC2518446

136. Sweeney WE, Jr, Hamahira K, Sweeney J, Garcia-Gatrell M, Frost P, Avner ED. Combination treatment of PKD utilizing dual inhibition of EGF-receptor activity and ligand bioavailability. Kidney Int. 2003;64(4):1310-9. http://dx.doi.org/10.1046/j.1523-1755.2003.00232.x PMid:12969149

137. Huang JL, Woolf AS, Long DA. Angiogenesis and autosomal dominant polycystic kidney disease. Pediatr Nephrol (Berlin, Germany). 2012.

138. Nakamura T, Ushiyama C, Suzuki S, Ebihara I, Shimada N, Koide H. Elevation of serum levels of metalloproteinase-1, tissue inhibitor of metalloproteinase-1 and type IV collagen, and plasma levels of metalloproteinase-9 in polycystic kidney disease. Am J Nephrol. 2000;20(1):32-6. http://dx.doi.org/10.1159/000013552 PMid:10644865

139. Fan LX, Zhou X, Sweeney WE, Jr., Wallace DP, Avner ED, Grantham JJ, et al. Smac-Mimetic-Induced Epithelial Cell Death Reduces the Growth of Renal Cysts. J Am Soc Nephrol. 2013. http://dx.doi.org/10.1681/ASN.2013020176

140. Liu W, Fan LX, Zhou X, Sweeney WE, Jr., Avner ED, Li X. HDAC6 Regulates Epidermal Growth Factor Receptor (EGFR) Endocytic Trafficking and Degradation in Renal Epithelial Cells. PloS one. 2012;7(11):e49418. http://dx.doi.org/10.1371/journal.pone.0049418 PMid:23152903 PMCid:PMC3496684

141. Fan LX, Li X, Magenheimer B, Calvet JP, Li X. Inhibition of histone deacetylases targets the transcription regulator Id2 to attenuate cystic epithelial cell proliferation. Kidney Int. 2012;81(1):76-85. http://dx.doi.org/10.1038/ki.2011.296 PMid:21900881 PMCid:PMC3409467

142. Zhou X, Fan LX, Sweeney WE, Jr., Denu JM, Avner ED, Li X. Sirtuin 1 inhibition delays cyst formation in autosomal-dominant polycystic kidney disease. J Clin Invest. 2013;123(7):3084-98. http://dx.doi.org/10.1172/JCI64401 PMid:23778143 PMCid:PMC4101988

143. Zhou X, Fan LX, Peters DJ, Trudel M, Bradner JE, Li X. Therapeutic targeting of BET bromodomain protein, Brd4, delays cyst growth in ADPKD. Hum Mol Genet. 2015;24(14):3982-93.
http://dx.doi.org/10.1093/hmg/ddv136 PMid:25877301

144. Chen L, Zhou X, Fan LX, Yao Y, Swenson-Fields KI, Gadjeva M, et al. Macrophage migration inhibitory factor promotes cyst growth in polycystic kidney disease. J Clin Invest. 2015;125(6):2399-412.
http://dx.doi.org/10.1172/JCI80467
PMid:25961459 PMCid:PMC4497763

145. Li X, Magenheimer BS, Xia S, Johnson T, Wallace DP, Calvet JP, et al. A tumor necrosis factor-alpha-mediated pathway promoting autosomal dominant polycystic kidney disease. Nat Med. 2008;14(8):863-8.
http://dx.doi.org/10.1038/nm1783
PMid:18552856 PMCid:PMC3359869

146. Park F, Sweeney WE, Jr., Jia G, Akbulut T, Mueller B, Falck JR, et al. Chronic blockade of 20-HETE synthesis reduces polycystic kidney disease in an orthologous rat model of ARPKD. Am J Physiol Renal Physiol. 2009 Mar;296(3):F575-82.
http://dx.doi.org/10.1152/ajprenal.90705.2008.
PMID: 19129252 PMCID: PMC2660198

147. Brookes ZL, Ruff LJ, Upadhyay VS, Huang L, Prasad S, Solanky T, et al. Pkd2 mesenteric vessels exhibit a primary defect in endothelial dependent vasodilatation restored by rosiglitazone. Am J Physiol Heart Circ Physiol. 2012. PMid:23103499 PMCid:PMC3543686

148. O Bukanov N, Smith LA, Klinger KW, Ledbetter SR, Ibraghimov-Beskrovnaya O. Long-lasting arrest of murine polycystic kidney disease with CDK inhibitor roscovitine. Nature. 2006;444(7121):949-52.
http://dx.doi.org/10.1038/nature05348 PMid:17122773

149. Seeger-Nukpezah T, Proia DA, Egleston BL, Nikonova AS, Kent T, Cai KQ, et al. Inhibiting the HSP90 chaperone slows cyst growth in a mouse model of autosomal dominant polycystic kidney disease. Proc Natl Acad Sci U S A. 2013;110(31):12786-91.
http://dx.doi.org/10.1073/pnas.1301904110
PMid:23858461 PMCid:PMC3732984

150. O'Meara CC, Hoffman M, Sweeney WE, Jr., Tsaih SW, Xiao B, Jacob HJ, et al. Role of Genetic Modifiers in an Orthologous Rat Model of ARPKD. Physiol Genomics. 2012;44(15):741-53.
http://dx.doi.org/10.1152/physiolgenomics.00187.2011
PMid:22669842 PMCid:PMC3774585