CHAPTER

16 Autosomal Dominant Polycystic Kidney Disease

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD; MIM 173990) is the most common hereditary renal disease occurring in 1:400 to 1:1000 individuals. It accounts for over 90% of all hereditary renal cystic diseases (Table 16.1). ADPKD is characterized by the presence of bilateral renal cysts that gradually grow and expand over time, resulting in significantly increased total kidney volume, progressive renal injury, and ultimately, end-stage renal disease (ESRD), usually in the sixth decade of life.

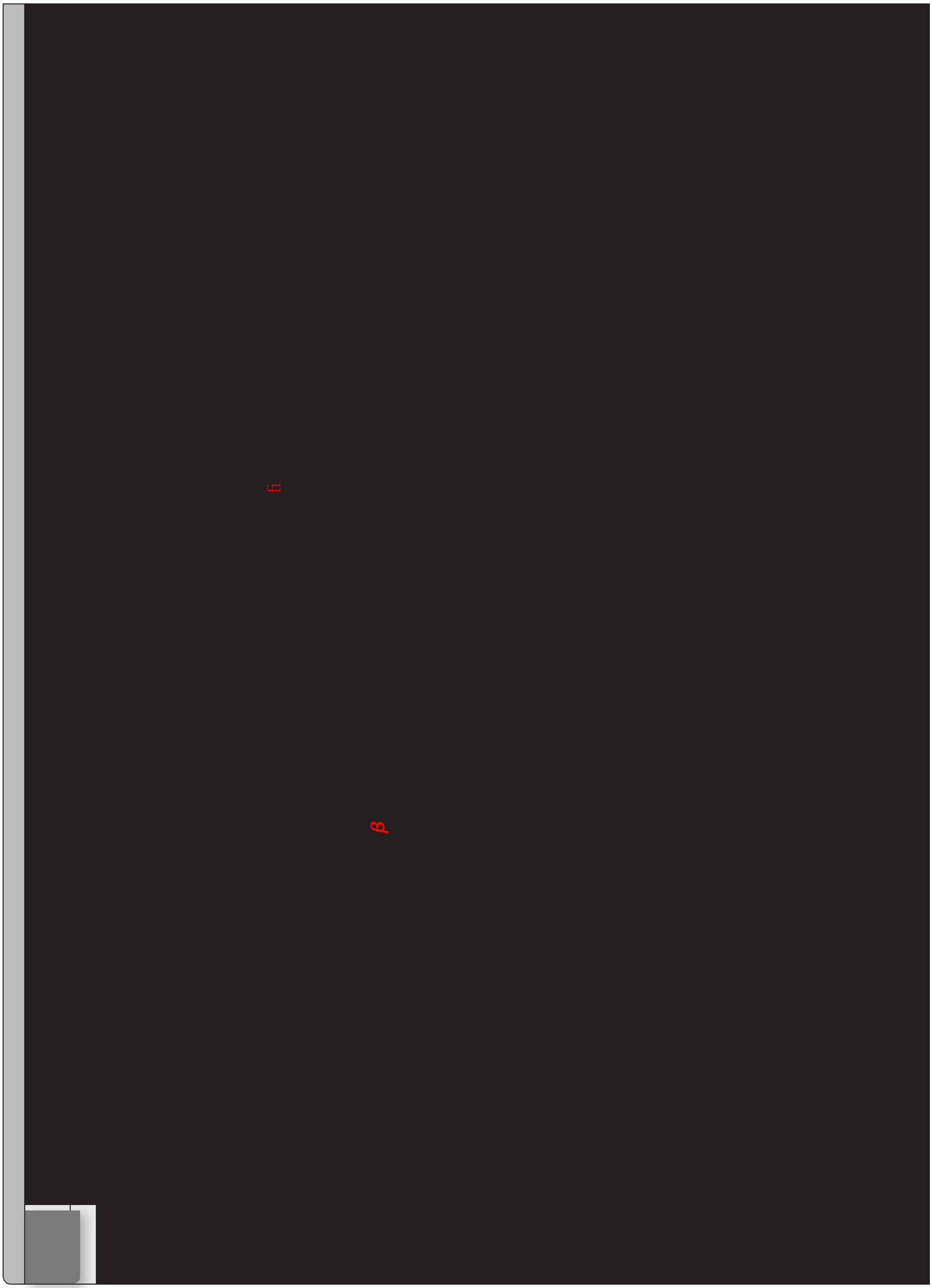
Other Mendelian diseases with varying degrees of fibrocystic involvement of the kidney are relatively rare. Autosomal recessive polycystic kidney disease (ARPKD; MIM 606702) occurs in 1:25,000; autosomal dominant tuberous sclerosis complex (TSC; MIM 191100 and 613254) occurs in 1:10,000; autosomal dominant medullary cystic disease or UMOD (MIM 174000) occurs in 1:35,000; and autosomal recessive familial juvenile nephronophthisis (NPHP; MIM 256100 and 602088) occurs in 1:40,000. In addition to the Mendelian diseases described previously, a variety of hereditary syndromes, such as Bardet-Biedl syndrome (BBS; MIM 209900) and Meckel Gruber syndrome (MKS; MIM 249000), result in a constellation of clinical manifestations that include renal cysts and are collectively termed ciliopathies (Table 16.1). In terms of clinical disease burden, however, all of the hereditary ciliopathies combined account for less than 1% of all renal cystic diseases.

This chapter will focus primarily on the single most common renal cystic disease, ADPKD. Current understanding of the epidemiology, clinical characteristics, and the pathology of ADPKD will be elucidated, and the appropriate approaches to the diagnosis and management of ADPKD will be provided. An overview of the genetics and the molecular pathways involving the polycystins is provided. Finally, a review of molecularly targeted therapeutic interventional trials will be presented to establish the potential future management for ADPKD individuals.

EPIDEMIOLOGY

Worldwide, ADPKD occurs between 1:400 and 1:1000 live births in all ethnicities when including ascertainment by autopsy.[1–3] Epidemiologic studies suggest that fewer than half of those with the disease are diagnosed during their life, with a majority of diagnoses occurring on autopsy after death from other causes.[1] Although not specifically evaluated in those studies, it is plausible that these individuals had a milder manifestation of disease. ADPKD has been estimated to be present in up to 600,000 individuals in the United States of America, and 12.5 million people worldwide (www.pkdcure.org). The disease accounts for about 6% of all patients on hemodialysis.[4] The incidence of ADPKD varies by genotype. PKD1 occurs in approximately 1:700 live births and PKD2 occurs in 1:15,000 live births. Reports from Japan, Denmark, the United States, Europe, India, Saudi Arabia, and Turkey show similar incidence rates, with no racial or ethnic predilection.[5–9] Patient and renal outcomes differ by PKD genotype. ADPKD resulting from mutations in PKD1 result in earlier mean age of onset of hypertension (29 versus 41 years of age), ESRD (55 versus 74 years of age), and death (68 versus 79 years of age) when compared to ADPKD due to PKD2 mutations.[10–12]

Current worldwide yearly incidence rates for ESRD due to ADPKD are 7.5 and 6.1 per million population for men and women, respectively. Gender differences with regard to disease progression and severity have been reported, with women having a more favorable renal outcome than men.[10,13] However, when gender differences and genotype are considered together, little or no differences in the age of onset of renal failure are found in PKD1 individuals. Importantly, significant differences in survival are found between men and women with PKD2 mutations (67.3 versus 71.0 years). In addition, previous age-adjusted sex ratios of the incidence of ESRD, which were greater in men than in women (1.4 to 1.6), are now beginning to reach parity in various countries, including Denmark and the United States.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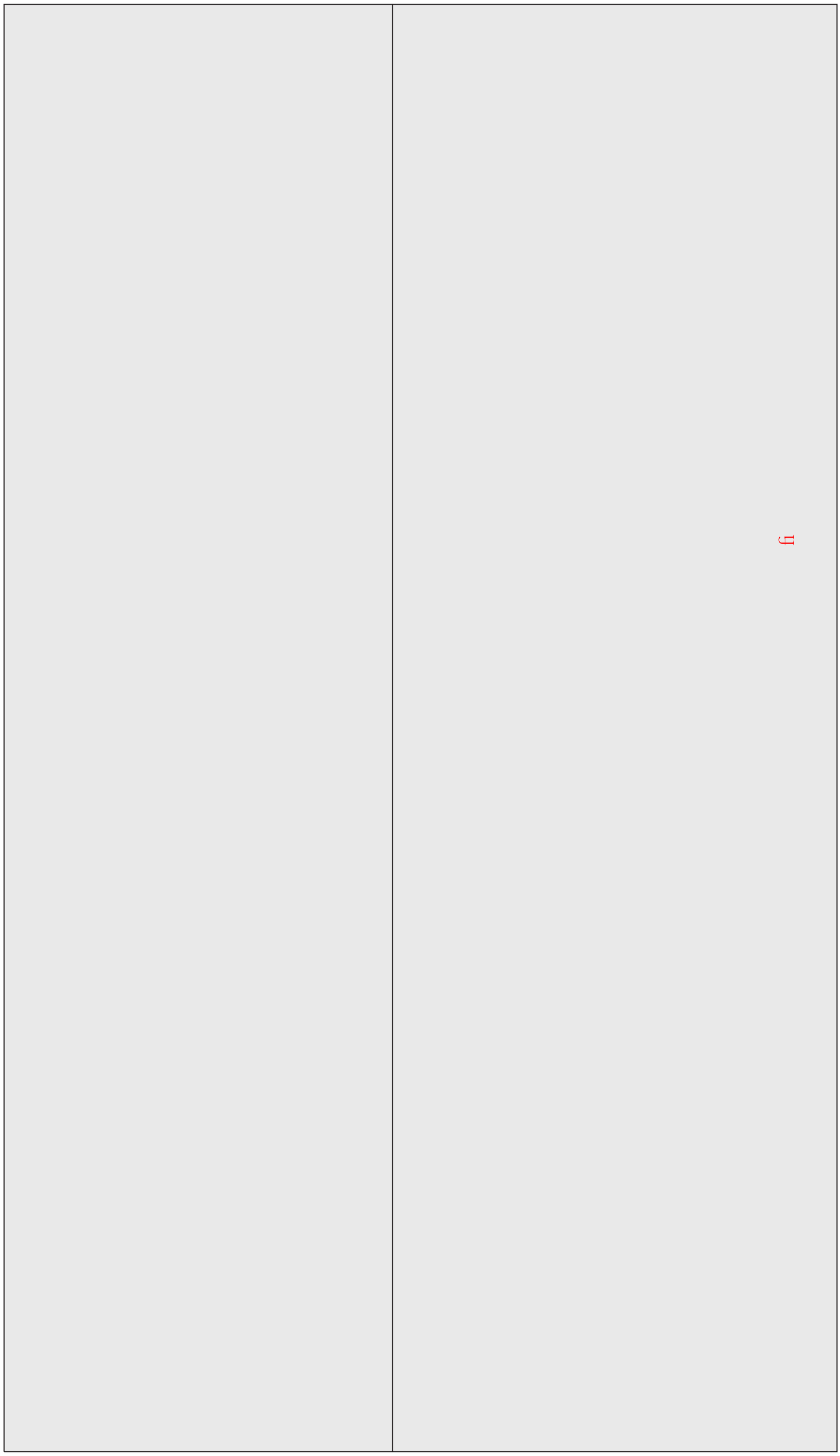
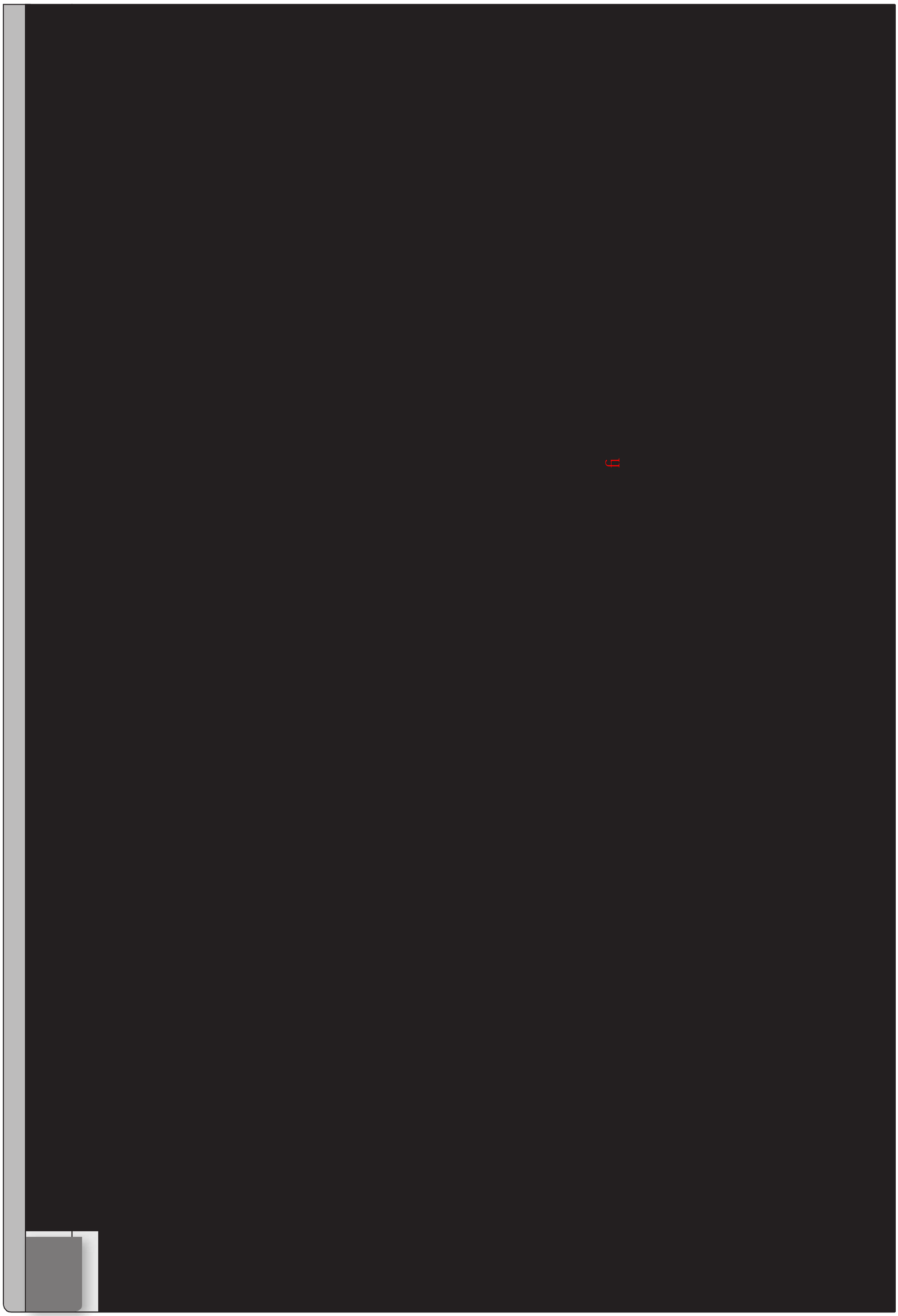




African American ADPKD patients have been reported to have a more aggressive renal course than their non-African American counterparts.[14–16] However, these reports are limited due to the small number of patients and the presence of other diseases affecting renal function, including the sickle cell disease or trait. Importantly, the relative incidence of ESRD due to ADPKD per million population in African Americans is lower than their non-African American counterparts.[4,17,18] Whether this relates to earlier mortality in African Americans or improved renal survival has not yet been determined.

During the past 3 decades, the average age of onset of ESRD, the incidence and prevalence rates of ADPKD in ESRD, and the survival rates of ADPKD in ESRD have increased. Incidence rates of ADPKD patients entering ESRD have increased significantly from 1990 to 2010 in the United States (35%), Japan (30%), and Denmark (33%).[5,17,19] The average age of onset of ESRD has increased in the United States (4.5 years), Denmark (5.1 years), and Japan (4.6 years). Importantly, the use and the number of antihypertensive agents, specifically inhibitors of the renin-angiotensin-aldosterone system (RAAS) are associated with decreased patient mortality and an increased age of onset of ESRD.[20,21] Taken together, these data suggest that patients are now more often surviving to start renal replacement therapy, and improved patient care has extended both renal and patient survival with a positive impact on patient mortality for those receiving renal replacement therapy.

DIAGNOSIS OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Although symptoms in ADPKD individuals can present at a young age, a diagnosis of ADPKD is confirmed either with radiographic imaging or genetic testing. Before undertaking a diagnostic evaluation, counseling should be done to educate the family about the risk for inheritance. The mode of presentation for diagnostic screening has not changed over the last half century, with approximately 40% of individuals with a positive family history presenting asymptomatically.[13,22] The remaining patients present with clinical complications such as new onset hypertension, gross hematuria, acute flank pain, or fevers. The average age of presentation for diagnosis has also remained unchanged for the last 4 decades. With a number of potential beneficial therapies becoming available and evidence for improved mortality due to standard medical care, an earlier presentation for screening of at risk individuals will most likely occur.

The risk for discrimination in terms of insurability and employment has been reduced, but not eliminated, by the passage into law of the Genetic Information Nondiscrimination Act (GINA).[23,24] GINA prohibits insurers from canceling, denying, refusing to renew, or changing the terms or premiums of coverage based on genetic information. It also prohibits employers from making hiring, firing, promotion, and other employment-related decisions based on genetic factors. Genetic information is defined as information about an individual's genetic tests, the genetic tests of family members, or occurrence of a disease in family members of the individual. GINA, however, applies only to individuals who are asymptomatic, does not prohibit underwriting based on information about current health status, and does not apply to life insurance, disability insurance, or long-term care insurance.

Ultrasound imaging is the initial imaging modality of choice for a diagnosis of ADPKD (Fig. 16.1). Ultrasound is cost-efficient as compared to magnetic resonance imaging (MRI) or computed tomography (CT) and is not associated with the radiation exposure that occurs with CT imaging. The vast majority of affected ADPKD patients can be diagnosed by ultrasound imaging alone. Since the initial ultrasound criteria for a diagnosis of ADPKD were developed in 1994,[25] the imaging resolution for detection of small cysts with ultrasound, CT, and MRI have vastly improved.[26,27] The limit of detection of cysts using CT and MRI is now as low as 1 mm in diameter as compared to 0.5 to 1 cm with ultrasound.[28] Importantly, and relevant to the value of diagnostic imaging in ADPKD, simple renal cysts >1 cm in diameter remain relatively rare in childhood, occurring in <0.1% in the general population.

MR- and CT-based imaging studies of healthy young adults without a family history of ADPKD show that simple renal cysts of diameters as small as 1 mm are relatively common, even in young adults, occurring in 11 out of 35 or 28% in 18- to 29-year-olds and 97 out of 190 or 51% in 30- to 44-year-olds.[26] Therefore, if Ravine criteria using cyst number alone is used with CT or MRI in individuals between the ages of 18 and 45 years of age, more than one third would erroneously qualify for a diagnosis of ADPKD. However, if only those with cysts >1 cm in diameter are considered, the size of the cyst commonly seen in ADPKD individuals and detectable by ultrasonography, the number of incorrectly diagnosed individuals would remain <1%. Therefore, in at-risk individuals, sensitivity and specificity for a correct diagnosis of ADPKD using ultrasound remains intact and a single renal cyst in an at-risk child from a family with ADPKD is sufficient to make a diagnosis (Table 16.2).[29]

An age-based renal cyst number is required for a diagnosis of ADPKD, given that simple renal cysts are present with increasing frequency as age increases in the general population. Ultrasound still carries high sensitivity and specificity for the majority of PKD1 individuals over the age of 30 years.[30,31] At age 30, a negative ultrasound indicates a less than 5% likelihood of having ADPKD in individuals from PKD1 families. Negative ultrasound imaging is also informative at earlier ages in at-risk individuals from PKD1 families, with a negative ultrasound in an at-risk 20-year-old conferring a less than 10% chance of carrying the disease. Additional experience with screening PKD2 individuals provides a more accurate estimate of the relatively high false–negative rates when screening at-risk individuals under the age of 40.[32] Although the specificity and positive predictive value of sonographic criteria is very high in PKD1 individuals, their sensitivity and negative predictive value are low when applied to PKD2 in the 15 to 29 age group (69.5 and

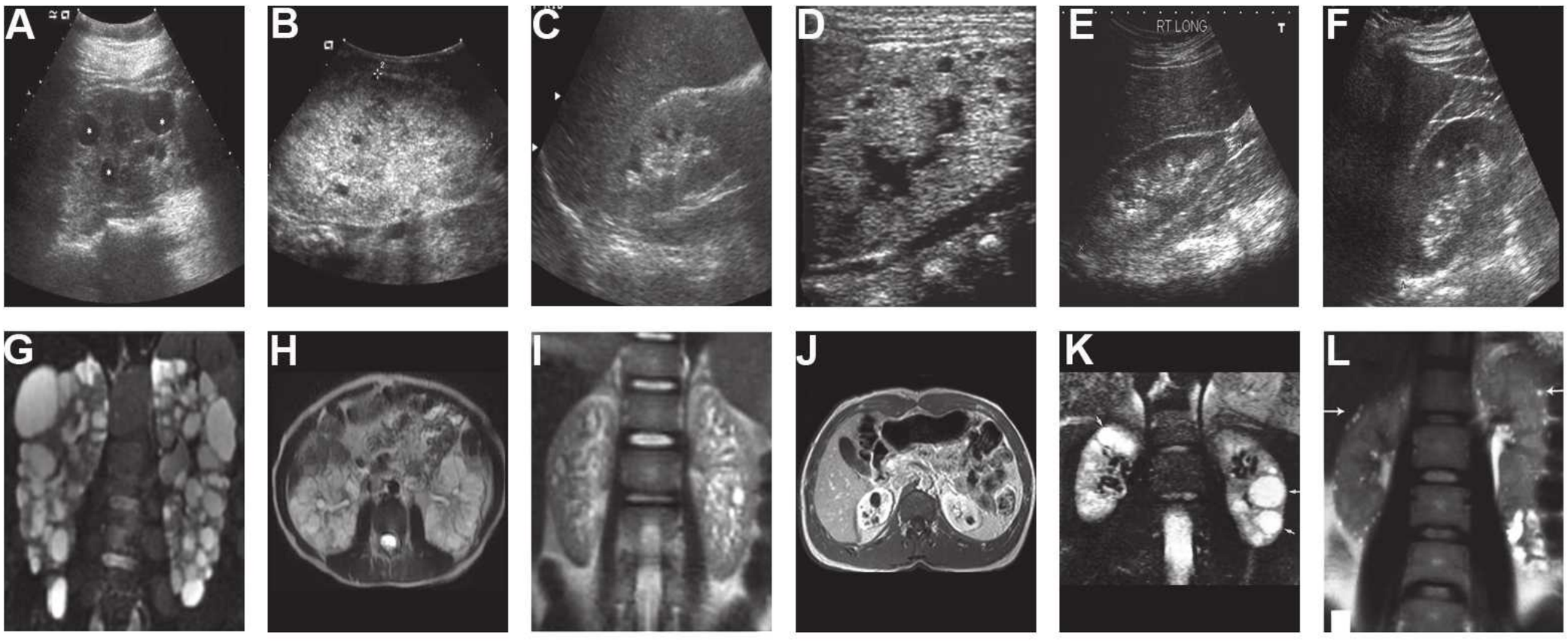


FIGURE 16.1 A radiographic appearance of hereditary renal cystic disorders. The top panels show ultrasonographic, longitudinal axis images of **(A)** autosomal dominant polycystic kidney disease (ADPKD), **(B)** autosomal recessive polycystic kidney disease (ARPKD), **(C)** familial juvenile nephronophthisis (NPHP), **(D)** glomerular cystic kidney disease (GCKD), **(E)** medullary cystic kidney disease (MCKD), and **(F)** tuberous sclerosis complex (TSC). The bottom panels show the same sequence of renal cystic disorders using either magnetic resonance imaging (MRI) or computed tomographic (CT) imaging: **(G)** a coronal MRI of early stage ADPKD, **(H)** an axial CT image of ARPKD, **(I)** a coronal MRI of NPHP, **(J)** an axial CT image of GCKD, **(K)** an axial CT image of MCKD, and **(L)** a coronal MRI of TSC.

16.2 Diagnostic Criteria for Autosomal Dominant Polycystic Kidney Disease

Age	PKD1	PKD2	Unknown ADPKD Gene Type
Diagnosis			
30–39 years	≥3 cysts[a] PPV = 100% SEN = 96.6%	PPV = 100% SEN = 94.9%	PPV = 100% SEN = 95.5%
40–59 years	≥2 cysts in each kidney PPV = 100% SEN = 92.6%	PPV = 100% SEN = 88.8%	PPV = 100% SEN = 90%
Exclusion			
30–39 years	≤1 cyst NPV = 100% SPEC = 96%	NPV = 96.8% SPEC = 93.8%	NPV = 98.3% SPEC = 94.8%
40–59 years	≤1 cyst NPV = 100% SPEC = 93.9%	NPV = 100% SPEC = 93.7%	NPV = 100% SPEC = 94.8%

[a]Unilateral or bilateral.
All values presented are mean estimates.
ADPKD, autosomal polycystic kidney disease; PPV, positive predictive value; SEN, sensitivity; SPEC, specificity; NPV, negative predictive value.
Derived from Pei Y, Obaji J, Dupuis A, et al. Unified criteria for ultrasonographic diagnosis of ADPKD. J Am Soc Nephrol. 2009;20(1):205–212.

78%, respectively). This is particularly a problem when evaluating potential young related kidney transplant donors, where the exclusion of ADPKD is important.

Based on this experience, Pei and colleagues[33] are now able to provide a unified age-based criteria for a diagnosis of ADPKD using ultrasound imaging for both PKD1 and PKD2 individuals (Table 16.2). This modification from the original Ravine criteria increases the age from 30 to 40 years for screening purposes. The presence of at least three (unilateral or bilateral) renal cysts and two cysts in each kidney are sufficient for a diagnosis of both at-risk individuals and those without a family history of ADPKD aged 15 to 39 years and 40 to 59 years, respectively. The requirement of three or more cysts (unilateral or bilateral) has a positive predictive value of 100% in the younger age group and minimizes false–positive diagnoses, because 2.1% and 0.7% of unaffected healthy individuals younger than 30 years have one and two renal cysts, respectively. In those 30 to 39 years old, both the original (two cysts in each kidney) and the revised (three cysts, unilateral or bilateral) criteria have a positive predictive value of 100%. Finally, for at-risk individuals aged greater than 60 years, four or more cysts in each kidney are required. Even with these criteria in place, there are still exceptions where ultrasound screening is not sufficient, usually when either a family history for ADPKD is absent and the clinical presentation is atypical, or when clinical suspicion for a positive diagnosis is high and evidence for renal cystic disease by ultrasound is lacking.

Although a minimum number of renal cysts are required for a diagnosis of ADPKD, other renal cystic diseases may also meet the requisite cyst number criteria to qualify for a diagnosis of ADPKD (Fig. 16.1). Additionally, given that approximately 15% of ADPKD individuals develop polycystic kidney disease (PKD) spontaneously and have unaffected biologic parents, other features of the clinical presentation are important to consider beyond simply the number of renal cysts identified. For example, the distribution and size of cysts can be informative. Cysts occurring predominantly in the medullary space with relatively small size are found in medullary cystic disease and familial juvenile nephronophthisis in the setting of normal or small kidney size and can be used to distinguish these from ADPKD. Angiomyolipomas are typically present in the kidneys of patients with tuberous sclerosis complex. Glomerular cystic disease is associated with relatively small widely distributed discrete cysts found predominantly in the cortex in the setting of normal kidney size.

In contrast to many other hereditary renal cystic diseases, ADPKD is characterized by significant renal enlargement in the setting of normal kidney function. Although renal enlargement is a feature of ARPKD, particularly in those diagnosed in utero or at birth, significant renal insufficiency usually accompanies this feature. The cysts in ARPKD tend to be diffuse, small, and relatively homogeneous and are more commonly described as fusiform and ectactic dilatations rather than discrete macrocysts. Significant renal enlargement is not present in other hereditary kidney diseases including von Hippel Lindau disease, nephronophthisis, and medullary cystic disease. Renal enlargement with significant renal cystic burden in the setting of normal kidney function, often with early onset, can be seen in specific individuals who have contiguous gene deletion mutations involving both the PKD1 and TSC2 genes.[34] This contiguous gene syndrome usually requires further genetic testing for accurate diagnosis. In addition to the diagnostic value of kidney enlargement in the setting of normal kidney function in ADPKD, the presence of radiographically visible liver cystic disease, when present, is also a unique and diagnostically useful feature of ADPKD. No other hereditary renal cystic disease is accompanied by polycystic liver disease with the exception of some instances of familial juvenile nephronophthisis. Importantly, familial instances of liver cystic disease indistinguishable from that seen in ADPKD but lacking kidney cysts is a genetically distinct disorder.[35]

Genetic testing may be required to confirm or exclude a diagnosis of ADPKD. Genetic testing is reserved for patients with renal cystic disease without a family history and with an uncertain presentation of ADPKD, or those with a negative ultrasound who are at risk for ADPKD but who need a confirmatory diagnosis for the purposes of living related kidney donation, family planning, or for occupational safety. Direct sequencing of the PKD1 and PKD2 genes is the most reliable approach to a genetic diagnosis.[36–38] A curated database of PKD1 and PKD2 mutations is available at http://pkdb.mayo.edu/. Mutation detection is successful in up to 85% of cases in research laboratories. Destructive mutations (i.e., those predicted to result in truncated proteins due to premature termination codons, aberrant splicing, or insertion-deletions resulting in frame shifting) are readily identifiable as pathogenic. The same is not true for mutations due to nonsynonymous amino acid substitutions, which may account for up to 30% of mutations in PKD1 and a significantly lower percentage of PKD2. The pathogenicity of missense sequence variations often need to be confirmed with segregation studies in other affected family members before a diagnosis can be confirmed. A genetic diagnosis is further complicated by the lack of commonly recurring mutations that have been identified in other diseases such as cystic fibrosis. As a result, most families have private mutations requiring the relatively expensive whole gene sequencing approach for detection that nonetheless yields a mutation detection rate (highest detection rate, 85%) lower than the rate of cyst detection by age-appropriate ultrasound (lowest detection rate, 99%). As a result, this approach is reserved in the clinical setting for a limited group of patients meeting the previous criteria.

PATHOLOGY OF POLYCYSTIC KIDNEY DISEASE

The kidneys of patients with polycystic disease gradually enlarge and attain an enormous size due to the growth of hundreds of cysts. Kidneys measuring 40 × 25 × 20 cm and weighing 7 to 8 kg have been reported. Usually, these greatly enlarged kidneys are seen in patients with ESRD undergoing

nephrectomy or at autopsy. These end-stage kidneys contain hundreds of fluid-filled cysts of widely differing sizes. The cyst walls can be thin and transparent, but calcification of cyst walls is also common.[39] The renal capsule may be thickened around infected cysts, and the kidney may be attached to adjacent abdominal organs such as the spleen and the adrenal glands by fibrous tissue.

Cut sections demonstrate cysts throughout the renal parenchyma. Islands of normal-appearing renal parenchyma can usually be found only in kidneys from young, nonazotemic patients. The cysts vary in size from 1 mm to 10 cm or more in diameter. Cysts in ADPKD arise from all segments of the nephron, and some cysts (~11%) retain the morphologic characteristics of proximal or distal tubules or collecting ducts. However, most (84%) are lined by a single layer of poorly differentiated columnar or cuboidal epithelium.[40,41] Approximately 5% of cysts are lined by a markedly hyperplastic epithelium, forming polyps and microadenomas.[40,42] This hyperproliferative epithelium typically has no signs of dysplasia or premalignant features. The cysts are surrounded by a fibrous stroma, which may contain bundles of smooth musclelike cells, likely transformed myofibroblasts. Inflammatory interstitial infiltrates are seen, and in advanced cases, the renal interstitium is replaced by fibrosis. Marked arteriosclerosis and arteriolosclerosis are found in nephrectomy specimens, evidence that ischemic injury and damage from hypertension contribute to tubular atrophy and glomerulosclerosis.[43]

Microdissection studies of human kidneys suggest that only 1% to 2% of nephrons are cystic.[40] These studies also have shown that cysts begin as focal dilatations of tubular segments.[44] When these dilatations exceed approximately 2 mm in diameter, they typically disconnect from the parent tubule; at least 73% of the cysts have no tubular openings when evaluated by scanning electron microscopy.[40] The cysts lining epithelial cells are joined together by junctional complexes like those seen in normal proximal tubules or by tight junctions typical of the distal renal epithelium.[41] Only a few microvilli are seen on the luminal surface and a few mitochondria in the cytoplasm. Some cells have prominent cilia, and different types of cells are found in some cysts. Occasional infoldings of the plasma membranes may be found on the basal surface. The basement membrane of most cysts is strikingly abnormal. There is pronounced splitting, duplication, thickening, and lamination of the basal lamina.

The osmolality of cyst fluids is similar to that of plasma, but sodium and nonsodium osmolyte concentrations vary significantly.[45–47] Sodium concentrations can vary between 3 and 207 mEq per liter, but often are either less than 60 mEq per liter or more than 75 mEq per liter.[46] Therefore, a distinction was made between low sodium and high sodium cysts. The high sodium cysts have sodium concentrations similar to plasma and therefore are also called nongradient cysts, whereas the low sodium cysts are gradient cysts because they are able to maintain steep concentration gradients not only for sodium but for protons, potassium, chloride, phosphates, and other ions.[48] Morphologically, the gradient cysts have long tight junctions (zonulae occludens depth >500 μm), making them impermeable to ions, whereas the nongradient cysts have short tight junctions (<500 μm), making them leaky for solutes and water.[46] These characteristics suggested that gradient cysts were derived from collecting ducts and nongradient cysts from proximal tubules. However, most nongradient cysts are lined by a poorly differentiated epithelium with few microvilli and few mitochondria, which does not resemble the proximal tubular epithelium.[46]

More recent studies have assessed the distribution of aquaporin-1 and -2 in ADPKD cysts. In normal kidneys, aquaporin-1 is expressed in proximal tubules and thin descending limbs of the Henle loop, whereas aquaporin-2 is expressed on the apical surfaces of the collecting duct epithelia. In ADPKD kidneys, approximately 30% of cysts stain positive for aquaporin-1, another 30% are positive for aquaporin-2, and the rest are negative for both aquaporin-1 and -2.[49,50] The aquaporin-1–positive cysts presumably are derived from proximal tubules or thin descending limbs, the aquaporin-2–positive cysts are from collecting ducts, and the negative cysts are from nephron segments that do not express these water channels (i.e., the ascending limb of the Henle loop and distal convoluted tubules). These results also imply that the expression of water channels is not a prerequisite for cyst expansion. Moreover, the aquaporins appear to retain their segment-specific expression in ADPKD even though the morphologic characteristics of proximal and distal tubules are lost.

In addition to electrolytes and water, cyst fluids also contain amino acids, glucose, urea; idiogenic osmoles such as sorbitol, betaine, and glycerophosphorylcholine; and proteins, such as β_2-microglobulin, erythropoietin, renin, and albumin.[47,48] Cytokines, specifically interleukin (IL)-1β, IL-2, and tumor necrosis factor (TNF)-α, growth factors (epidermal growth factor [EGF], hepatocyte growth factor, endothelins), and a nonpolar lipid cyst activating factor, are present in cyst fluids as well and likely play a significant role in the pathophysiology of ADPKD.[51–56]

Therefore, the cysts of polycystic kidneys are not simply impermeable cul-de-sacs that collect and store urine from more proximal nephron segments. They are complex structures that proliferate and undergo apoptosis; that synthesize or transport various proteins, hormones, and cytokines; and that actively secrete chloride and water. Under certain conditions, they also may be able to absorb solutes and water.[45] Most cysts are permeable to small solutes, but some are highly impermeable. Although most cysts are lined by morphologically undifferentiated epithelium, the differential expression of water channels is maintained.

CLINICAL CHARACTERISTICS OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Although ADPKD derives its name from the kidney, it is a systemic disorder with extrarenal manifestations that are unique to ADPKD.[3,57,58] Renal manifestations of ADPKD are

the most common and include the presence of renal cysts, renal enlargement, a decreased renal concentrating ability, polyuria, nocturia, and increased thirst.[59,60] In addition, renal complications of ADPKD include flank or abdominal pain, gross hematuria, hypertension, urinary tract infections, and nephrolithiasis.[13,61,62] Extrarenal manifestations are common in ADPKD and involve the cardiovascular, gastrointestinal, male and female reproductive systems, and the thyroid, subarachnoid, pericardial, and bronchial spaces.[63–67]

Although ADPKD is a hereditary renal disease, patients are relatively oligosymptomatic until the second or third decade of life. Renal complications are the most common and occur with increasing frequency with age. Pain is the most common complication, followed by hypertension and gross hematuria. The age-dependent presentation of these manifestations relate closely to kidney size or total kidney volume.[62] By the third decade of life, less than 10% of all ADPKD patients are complication free, even though the mean age of diagnosis of ADPKD is 27 years.[13] Patient-centered outcome reporting demonstrates that thirst, pain, and urinary frequency are the most common patient concerns.[68] However, close attention to other renal complications is important, given their contribution to progressive renal insufficiency and ESRD. Not surprisingly, renal complications are associated with poorer renal and patient outcomes.

Pain is the most common clinical manifestation of ADPKD and is responsible for the majority of presentations for symptomatic diagnosis.[69,70] Pre-ESRD patients completing quality of life questionnaires demonstrate lower scores on the physical component summary suggesting that symptoms of discomfort significantly impact their quality of life. Focus groups determining the most common patient-reported outcomes find that pain along with thirst and polyuria are the most important. Pain can be managed effectively in most patients, but in a minority, chronic pain limits individuals' ability to function, resulting in sleep deprivation, fatigue, anxiety, and a decreased quality of life.[71] Acute and chronic pain in ADPKD is due to different causes. Acute pain syndromes in ADPKD are most often associated with cyst rupture, hemorrhage, renal infections, or nephrolithiasis. Chronic pain is a more complex and less defined problem. ADPKD patients report pain located in the back (71%), abdomen (61%), head (49%), chest (30%), and legs (27%).[72] Renal and nonrenal sources of pain not related to cystic disease should be considered including diverticulitis, ovarian cyst rupture, aortic or iliac aneurysms, or incarcerated hernias.

Chronic pain management related to polycystic kidneys requires a staged approach beginning with nonpharmacologic interventions including ice, heat, whirlpool, massage, and physical therapy as well as exercises to improve vertebral and abdominal wall support. When these approaches are not successful, other therapies including intermittent transcutaneous electrical nerve stimulation (TENS) unit and nonopioid analgesics, such as acetaminophen, can improve the level of pain in polycystic patients. There is less objective information regarding the benefits of other treatments including short- and long-term opioid medications, tramadol (Ultram), clonidine, gabapentin, or pregabalin. Nontraditional complementary medical approaches such as acupuncture may be helpful, although this may involve a placebo effect. Surgical approaches to pain in ADPKD patients are reserved for those who have systematically attempted all nonmedical and medical therapies over a reasonable period of time. The least invasive approach is percutaneous cyst aspiration with alcohol injection, typically done in patients with symptoms that can be matched locally to candidate cysts identified using CT or MRI. This can be done in interventional radiology suites as an outpatient procedure. Multiple cyst fenestrations or deroofing procedures (Rovsing procedures) can be done in more severe and complicated cases. Prospective studies report an immediate improvement in 85% to 90% of individuals with close to two thirds maintaining a benefit up to 2 years after treatment.[73–76] More recently, renal denervation procedures both abdominally and thoracoscopically with and without nephropexy have demonstrated early short-term pain relief.[77,78] Whether there are long-term benefits resulting from these interventions is not yet clear. Finally, partial or full nephrectomy or volume reducing procedures, including transcatheter arterial embolization, have been used with success in small numbers of patients with intractable pain.

Hypertension

Hypertension is common in ADPKD and, unlike in other tubulointerstitial diseases, it occurs in the majority of patients prior to the loss of kidney function.[79–81] The average age of onset is 29 years, and men are more often hypertensive than women early in the course of disease.[11,80] Evidence suggests that carotid and left and right ventricular structure are abnormal in asymptomatic ADPKD patients early in the course of disease prior to the development of hypertension. This is manifest by increases in carotid intimal wall thickness, reduced end-diastolic relaxation, decreased aortic relaxation, increased left ventricular mass, and left ventricular hypertrophy.[82–84] Hypertension is common in children with ADPKD, affecting 10% to 25% of individuals,[85–87] and it is associated with evidence of end-organ damage including increased left ventricular mass index and left ventricular hypertrophy. Whether primary cardiovascular abnormalities or increased systemic blood pressure are the primary hemodynamic abnormality to develop in ADPKD and how they relate to each other is unclear. A recent study suggested that an early intervention in ADPKD, particularly with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, may decrease the occurrence of left ventricular hypertrophy and has the potential to decrease cardiovascular mortality.[88]

Total kidney volume (TKV) is greater in hypertensive ADPKD adults and children with normal kidney function when compared to the respective normotensive ADPKD controls.[89–91] The increased cyst burden found in hypertensive ADPKD individuals is associated with evidence of systemic activation of the RAAS. Vascular imaging and MR-based quantification of renal blood flow demonstrate attenuated renal vasculature and reduced renal blood flow,

both of which occur early and are associated with hypertension and increased TKV.[92,93] Activation of the RAAS in ADPKD is most likely due to increased intrarenal ischemia secondary to cyst formation and expansion. Distortion of the renal vasculature due to increased cyst burden results in decreased renal nitric oxide production, increased reactive oxygen species formation, and further activation of the intrarenal RAAS.[94] Currently two large randomized clinical trials are under way to determine the impact of inhibition of the RAAS and the value of rigorous blood pressure control in disease progression in ADPKD.[95] Results of these trials will be available in 2014.

Gross Hematuria

Gross hematuria is a common initial clinical presentation in ADPKD, often presenting prior to the onset of hypertension. Although not prospectively established, gross hematuria tends to associate with rapid cyst expansion, increased physical activity, and cyst wall calcifications. Gross hematuria is significantly associated with increased kidney size and a poorer renal prognosis.[62,96,97] Gross hematuria may or may not be associated with renal pain. In patients with gross hematuria who are asymptomatic, cyst rupture into the urinary collecting system is the most likely cause. Renal imaging is encouraged to rule out other treatable causes of gross hematuria. In patients in whom symptoms develop, localized pain, fever, and dysuria are common. When these clinical signs and symptoms occur, it is important to rule out cyst infection, nephrolithiasis, pyelonephritis, or lower urinary tract infections.

Gross hematuria secondary to cyst rupture is typically self-limited and usually lasts 2 to 5 days. Increased hydration with oral fluid intake and bed rest with close monitoring of blood pressure is indicated given the increased risk for acute reversible kidney injury in the setting of antihypertensive medication intake, particularly angiotensin-receptor blocking agents and angiotensin-converting enzyme inhibitors.[98] Often, it is advised to temporarily discontinue these agents until the episode of gross hematuria resolves. It is important to monitor blood pressure closely with home blood pressure monitoring devices during this time.

Urinary Tract Infections

Urinary tract infections are common in ADPKD and occur more often in women as compared to men.[99] Unlike hypertension and gross hematuria, it is not well established whether urinary tract infections are associated with progressive renal injury. Given that lower urinary tract infections are relatively common in the general population, their occurrence in ADPKD may or may not be disease related. Differentiation between lower and upper urinary tract infections can be difficult, further complicating the discovery of any link between urinary tract infections and disease severity. Upper urinary tract infections in ADPKD may be due to cyst infections, nephrolithiasis, or pyelonephritis and require careful evaluation.[100,101] Therapy for cyst infections requires different antibiotic treatment than those recommended to treat pyelonephritis in the general population. Antibiotics that provide adequate cyst fluid concentrations are necessary.[102] In addition, a more prolonged course of therapy is needed to ensure successful eradication of the infection. Current recommendations for the treatment of cyst infections include a 2-week course of an oral quinolone or possibly trimethoprim-sulfamethoxazole.

The diagnosis of a cyst infection is often difficult. Clinical presentations vary ranging from local tenderness, fever, leukocytosis, and leukocyturia with positive urine cultures to diffuse abdominal discomfort or pain, absence of a fever, and negative urine cultures.[103] Importantly, blood cultures may more often provide evidence of the infecting organism than urine cultures given that many infected cysts do not directly communicate with the urinary collecting system. Occasionally, cyst infections do not respond to appropriate oral antibiotic therapy. Typically, this occurs in larger cysts (>5 cm in diameter) or when intracystic antibiotic levels are inadequate. It may be necessary to administer parenteral antibiotics, conduct imaging studies to rule out other causes of fever and pain (including nephrolithiasis), and to consider percutaneous cyst aspiration to obtain cultures or to decompress the large infected space.[104] In rare circumstances, frank pyonephritis may develop associated with sever malaise, sepsis, and shock and may necessitate partial or total nephrectomy.

Nephrolithiasis

Kidney stones are tenfold more common in ADPKD patients than the general population, occurring in approximately 25% of affected individuals.[105] Symptomatic nephrolithiasis typically occurs later than other renal complications in ADPKD.[96] Nephrolithiasis associates with increased TKV in ADPKD patients with normal kidney function. All types of kidney stones can occur in ADPKD; however, urate nephrolithiasis is more common than other types of kidney stones.[106] ADPKD patients develop hypocitraturia, even prior to a loss of renal function, and this may contribute to the increased frequency of urate nephrolithiasis. Whether the hypocitraturia associated with ADPKD is due to abnormalities in renal ammonia generation or other tubular defects is unknown. Of note, urinary biochemical parameters in ADPKD patients uniquely demonstrate normal urinary calcium excretion with increased oxaluria. Patients with nephrolithiasis typically present with unilateral flank pain, with or without radiation, and may have micro- (or rarely, macro-) hematuria. Those with nephrolithiasis diagnosed incidentally during renal imaging more commonly report lower unilateral back pain. Importantly, fevers and chills may occur in the setting of nephrolithiasis. This constellation of signs and symptoms overlap significantly with cyst infections and cyst hemorrhage. An evaluation of nephrolithiasis almost always requires renal imaging—most often, noncontrast CT imaging.[107] Ultrasound has a reduced sensitivity for the detection of kidney stones as compared to CT imaging

in ADPKD individuals. Excretory urography, abdominal flat plate X-rays, and ultrasound can all be used; however, the localization and detection of renal stones is achieved best with CT imaging. The differentiation of renal cyst wall calcification and nephrolithiasis is important and can be easily done when CT imaging is performed. Cyst wall calcifications are more common in ADPKD patients who demonstrate nephrolithiasis than those who do not.

The approach to the management of nephrolithiasis in ADPKD patients should involve a biochemical analysis of the urine and stone using crystallography if possible. Estimates of daily fluid intake and dietary intake of stone-forming elements should be established. Both of these evaluations can be determined from a single 24-hour urine collection. Urinary biochemical analysis should include calcium, urate, oxalate, citrate, and pH.[108] For the majority of stones formed in ADPKD, increases in fluid intake are the cornerstone of therapy. A minimum of 3 L per day of fluid intake should be established using home monitoring coupled with monthly 24-hour urine collections. The addition of bicarbonate or citrate is also helpful for those patients with urate nephrolithiasis to decrease urinary acidification and to increase potential stone dissolution. Dietary education is also helpful with regard to dietary intake of urate, calcium, and oxalate. For patients with calcium oxalate stones, the addition of thiazide diuretics will help to reduce urinary calcium excretion and, coupled with increased fluid intake to greater than 3 L per day, will reduce the concentration of urinary calcium and inhibit initial stone formation.

The most complicated stone in ADPKD patients is the struvite stone, or staghorn calculus. These stones are a constant nidus for infection, which can recur shortly after each treatment course and must be removed to avoid complications. These stones are a nidus for infection, which recurs after each treatment course, and must be removed to avoid complications. Collaboration with the urologic specialists is essential for the management of these patients. Depending of the size of the stone and its location, retrograde lithotripsy, extracorporeal shock wave lithotripsy (EWAL) therapy, or percutaneous stone removal may be necessary.

EXTRARENAL MANIFESTATIONS IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

Polycystic Liver Disease

Liver cyst formation is the most common extrarenal manifestation in ADPKD. Polycystic liver disease is due to the presence of multiple scattered cysts of biliary origin in the liver parenchyma. Among the hereditary renal cystic disorders, it is only found in ADPKD and, when present, is a useful adjunct in securing the diagnosis. In individuals with kidney cysts and no family history of ADPKD, the presence of liver cystic disease provides confirmation of the clinical diagnosis. Liver cystic disease occurs in over 85% of PKD1 patients by the age of 30.[109] An MRI analysis performed as part of the Consortium for the Radiographic Imaging Studies of Polycystic Kidney Disease (CRISP) study demonstrated that the prevalence of liver cysts increases with age, occurring in 58%, 85%, and 94% of affected individuals age 15 to 24, 25 to 34, and 35 to 46 years, respectively. The severity of cystic liver disease appears to parallel the severity of cystic kidney disease.[110,111] Liver cystic disease varies from a few cysts to massive cystic liver enlargement. Importantly, liver parenchyma and liver function are normal even in the setting of massive polycystic liver disease, and portal hypertension does not occur. Biochemically, the only liver function abnormalities found are mild elevations in the alkaline phosphatase and bilirubin. In contrast to renal cystic disease, polycystic liver disease occurs earlier and is more likely to be severe in women than in men and is influenced dramatically by estrogen exposure.[110] Liver cysts develop within specific segments of the liver, and there is no predictable segment sparing.

The signs and symptoms of polycystic liver disease include increased abdominal girth, increased clothing size, shortness of breath, early satiety, abdominal pain, and umbilical herniation. Morphologic studies of liver cysts demonstrate that they originate from biliary microhamartomas that arise from biliary ductules and peribiliary glands. As in the kidney, as liver cysts expand and enlarge, they become detached from their biliary tree of origin.[112] Similarly to polycystic kidney disease, cyst expansion is the result of multiple effects of proliferation of cyst-lining epithelia, fluid secretion, remodeling of the extracellular matrix, and neovascularization.[112] The genetic and molecular signaling mechanisms found in renal cystic epithelia have also been found in liver cystic disease in ADPKD, suggesting that the underlying disease biology in both organs are closely related.

Isolated Polycystic Liver Disease

Isolated autosomal dominant polycystic liver disease (ADPLD; MIM 177060, 608648) is an autosomal-dominant familial disease with significant genetic heterogeneity.[35,113] It is relatively rare, with an estimated incidence of $< 0.01\%$ of the population. This may be related to the low rate of clinical symptoms; autopsy studies suggest a rate of occurrence that is only slightly lower than that of ADPKD.[114] Although isolated ADPLD was reported as early as 1906,[115] it was not until 2003 that linkage analysis in eight Finnish families confirmed that isolated ADPLD is a disease genetically distinct from polycystic kidney disease. Subsequent gene discovery studies in patient families showed that ADPLD is genetically heterogeneous, with a subset of affected families having heterozygous mutations in PRKCSH or SEC63 in the setting of clinically indistinguishable clinical presentations.[116–118] Further genetic heterogeneity is suggested by the finding that only approximately 30% of ADPLD families have mutations in either of these two genes.[119] As a result, DNA testing in ADPLD patients has limited use because the mutated genes responsible for ADPLD have not been identified for the majority of families.

The natural history of ADPLD is relatively oligosymptomatic, characterized by associated symptoms in less than 30% of individuals. Those with symptomatic ADPLD complain of abdominal distention, fullness, discomfort, early satiety, and dyspnea and back pain. Individuals with ADPLD also demonstrate mild elevations in serum alkaline phosphatase as well as total bilirubin associated with lower total cholesterol and triglyceride levels. As in ADPKD, ADPLD women show a tendency toward significantly more liver cystic burden than men. As compared to unrelated and related unaffected individuals, mitral leaflet abnormalities may be more common, and other vascular malformations including intracranial aneurysms, carotid artery dissections, and ectatic cavernous arteries have been seen.[35] The differential diagnosis of ADPLD includes simple liver cysts and liver cysts resulting from other diseases, including ADPKD. Because simple liver cysts are common in the general population and occur with increasing frequency with increasing age, at least four liver cysts visible by ultrasonography are required for the diagnosis of ADPLD in individuals over the age of 40.

Intracranial Aneurysms and Other Vascular Abnormalities

The frequency of intracranial aneurysms (ICAs) is increased in ADPKD. A recent meta-analysis of 645 ADPKD patients with ICA demonstrated a 6.6-fold increased likelihood of an ICA developing compared to the general population.[120] This represents a frequency of 5.8% in selected ADPKD populations (as compared to 2.8% in the general population) and a 12% frequency in ADPKD patients with a positive family history of an ICA. ICAs tend to cluster in a small number of ADPKD families, and a positive family history of ICA is the only established risk factor associated with ICA in ADPKD. Gender, age, smoking exposures, hypertension, and race do not contribute to the risk of ICA formation in ADPKD. Mutations in the PKD1 gene tend to be closer to the 5′ end of the gene in families with intracranial aneurysms[121] and a common PKD1 mutation has been reported in individuals with a variety of vascular malformations including ICA,[122] but the genetic basis of ICA beyond the tendency to cluster in certain families is not well understood.

As compared to the general population, ICAs are more often found in the anterior circulation (84%) and rupture at an earlier age in ADPKD, but they do not differ in size at the time of rupture. As with all ICAs, the risk of rupture increases significantly once size reaches 10 mm in diameter. Given the serious consequences of an ICA rupture with permanent morbidity and mortality in excess of 40%, preventative screening and management are important aspects to patient care. Given that aneurysms are relatively rare, selective screening should be considered. Multiple studies of asymptomatic ADPKD patients demonstrate that only a positive family history associates with an ICA.[123,124] Repeat screening in individuals following an initial negative screen provided a very low yield of 2.4% in 76 individuals over 10 years.[20] Two longitudinal imaging studies of ADPKD individuals with documented small intact ICAs demonstrated a low frequency (8 out of 65) of increases in diameter over 243 patient years with the occurrence of six de novo aneurysms.[125,126] Taken together, these data suggest that the presence of ICAs in ADPKD patients is reflective of an initial expansion at the time of formation, perhaps with a higher risk of rupture. If the initial screening does not show vascular abnormalities, further imaging is not required unless individuals are symptomatic. Specific subgroups of ADPKD patients in addition to those with a positive family history of ICA, such as those considering organ donation or receipt, commercial pilots, or those with considerable personal burden due to concern about their status should undergo an initial screening for ICA.

Potential imaging modalities to assess the intracerebral vasculature include CT angiography, four vessel arteriography, or MRI. All modalities have excellent resolution, accuracy, and reliability. CTs and angiographies are associated with increased radiation exposure and potential complications. Therefore, MR angiography is the imaging modality of choice for screening. MRs with and without gadolinium can be used to clearly outline the cerebral vasculature. The management of ICAs in ADPKD patients relate primarily to the size of the ICA but also depend on location and whether they are asymptomatic. Typically, ICAs less than 5 mm in diameter are at low risk of rupture. In symptomatic individuals or those with ICAs greater than 7 mm, either surgical ablation or coil ablation or thrombosis can be used, depending on the size and location of the ICA. Complications related to surgical intervention are low (< 1%), but when they occur, they have significant morbidity, particularly with procedures performed in the posterior circulation of the circle of Willis. Therefore, patients with ICAs are advised to carefully review the risks of rupture and complications of treatment before moving forward with surgical or endovascular interventions.

Fertility in Autosomal Dominant Polycystic Kidney Disease

Women with ADPKD demonstrate fertility rates similar to the general population. However, an increased rate of ectopic pregnancy[127] has been reported that is potentially associated with abnormalities in fallopian tube function or ciliary motility. Importantly, seminal vesicle cysts are common in men and can be detected by transrectal ultrasonography in up to 40% of male ADPKD patients.[128] Abnormal sperm motility occurs in the majority of men with ADPKD, and although this has not been shown to directly relate to fertility, it may play a role in the increased occurrence of azoospermia reported in men with ADPKD.[129] Although women with ADPKD demonstrate a normal ability to become pregnant, the course of pregnancy is associated with increased maternal and fetal complications. In general, the likelihood of a successful pregnancy in ADPKD is similar to the general population,[127,130] but there are subgroups of patients, such as those with preexisting hypertension or with established renal insufficiency, who are at an increased risk for fetal loss.

Premature delivery, small for gestational age babies, and congenital abnormalities occur in a small percent of offspring

born to women with ADPKD, typically those older than 30 years or with preexisting hypertension.[127] In a large series of 605 pregnancies in 235 women with ADPKD, only 2 individuals had serum creatinine concentrations greater than 1.2 mg per deciliter prior to becoming pregnant. This is in large part due to the typically delayed occurrence of renal insufficiency in the fourth to sixth decades of life in ADPKD individuals. Given that renal function is usually intact in ADPKD individuals during their reproductive years, the typical complications of polyhydramnios and preterm labor that are associated with pregnancy in women with established renal insufficiency are not typical features of pregnancy management in ADPKD. Maternal complications occurred in 35% of women with ADPKD who become pregnant, including new-onset hypertension, worsening hypertension, preeclampsia, and acute kidney injury. These complications tend to be relatively mild and resulted in uncomplicated pregnancies in the majority of women with ADPKD.

In women with ADPKD who are planning a pregnancy, proactive management before and during pregnancy is critical. For women with hypertension planning to become pregnant, all inhibitors of the RAAS should be stopped prior to pregnancy given the untoward effects on the fetus even with first trimester exposure to this class of drugs. Once pregnant, women with ADPKD should be seen by a high-risk obstetrician and a nephrologist beginning in the middle of the second trimester, particularly if prepregnancy renal function is not normal. Monthly screening for the development of new or worsening hypertension should be conducted. Patients should also check their blood pressure in their home environment on a regular basis. Patients should have their urine reviewed for the presence of new or increased proteinuria, which is a potential sign for the development of preeclampsia. Blood pressure management during pregnancy should include using antihypertensive therapies approved for use in pregnancy including aldomet, hydralazine, clonidine, labetalol, or a dihydropyridine. Immediately postdelivery, women with ADPKD should be monitored closely for signs of worsening hypertension and should have their level of kidney function and blood pressure established approximately 6 weeks after delivery. Longitudinal studies of risk factors for the progression to renal failure have suggested that pregnancy number (particularly for those with more than three pregnancies) is an independent risk factor for the development of ESRD in ADPKD.[131] This association is weak compared to other risk factors such as the presence of hypertension or total kidney volume. The association with pregnancy number or use of estrogen/progesterone agents use is much stronger for liver cyst burden.[132]

THE PKD GENES AND THEIR PROTEIN PRODUCTS

The evolving understanding of the pathogenesis of polycystic kidney diseases has been punctuated by several critical discoveries. The most fundamental of these advances came with the identification of the genes and the respective protein products that are mutated in families with these diseases.[116–118,133–137] At the time of their discovery, the genes for ADPKD (and ARPKD) were completely novel and did not readily fit into in any known biologic pathways. The initial clues regarding their putative roles had to come from the predicted structure of the respective protein products and the knowledge that their functions are expected to intersect at the level of clinical human disease phenotype manifested as the dysregulated nephron tubule structure. This section will review the current state of knowledge regarding the protein products of the various genes associated with human polycystic kidney and liver disease.

PKD1 and Polycystin-1

PKD1 is located on chromosome 16p13.3.[133–135,138] The structure of the gene locus is complicated by the fact that the 5′ two-thirds of the gene is duplicated multiple times with very high sequence fidelity in pseudogenes located on more proximal regions of chromosome 16.[139–142] The need to resolve sequence variants occurring in the PKD1 gene itself as opposed to its homologs for purposes of mutation detection has complicated genetic testing in ADPKD, although current sequence–based technologies are able to address this complication. The protein encoded by PKD1 is called PC-1. PC-1 is a large, low abundance, polytopic integral membrane protein with complex domain structure suggestive of receptor function that undergoes multiple proteolytic cleavage processes (Fig. 16.2). This constellation of features coupled with the absence of direct biochemical and cell biologic assays for its function has made deciphering the mechanisms of ADPKD challenging despite the successful identification of the genes almost 2 decades ago.

Human PC1 is comprised of 4302 amino acids with a 3074 amino acid extracellular NH_2-terminus, 11 transmembrane domains, and a 198 amino acid cytosolic COOH-terminus (Fig. 16.2).[143] The extracellular NH_2-terminal domain contains a number of protein motifs including leucine-rich repeats, a WSC homology domain, C-type lectin domain, a low density lipoprotein (LDL)-A related domain, 16 immunoglobinlike PKD repeats,[134,144,145] a receptor egg jelly (REJ) module,[146] and a G-protein–coupled receptor (GPCR) proteolytic site (GPS).[147] The Ig-like polycystic kidney disease (PKD) domains occupy 40% of the extracellular portion of PC1 and contain a distinct β-sandwich fold structure[148] that is resistant to unfolding under mechanical force.[149–151] The stability of these PKD domains is altered by naturally occurring mutations in PKD patients.[152] The REJ module is comprised of four fibronectin type III β-sheet domains.[153] The first intracellular loop contains a highly conserved polycystin-1, lipoxygenase, alpha-toxin (PLAT) domain that may be involved in protein interactions.[154] The extracellular loop between the sixth and seventh transmembrane domains contains a highly conserved domain that is common to both PC-1 and PC-2 family members and is not found in any other protein families.[155] The region of the last six transmembrane domains of PC1 share sequence similarity with

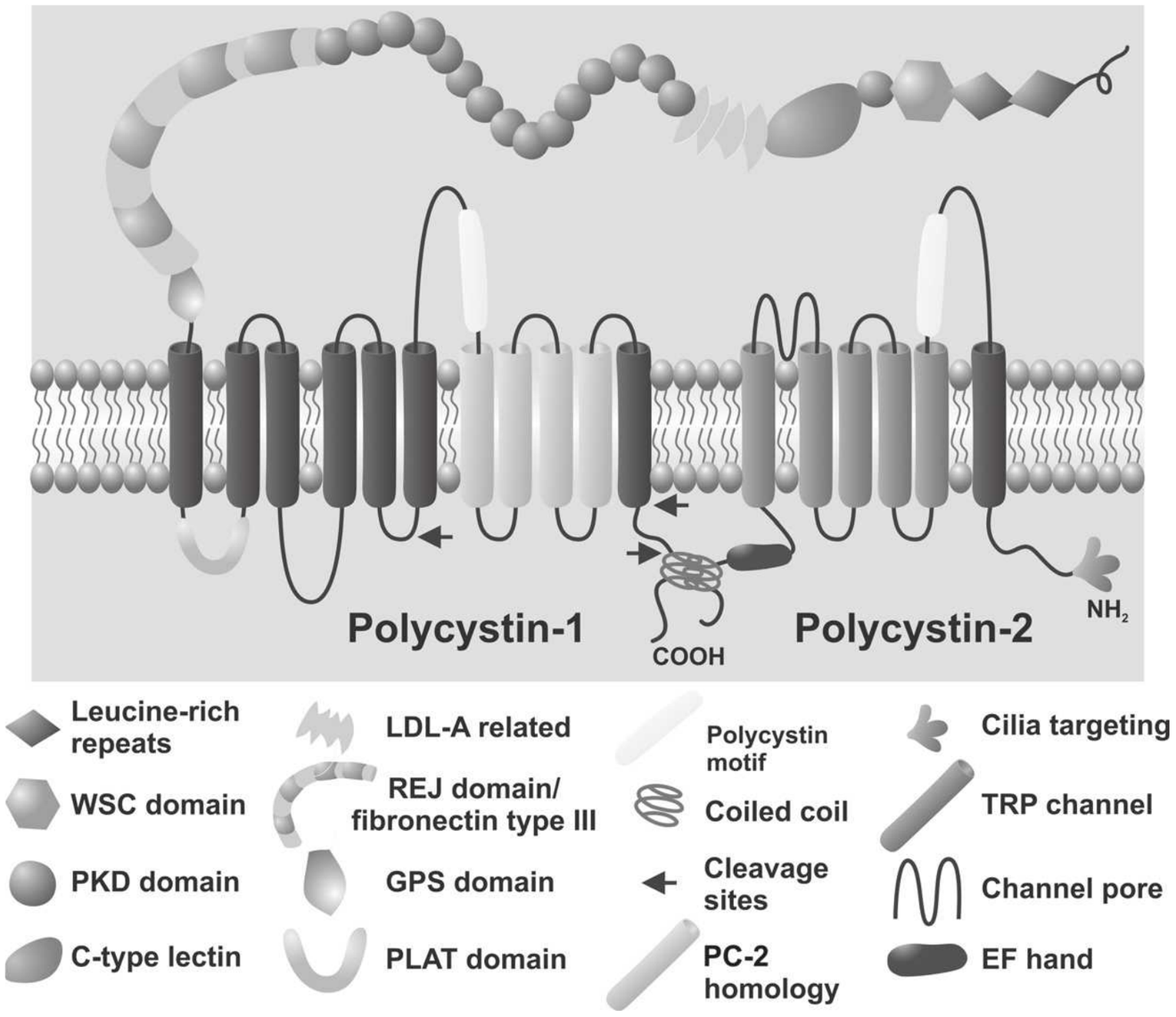


FIGURE 16.2 The protein products of the autosomal dominant polycystic kidney disease (ADPKD) genes *PKD1* and *PKD2*. The schematic drawing highlights the predicted domain structure of polycystin-1 (PC-1) and polycystin-2 (PC-2). PC-1 and PC-2 interact via coiled coil domains in their respective cytoplasmic carboxy (COOH)-termini to form a predicted receptor-channel complex; the most likely stoichiometry is three PC-2 molecules (only one is shown) and one PC-1 molecule. The extensive extracellular NH_2-terminal domain of PC-1 is cleaved at the G-protein–coupled receptor proteolytic site (GPS) in the endoplasmic reticulum (ER) but remains noncovalently associated with the intramembranous COOH-terminal PC-1 fragment. Additional putative cleavage sites are indicated by *arrows*. See the text for further discussion of the structural features of both proteins. PKD, polycystic kidney disease; LDL-A, low density lipoprotein-A; REJ, receptor egg jelly; PLAT, polycystin-1, lipoxygenase, alpha-toxin; TRP, transient receptor potential. (See Color Plate.)

PC-2 but lack critical residues suggesting that PC1 does not have the channel activity associated with PC-2 (see the following). The COOH terminus of PC1 contains a coiled coil domain that is necessary for interaction with PC-2.[156–158] In addition to the repeated partial PKD1 sequences on chromosome 16, there are four homologous protein products in the PKD1 gene family: PKD1L1, PKD1L2, PKD1L3, and PKDREJ. A complex of PKD1L3 protein with the PKD2 homolog, PKD2L1, has been assigned chemosensory function in sour taste and pH sensation,[159,160] although studies with Pkd1L3 knockout mice have called this into question.[161] PKD1L1, but not PKD1, has been implicated in left–right axis determination in mammals.[162]

Several functional cleavage processes have been defined for PC1. The best characterized of these is the autoproteolytic cleavage within the sequence HL↓T[3049] at the GPS in a process that requires an intact REJ module.[163,164] The GPS cleavage process occurs early in the secretory pathway, most likely in the endoplasmic reticulum (ER), and requires N-glycan attachment.[164] The resultant extracellular NH_2-terminal fragment and the intramembranous COOH-terminal fragment remain noncovalently associated with each other.[163] Although the GPS site is conserved in all PC1 homologs within and across species, at least two homologs, PKDREJ and the sea urchin protein SuREJ2, do not undergo GPS cleavage.[165,166] Experimental evidence for the functional importance of GPS cleavage in PC-1 comes from findings that pathogenic patient mutations in the REJ abrogate GPS cleavage, that cleavage deficient PC-1 does not support tubulogenesis and STAT1 activation in a cell culture assay, and that a GPS cleavage mutant knockin functions as a hypomorphic allele in mice.[163,167] GPS cleavage appears to promote cell surface expression of PC-1.[168] Cleaved PC-1 has been identified in urinary exosome–like vesicles, raising the possibility of a signaling function for shed polycystins.[169]

Additional cleavage products of PC-1 have been identified, although these are less well understood than the GPS cleavage. P100, a second intramembranous cleavage product of PC-1 encompassing the last six transmembrane domains, has been shown to diminish store-operated calcium entry by altering the translocation of the ER calcium sensor protein STIM1 to the cell periphery.[170] Two cleavages liberating different fragments of the cytoplasmic tail of PC-1 have also been identified. The first yields a 35 kDa fragment that translocates to the nucleus following cleavage step that is dependent on the presence of functional PC-2.[171,172] This fragment is released by gamma-secretase–mediated cleavage and regulates the Wnt and C/EBP homologous protein (CHOP) pathways by binding to respective transcription factors (TCF) and CHOP, thereby disrupting their interaction with a common transcriptional coactivator p300.[173,174] The second proposed COOH terminal cleavage product is a 15 kDa fragment that interacts with the transcriptional activator STAT6 and the coactivator p100 in a process that is enhanced by the cessation of flow-induced mechanical stimuli.[175] Inhibition of STAT6 in a Pkd1 mouse model results in the slowing of cyst growth.[176]

PKD2 and Polycystin-2

PKD2 encodes PC2, a 968 amino acid integral membrane protein with six transmembrane spans and intracellular NH_2 and COOH termini (Fig. 16.2).[135,177,178] It is a member of the transient receptor potential (TRP) family of cation channels and is also known as TRPP2.[179–182] Two mammalian homologs of PKD2, PKD2L1 (TRPP3) and PKD2L2 (TRPP5), have been identified. The TRP channel family is comprised of

28 different gene products, which function in diverse, mostly sensory, cellular processes including sensation of pain, temperature (hot and cold), taste, pressure, and vision.[183] The last five transmembrane spans of PC-2 have the greatest structural similarity with other TRP channels, with the region between the fifth and sixth transmembrane domains comprising the ion selectivity pore. An RVxP motif in the NH_2 terminus of PC-2 is necessary for its localization in cilia, and PC-2 can traffic to cilia independently of PC-1 (see the following).[184] Phosphorylation at serine 812 in the COOH terminus of PC-2 affects the channel properties[185] and trafficking[186,187] of the protein. The subcellular immunolocalization of PC-2 has been controversial. There is general consensus that PC-2 is abundantly expressed in the ER[177,179,188] and the primary cilium.[189,190] COOH truncated forms of PC-2 readily traffic to the plasma membrane,[177,184] and it has been suggested that coassembly with PC-1 is required for trafficking of full-length PC-2 to the generalized plasma membrane.[180] PC-2 has also been reported associated with centrosomes[191] and the mitotic spindles of dividing cells.[192]

The cellular mechanisms for trafficking PC-2 to the cilium and the somatic plasma membrane are divergent.[193] Trafficking begins with a coat protein complex II (COPII)-dependent process that delivers PC-2 from the ER to the cis side of the Golgi. From there, the bulk of PC-2 is returned to the ER in a process dependent on a 34 amino acid retrieval signal in the COOH terminus of PC-2. A minority of PC-2 enters a vesicular transport process directly from the cis part of the Golgi that delivers the protein to the cilium in a process that depends on Rab8a as well as the RVxP motif. If PC-2 is also to be delivered to the somatic plasma membrane (e.g., by truncation of the COOH terminus retrieval signal), this process traverses the Golgi in the conventional manner of other integral membrane and secreted proteins. PC-2, like PC-1 and the ARPKD (PKHD1) gene product fibrocystin, is a prominent component in urinary exosomeslike vesicles that are produced by the multivesicular body sorting pathway.[169] The PKD-related proteins and the exosomes that contain them may play a role in novel urinary signaling pathways in the kidney.

The COOH terminus of PC-2 contains EF hand[135,194,195] and coiled domains[156–158,195,196] and has been the subject of several biophysical and biochemical studies. The EF hand binds calcium[194] and may have a role in modulating channel activation and inhibition. The coiled coil domain is responsible for homo- and hetero-multimerization of PC-2 with itself and with PC-1, respectively. The structural data are most consistent with a complex consisting of three PC-2 molecules and one PC-1 molecule interacting through their respective coiled coil domains.[157,197] Critical residues in both proteins that weaken these interactions have been identified and should prove useful in modulating activity of the polycystins in experimental systems.[158,196] In addition to interacting with each other, PC-2 and to a lesser but still significant extent, PC-1, have acquired an extensive list of interacting proteins primarily associated with their respective COOH termini.[58] Although many of these interactions have shown functional effects in a variety of biologic systems, a direct role in the pathogenesis of ADPKD is lacking in most of them. This may in fact highlight the likelihood that PC-1 and PC-2 serve additional cellular and tissue functions that may not be directly related to their role in PKD. Identifying the roles specific to ADPKD remains a challenge especially in light of the fact that those roles might be subsumed by the minute fraction of each protein that appears in the primary cilium (see the following).

The Genes for Autosomal Dominant Polycystic Liver Disease

The two known genes for ADPLD, PRKCSH [116,117] and SEC63,[118] respectively encode the noncatalytic beta subunit of glucosidase II (GIIβ)[198,199] and SEC63p. These proteins work at the level of the ER to ensure the proper biogenesis of integral membrane and secreted proteins (Fig. 16.3). As such, their client proteins include up to one-third of the cellular proteome. GII is an ER luminal enzyme involved in glucose trimming of N-glycan moieties in the calnexin–calreticulin cycle. GII activity is necessary for proper folding and quality control of proteins passing through the ER translocon.[200] The ADPLD-associated GIIβ subunit contains an ER luminal retention signal and is required for the function of the GII holoenzyme.[201] SEC63p, an integral protein of the ER membrane, works upstream of GIIβ in concert with the SEC61 translocon pore and BiP, the major Hsp70 chaperone in the ER to effect the cotranslational targeting of precursor proteins with NH_2-terminal cleavable or noncleavable signal peptides.[202–205] SEC63p has a DnaJ-like domain located in the ER lumen, which recruits BiP to the translocon complex. BiP and SEC63p form a molecular ratchet that is responsible for the ATP-dependent vectorial movement of polypeptides into the ER lumen.[206] In contrast to the still incompletely understood functions of the polycystins, it is fairly clear that the two ADPLD gene products work together to facilitate cotranslational translocation across the ER membrane and the proper folding of nascent peptides destined to become either secreted or membrane-inserted proteins. Recent studies have elucidated the interrelationship of this function with polycystic kidney disease (see the following).

PKHD1 and Fibrocystin/Polyductin

A single gene, PKHD1, is known to be mutated in human ARPKD. Heterozygous carrier parents are typically asymptomatic, although a recent report has suggested that they have a predisposition to polycystic liver disease and increased renal medullary echogenicity by ultrasound,[207] whereas affected offspring show bile duct proliferation associated with fibrosis in the liver and relatively homogeneous fusiform dilation of collecting duct segments in the kidney. The protein product of PKHD1 is a 4074 amino acid type I integral membrane protein with a 3858 amino acid extracellular NH_2-terminus, a single transmembrane domain, and a 192 amino acid cytoplasmic tail called fibrocystin/polyductin

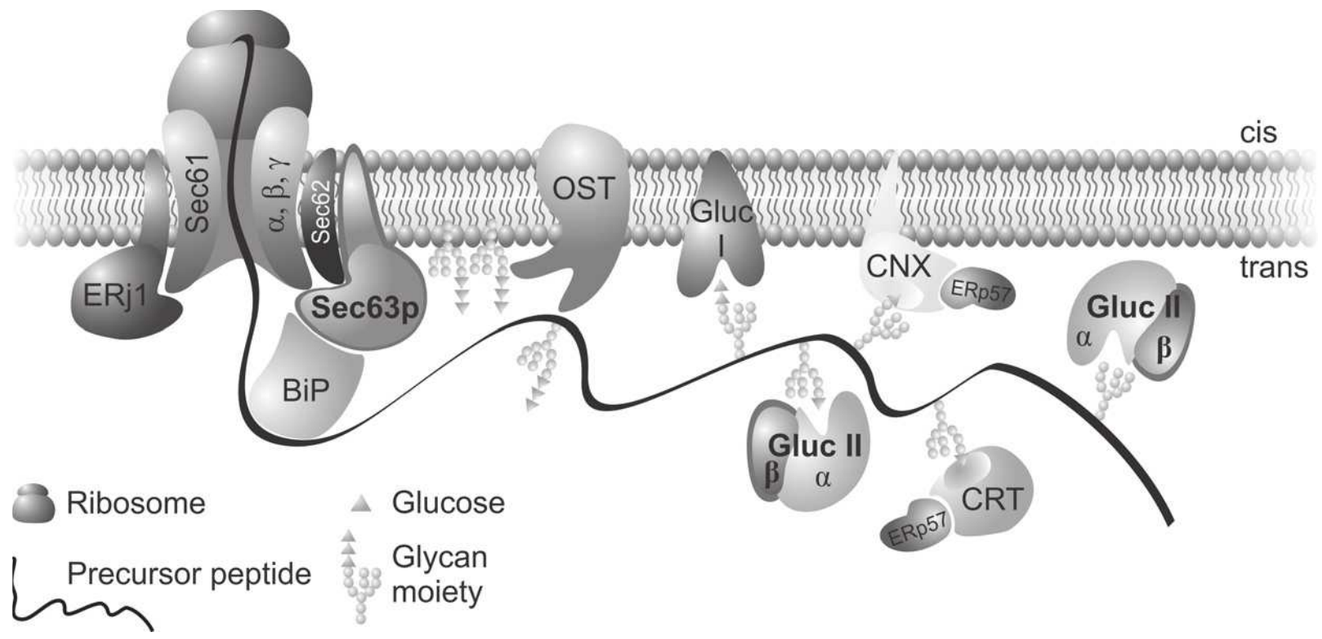


FIGURE 16.3 The functional pathway for isolated polycystic liver disease genes, *SEC63* and *PRKCSH*. The respective products Sec63p and glucosidase IIβ (Gluc IIβ) are resident endoplasmic reticulum (ER) proteins that function in the biogenetic pathway for integral membrane and secreted proteins. The ribosome and precursor polypeptide docks with its receptor comprised of the Sec61α,β,γ/Sec62 complex on the cytoplasmic (*cis*) aspect of the ER membrane. The ER luminal Hsp70-type chaperone protein BiP, acting in concert with the Hsp40 type cochaperones, Sec63p and ERj1, facilitates the cotranslational translocation of nascent peptides with cleavable or noncleavable NH_2-terminal signal peptides. The J domain of Sec63p recruits BiP to the translocation pore complex and activates it by converting its low substrate affinity ATP-bound form to its high affinity ADP-bound form. BiP binds the nascent peptide and acts as a molecular ratchet, facilitating translocation. Oligosaccharyl transferase (OST) catalyzes the attachment of the core glycan moiety to asparagine residues (*N*-glycosylation). Gluc I removes the terminal glucose from the glycan and Gluc II, comprised of α and β subunits, removes the second glucose. This allows the nascent peptide to complex with the chaperone proteins calnexin (CNX) and calreticulin (CRT), both of which associate with thiol-disulfide oxidoreductase ERp57 and promote proper folding and quality control of the precursor polypeptides. Gluc II removes the third glucose from the *N*-linked glycan once the peptide is properly folded. Proteins failing to fold properly are targeted for ER-associated degradation (ERAD) by retro-translocation through the translocon complex followed by proteasomal degradation in the cytoplasmic compartment (not shown).

(FPC).[136,137,208] FPC undergoes "notchlike" proteolytic processing that leads to the shedding of the extracellular domain and the release of the intracellular COOH-terminal fragment through regulated intramembranous proteolysis.[209] FPC, like PC-1 and PC-2, has been found in urine and bile in exosomelike vesicles (ELV),[169] with a recent study suggesting that the majority of mature FPCs are targeted to ELVs.[210] ELV components may have a role in noncell autonomous signaling along the nephron.

MOLECULAR GENETICS OF AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

The discovery of the genes for ADPKD, ADPLD, and ARPKD has enabled an emerging understanding of the increasingly complex molecular bases for cyst formation. Elucidation of these mechanisms is essential for the future development and validation of therapies for ADPKD. The discovery of the genes for ADPKD demonstrated that the preponderance of human disease mutations in both PKD1 and PKD2 were heterozygous loss-of-function variants. This made it unlikely that ADPKD occurred by a true dominant or gain-of-function mechanism, leaving the paradox of an apparent disconnect between germline heterozygous mutations that affect all cells in the body and the focal nature of cyst formation affecting discrete points in a small subset of nephrons. Studies using human material and mouse models of ADPKD and related diseases have implicated a complex interplay between multiplicity of factors, all related to germline mutations in PKD1 or PKD2, giving rise to cyst formation. Over the past decade, advances in the field have defined the occurrence and timing of somatic second hit mutations, the dosage of PKD genes, and most specifically, of PKD1. The effects of noncell autonomous factors including kidney injury, inflammation, and as yet undefined local signals all play a central role in determining the severity and progression of polycystic kidney disease.

The "Two-Hit" Mechanism

A preponderance of evidence supports the notion that homozygous inactivation of either PKD gene during kidney development or adult life is sufficient to result in cysts. Such a cellular recessive mechanism proposes that the critical cyst-initiating event in an affected heterozygous individual occurs when a somatic mutation inactivates the remaining normal copy a PKD gene in an epithelial cell(s) along the nephron. Such a cell undergoes a change in phenotype manifest through increased proliferation coupled with other processes such as a change to a secretory phenotype that, over time, give rise to the focally derived cysts that predominate in ADPKD (Fig. 16.4A). Direct experimental evidence of such a mechanism was first described using human polycystic kidneys from which cells lining individual cysts were

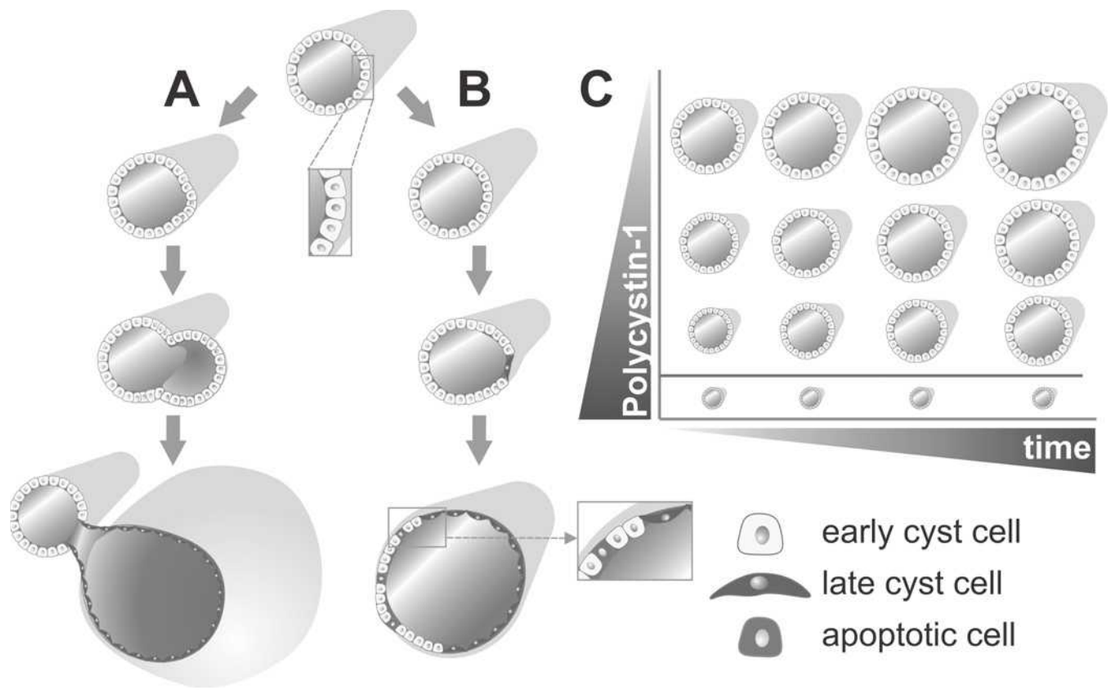


FIGURE 16.4 Mechanisms of cyst formation. **A**. Individual tubular cells undergo a somatic second hit mutation of the normal allele (early cyst cell) and these cells proliferate, forming a focal out-pouching from the tubule that progressively enlarges and eventually loses its connection with the tubule of origin. **B**. Additionally, as the early cyst cell mass expands following the second hit, non–cell autonomous processes can contribute to apoptosis in surrounding cells and to expansion of the tubule to form mosaic cysts comprised of normal tubule cells as well as early and late cyst cells. **C**. Cyst formation can occur as a function of reduced polycystin (PC)-1 dosage and time. When there is sufficient PC-1 (below the *line*), tubules maintain normal structure. Once PC-1 levels fall below the critical threshold (above the *line*), progressive cyst formation ensues. The *vertical axis* illustrates the concept that the lower the dose of residual PC-1, the more quickly cyst growth occurs. The *horizontal axis* illustrates that at each level of reduced PC-1 dosage, cyst growth is progressive over time.

isolated and examined for a loss of heterozygosity (LOH) as a marker for the loss of the normal PKD1 allele.[211] Several subsequent studies confirmed the occurrence of LOH in a subset of cysts in both the kidney and liver due to mutations in either PKD1 or PKD2.[212–214] Together, these studies demonstrate an association between LOH and cysts and support the hypothesis that individual cysts represented clonal expansions of cells that had undergone somatic second hits.

Dynamic evidence of the two-hit mechanism of cyst formation was initially provided by a mouse model of Pkd2 in which the gene-targeting event resulted in a serendipitous allele, $Pkd2^{WS25}$, which undergoes spontaneous inter- or intragenic recombination resulting in conversion to a null allele or reversion to the wild-type allele.[215] This model spontaneously develops cysts over time that result from stochastic gene inactivation events that most closely models the human disease. Subsequently, the principle that second hit mutations are sufficient for cyst formation has been demonstrated in a multitude of knockout mouse models in which conditional alleles produced by flanking loxP sites in the mouse orthologs of Pkd1 or Pkd2 are inactivated by transgenically expressed Cre recombinase enzyme.[211,216–223] The expression of the Cre recombinase can be controlled spatially by tissue and nephron segment–specific promoters and temporally by using inducible forms of the Cre recombinase. The past decade has seen extensive use of these animal models to define additional mechanisms of cyst formation and to evaluate candidate target pathways in preclinical evaluations of therapy.[224–226]

Studies comparing the number and rate of growth of cysts in human PKD1 and PKD2 show that the relatively slower progression of disease in PKD2 patients is associated with a reduced number of cysts, but not with differences in the rate of growth of PKD1 and PKD2 cysts.[227] PKD2 patients also have the same spectrum of extrarenal manifestations as PKD1 patients. These data are most consistent with the interpretation that the rate of somatic second step mutations is lower for the much smaller protein coding region in the PKD2 gene, resulting in a reduced rate of cyst initiation and, therefore, a smaller number of cysts. Biologically, once either PKD gene is lost, they appear to be functionally equivalent as indicated by similar rates of PKD1 and PKD2 cyst growth in humans, similar cystic phenotypes in knockout mouse kidneys,[217,228] and the interchangeability of a mating defect observed in male Caenorhabditis elegans nematodes with inactivation of either gene's ortholog.[229]

Conditional and inducible gene inactivation models in the mouse have also played a critical role in defining the importance of cilia to the pathogenesis of PKD. The intraflagellar transport proteins and their associated motor proteins are necessary for the formation and maintenance of intact primary cilia in renal tubular epithelial cells. Inactivation of these genes in the mouse kidney results in cyst formation that is reminiscent of the cysts formed following the inactivation of Pkd1 and Pkd2.[230–232] These and related findings have solidified the link between the primary cilium in the pathogenesis of PKD (see the following). In addition, kidney-specific inactivation in mice has defined an in vivo system by which candidate genes whose function is thought to be central to maintaining normal tubular structure can be evaluated to determine whether or not they are associated with cyst formation. Because work with mouse models is both time

consuming and costly, the discovery that the inactivation of cilia and PKD-related genes in the vertebrate genetic model organism zebrafish can model cystic diseases[233] has permitted more rapid discovery and validation of important genetic components in the cyst formation process.

The Timing of Gene Inactivation

Taking advantage of the ability to temporally control activity of the Cre recombinase, and therefore of the timing of the inactivation of the mouse orthologs of Pkd1 or Pkd2, investigators set out to determine the differential effects of inactivation of the respective genes during and after kidney development. Inactivation of Pkd1 during kidney growth and development resulted in explosive cyst growth,[220,223] whereas inactivation in the postdevelopmental adult kidney resulted in a much slower, indolent progression of cystic disease.[220] These differences based on timing of gene inactivation were also seen with inactivation of Ift88,[231] an intraflagellar transport protein, and Kif3a,[234] a component of the heterotrimeric kinesin II motor protein complex required for integrity of cilia. These findings have raised questions regarding the timing of second step mutations in human ADPKD. Computational models based on the measured rate of cyst growth observed by volumetric MRI in human subjects suggest a disconnect between cyst size and the simple two-hit model beginning with single cells that can be reconciled if the bulk of the second hits take place in utero and are associated with extraordinary prenatal cyst growth.[235] An alternative explanation may be that cyst formation entails additional factors beyond the simple two-hit model beginning with a single cell.

The Role of Noncell Autonomous Factors in Cyst Progression

Studies in both heterozygous and knockout animal models of PKD orthologous genes or genes related to cilia structures have shown that acute injury promotes accelerated cyst growth in mice. Injury models using ischemia reperfusion,[234,236–238] nephrotoxins,[239] and compensatory hypertrophy following unilateral nephrectomy[240] resulted in marked acceleration of cyst progression in Pkd1 and Pkd2 heterozygotes, and Pkd1, Kif3a, or Ift88 adult knockout models. These findings have led to the proposal that environmental "third hits" are an essential part of disease progression in human ADPKD.[241] This effect is presumably related to the induction of a proliferative response following kidney injury because cells with reduced or absent polycystin expression or cells lacking cilia have a greater proliferative potential. It is likely that instances of acute kidney injury or perhaps subclinical injury in patients with ADPKD have deleterious effects on the progression of polycystic disease. Nonetheless, it should be kept in mind that cyst formation occurs, albeit at a slower pace, following adult second hit mutations without the requirement for third hits.[220,242,243] Therefore, the clinical significance of the contributions from kidney injury to cyst progression in the majority of ADPKD patients remains uncertain.

An intriguing study using chimeric mice produced by aggregation of $Pkd1^{-/-}$ pluripotent embryonic stem cells and wild-type morulae showed that cysts can be mosaic (i.e., comprised of both $Pkd1^{-/-}$ and $Pkd1^{+/+}$ cells).[244] The wild-type $Pkd1^{+/+}$ morulae were derived from mice that express lacZ ubiquitously so that cells from the wild-type lineage could be stained blue by adding substrate for β-galactosidase. The $Pkd1^{-/-}$ cells did not express lacZ and so could be distinguished from cells of wild-type origin throughout the life of the animals. The degree of cyst formation correlated with the extent of chimerism in this model; the greater the contribution from $Pkd1^{-/-}$ cells, the greater the cyst burden. Individual cysts were mosaic, comprised of both wild-type cells that could be stained blue and that retained their cuboidal epithelial shape as well as $Pkd1^{-/-}$ cells that did not stain blue and that had a squamoid shape typical of Pkd1 knockout cyst cells. Over time, the $Pkd1^{-/-}$ cells induced apoptosis in surrounding wild-type cells by a c-Jun N-terminal kinase (JNK)–dependent pathway.[244] This constellation of findings raises the possibility that noncell autonomous processes are active in cyst formation and that cystic disease progression and tissue remodeling in ADPKD involves proliferative expansion of the $Pkd1^{-/-}$ cells' mass coupled with either inclusion or programmed cell death of surrounding wild-type cells (Fig. 16.4B).

Inflammatory and fibrotic processes have long been identified in human ADPKD tissues. In most cases, this has involved late stage cystic kidneys that have undergone a lifetime of cyst infection and hemorrhage as well as systemic damage from hypertension and other factors. Proinflammatory cytokines such as IL-1β, TNF-α, and IL-2 have been identified in cyst fluid samples from human kidneys.[56] Monocyte chemoattractant protein-1 (MCP1) has been found in the urine of ADPKD patients.[245] Expression of MCP1 and macrophage infiltration was found in the nonorthologous Han:SPRD polycystic rat model,[246] and a transcriptome analysis revealed a strong innate immune response signature in another nonorthologous model, the cpk mouse.[247] Most recently, studies using early onset orthologous gene models based on Pkd1 and Pkd2 showed infiltration by an abnormally large number of alternatively activated macrophages in cystic mouse kidneys.[248] Therapeutic depletion of these macrophages resulted in decreased cyst formation, decreased proliferation of cyst cells, and improved preservation of renal function, suggesting that macrophage infiltration and differentiation may be another factor promoting progression of polycystic kidney disease.

Gene Dosage Effects

There is growing evidence to support the role of threshold dosage variation in both the initiation of cysts and the progression of PKD. The absence of pervasive cyst formation along the entire nephron in human ADPKD and in

heterozygous animal models indicates that a 50% reduction of PKD1 or PKD2 gene dosage resulting from the heterozygous germline state in ADPKD is not sufficient for clinical cyst growth. An analysis of individual human cysts identified some with transheterozygous mutations (i.e., mutations affecting one copy of PKD1 and one copy of PKD2 in the same cyst).[249] Subsequent studies in a unique family with a bilineal inheritance of PKD1 and PKD2[250] as well as transheterozygous mouse lines[218] showed that compound transheterozygous mutations in PKD1 in PKD2 are also not sufficient for cyst initiation. The two individuals in the family with bilineal inheritance who had mutations in both genes manifested severe but not explosive PKD with the onset of ESRD in their late 40s.[250] Transheterozygous mice developed more severe cystic disease than would be expected from a simple additive effect of second hits on both Pkd1 and Pkd2, but nonetheless showed that the transheterozygous state is not sufficient for cyst formation.[218] The extra additive effect on cyst formation in the transheterozygous mice suggested a possible threshold effect whereby second hit mutations producing hypomorphic alleles that normally would result in very slow or absent cyst formation can result in more active proliferation when there is haploinsufficiency of both PKD genes.[218]

More severe reductions in gene dosage, particularly of PKD1, have subsequently been associated with graded increases in the severity of cystic response, with a complete loss of polycystins leading to the most severe disease. The importance of dosage is apparent from animal models with mutant Pkd1 alleles that express reduced rather than absent functional PC-1. Mice homozygous for two such hypomorphic alleles develop polycystic kidneys.[251,252] Another example of cyst formation resulting from a reduced dosage of polycystin is seen following inactivation of the RNA-binding protein bicaudal C.[253] Bicaudal C normally antagonizes the inhibitory effect of the microRNA miR–17 on expression of PC-2, and the markedly reduced expression of PC-2 in the absence of bicaudal C is thought underlie cyst formation in this model.

The most compelling experimental data for the centrality of gene dosage come from a study that combined orthologous gene models of isolated ADPLD (Prkcsh, Sec63) with models of ADPKD (Pkd1, Pkd2) and ARPKD (Pkhd1) showing that PC-1 dosage is the central determinant of kidney cyst progression in all of these diseases.[254] The study showed that conditional inactivation of either Prkcsh or Sec63 in the kidney resulted in PKD. This finding extended the phenotypic interrelationship between ADPLD and ADPKD to include the kidney and showed that ADPLD likely occurs via a cellular recessive second hit mechanism similar to ADPKD.[255] The study went on to show that reducing the dosage of PC-1 or PC-2 further exacerbated the kidney cysts in the ADPLD knockout mice. Conversely, increasing the expression of PC-1 (but not PC-2) by transgenic expression ameliorated the kidney cystic disease. The ADPLD genes affected cyst formation by significantly reducing the steady-state levels of PC-1 due to defective biogenesis (Fig. 16.3). The ability to worsen and improve kidney cysts following ADPLD gene inactivation by either reducing or increasing the PC-1 dosage, respectively, indicates that PC-1 is the rate limiting component in this process. The rescue of the ADPLD cysts by overexpression of PC-1 was durable but not permanent, indicating that the time required for cyst formation is inversely related to the degree of reduction of PC-1 dosage. Taken together, these findings indicate that a combination of PC-1 dosage and time are key determinants of cystic progression (Fig. 16.4C). Furthermore, reduced PC-1 dosage resulted in worsened cyst formation following homozygous inactivation of the ARPKD gene, Pkhd1, suggesting that at least in mouse models the expressivity of the ARPKD phenotype in the kidney is modulated by functional PC-1 dosage.[254,256] In aggregate, this study defines dosage- and time-dependent interrelationships between ADPKD, ARPKD, and ADPLD in orthologous mouse models and establishes PC-1 activity as the central determinant of the phenotypes in all three disease models.

Genotype–Phenotype Correlations and Genetic Modifiers

Genotype–phenotype correlations are variations in disease progression (the phenotype) based on different mutations (the genotype) in the primary gene underlying a human Mendelian disease. The major genetic determinant of severity in ADPKD is the underlying disease gene locus effect—PKD1 mutations result in ADPKD with mean age of ESRD almost 2 decades earlier than PKD2.[10,227] In clinical studies, 85% of ADPKD families have PKD1 mutations and only 15% have PKD2 mutations. The milder phenotype has likely caused underascertainment of PKD2 families in these studies, and population-based ascertainment suggests that 29% of ADPKD families have PKD2.[13] In the group of individuals entering ESRD after age 65, 50% are PKD2 families.[257] Within the PKD1 population, a small subset of patients with mutations resulting in a contiguous gene deletion syndrome affecting the tuberous sclerosis complex 2 gene, TSC2, have severe PKD, often presenting in early childhood.[258,259]

Human ADPKD families with recessive inheritance of nonsynonymous amino acid substitution mutations in PKD1 have recently been described[260] and have been found to mimic ARPKD.[261] Although fetuses homozygous for complete loss-of-function PKD gene alleles are presumed to be nonviable, these recessively inherited hypomorphic PKD1 alleles have reduced function, allowing for live-born progeny. They develop early onset cystic disease with cysts that are homogeneous in size and distribution. This is in contrast to the usual heterogeneous and focal cyst population seen in typical ADPKD and are more reminiscent of ARPKD. Similar findings have been described in an individual homozygous for a PKD2 missense mutation due to uniparental disomy (two copies of part of a chromosome from one parent and none from the other).[262] A weak modifier effect resulting in

greater severity of ADPKD from PKD1 mutations in the 5′ end of the gene compared to the 3′ end has been reported.[263] Recently, a dominantly inherited heterozygous missense variant in PKD1 was identified in a family segregating a mild form of ADPKD that was clinically similar to PKD2-based disease.[264] This finding suggests that hypomorphic alleles in the heterozygous state in PKD1 can also result in disease that is clinically milder.

Genetic variations at loci other than the primary disease gene can modify disease severity. Because all affected individuals in a given family have the same germline mutation in either PKD1 or PKD2, the high degree of intrafamilial variability observed in the severity of ADPKD has been taken to suggest that genetic modifiers and environmental factors influence the progression of ADPKD. This conclusion should be tempered in light of the fact that the timing and extent of somatic second hit mutations will also contribute to intrafamilial variability. Although no strong genomewide genetic modifier effects have been identified in ADPKD, several lines of evidence support the hypothesis that such modifiers exist and should be discoverable. The observation that a variation in age at ESRD among siblings is significantly greater than the variation in genetically identical twin pairs is likely attributable to the existence of genetic modifier effects.[265] Similarly, the occurrence of severe neonatal PKD in the progeny of parents with very mild ADPKD due to PKD2 mutations suggests that genetic modifiers at non-PKD gene loci may impact disease progression.[266] Two studies[267,268] used variance component analysis to determine heritability in ADPKD (i.e., the proportion of phenotypic variance explained by modifier genes). They found that between 32% and 42% of the variance in creatinine clearance and 43% to 78% of the variance in age at ESRD were heritable.

The existence of genetic modifiers has been directly demonstrated in selected cases of ADPKD. A report identified severely affected ADPKD patients in whom heterozygous mutations in PKD1 were accompanied by heterozygous mutations in the transcription factor hepatocyte nuclear factor-1β (HNF-1β).[269] Recessively inherited mutations in HNF-1β result in glomerulocystic disease in maturity onset diabetes of the young type 5 (MODY5) and HNF-1β regulates transcription of several PKD genes, including PKD1.[270–272] This suggests that the severity of ADPKD may be modified by mutations that indirectly affect expression of PKD genes. A directed genetic association study analyzing 173 biologic candidate genes in 794 ADPKD patients from 227 families identified Dickkopf 3 (DKK3) as a possible genetic modifier for disease severity in ADPKD.[273] DKK3 antagonizes Wnt/β-catenin signaling, a pathway that has been implicated in cyst growth (see the following).

CILIA AND CYSTIC KIDNEY DISEASE

Following the discovery of the genes responsible for ADPKD, the next major quantum of advancement in the field arose from the understanding that the structure and function of the primary cilium is central to the pathogenesis of polycystic diseases.[274,275] All cells in the kidney tubule with the possible exception of intercalated cells have a single primary cilium extending from the apical surface into the tubule lumen. Primary cilia differ from motile cilia in that they have nine pairs of radially arrayed microtubule bundles but lack the central pair, hence they are called 9+0 cilia (Fig. 16.5). Cilia comprise a unique cellular compartment that is devoid of intracellular components such as membrane-bound vesicles and ribosomes.[276] As a consequence, all the protein components of cilia must be synthesized in the cell body

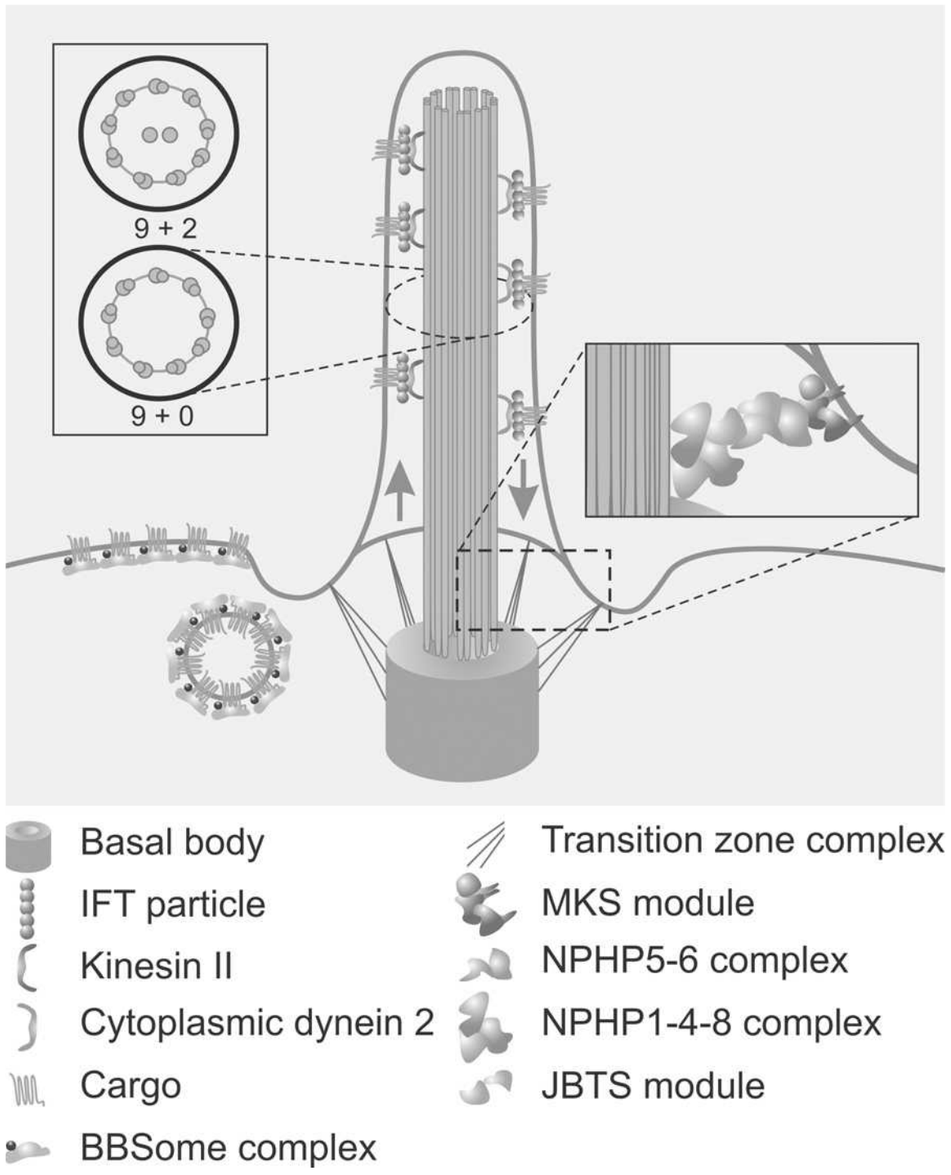


FIGURE 16.5 Cilia structure and function. Primary cilia are structured on nine pairs of radially arrayed microtubules without the central pair found in motile cilia. The ciliary axoneme emanates from the basal body, and the cilia compartment is separated from the body of the cell by the transition zone complex. The delivery of integral membrane proteins likely occurs by targeted exocytosis near the base of the cilia. The sorting of specific proteins destined for cilia may be mediated by the BBSome coat complex, which contains several of the gene products associated with Bardet-Biedl syndrome (BBS). The protein-sorting process is regulated by the transition zone complex, which has associated with it the protein products of the ciliopathy genes. The membrane proximal component of this complex is primarily composed of Meckel Gruber syndrome (MKS) proteins. Two nephronophthisis (NPHP) complexes, respectively based on NPHP5/6 and NPHP1/4/8 and in association with Joubert syndrome (JBTS) gene products, have also been identified. Within the cilium, cargo proteins are transported on IFT particles with kinesin II motor proteins responsible for anterograde transport away from the cell body and cytoplasmic dynein motor proteins responsible for retrograde transport back toward the cell body. (See Color Plate.)

and transported to cilia; similarly, the turnover of cilia components requires retrograde transport to the cell body. These transport processes are collectively referred to as intraflagellar transport (IFT). IFT particles are protein complexes necessary for bidirectional transport of cilia components that are moved along the microtubular ciliary axoneme by molecular motors.[276,277] The cilium is nucleated on the apical surface of epithelial cells by the basal body complex comprised of the centrioles in nondividing cells. The base of the cilium has a transition zone that serves as a sorting complex to regulate the trafficking of proteins into and out of the cilia.[278–280] Primary cilia subsume a broad array of sensory functions in different tissues and cell types.[281,282] As sensory organelles, cilia make use of their specialized structural features and the restricted access of cellular components to uniquely integrate signals from the cell's surroundings.

Several convergent lines of evidence support the connection between cilia function and the group of renal cystic disorders that include ADPKD and ARPKD as well as for a broader group of recessively inherited "ciliopathy diseases" such as NPHP, BBS, Joubert syndrome (JBTS), and MKS (Table 16.1). The early evidence for a connection between cilia and PDK came indirectly from findings in model organisms. The first gene identified for a recessive polycystic kidney phenotype in the mouse, Tg737,[283,284] was subsequently shown to be Ift88, an IFT complex B component.[285] Independently, the C. elegans homolog of PKD1, called lov–1, was found expressed in sensory neuronal cilia in male nematodes.[286] More direct evidence for the central role of cilia in ADPKD was obtained when PC-2 and PC-1 were localized to cilia in cells and tissues.[189,190] These findings led to a prospective study showing that kidney-selective inactivation of Kif3a, a component of the heterotrimeric kinesin-2 motor complex, resulted in the loss of cilia along the nephron, which recapitulated a polycystic kidney phenotype.[230] An unbiased phenotype-driven forward genetic screen for recessive loss-of-function alleles resulting in pronephric cysts in zebrafish identified 10 genes promoting cyst formation.[233] These included Pkd2 and Hnf-1β, IFT-related genes, and novel cilia-related genes, thus solidifying the connection between cilia structure and function and kidney cyst formation in vertebrates. Finally, human gene cloning for an extensive series of diseases that shared fibrocystic kidney phenotypes (e.g., NPHP, JBTS, MKS, and BBS) found that the respective protein products of these disease genes were mostly expressed in the cilia-basal body complex (Table 16.1).[275,287]

Polycystins have been localized to cellular compartments other than cilia.[288] Although it is widely believed that the function of polycystins in cilia is central to the pathogenesis of ADPKD, the contributions of polycystins expressed in other subcellular locations is uncertain. PC-1 has been localized to the basolateral membrane,[289] at sites of cell matrix adhesion[290] and intercellular adhesion,[291] and at desmosomes.[292] There is universal agreement that PC-2 shows its most abundant expression in the ER in cells[177] and in kidney tissues.[179] The localization of PC-2 to the generalized plasma membrane outside of cilia has been controversial.[177,185] The surface expression of PC-2 has been proposed as requiring coassembly with PC-1,[180] although PC-2 is able to traffic to cilia independently of PC-1.[184] The expression of PC-1 has shown developmental regulation with higher levels early in development and a reduced level of expression in adult tissues.[293,294] Similar changes in the expression of PC-2 with developmental stage have not been reported.

Ciliopathies

The recessive ciliopathy disorders (e.g., NPHP, JBTS, MKS, and BBS) have both clinical and genetic overlap amongst each other. The clinical overlap involves the range of tissues in which cilia function plays a central role.[275,282,295] For example, the outer segment of the retina represents a modified cilium, and retinal degeneration is seen in the Senior Loken variant of NPHP, as well as in JBTS, MKS, and BBS.[296] Cilia are also essential to Hedgehog signaling, which is important for patterning of the digits, and MKS, BBS, and another ciliopathy, such as orofacial digital syndrome, show digital defects.[282] Other manifestations associated with recessive cilia mutations include left–right asymmetry defects and associated cardiac heterotaxy syndromes,[297–299] central nervous system (CNS) malformations with developmental delay,[296] obesity,[231] anosmia,[300] and skeletal defects.[301] Genetic overlap among the ciliopathies occurs because mutations in the same gene can give rise to different diseases along this phenotypic spectrum (e.g., mutations in MKS3 can cause both MKS and JBTS; mutations in CEP290 can cause NPHP, JBTS, MKS, and BBS; and mutations in TMEM216 cause MKS and JBTS).[302,303]

The ciliopathy disease gene products have been segregated into distinct functional complexes within cilia (Fig. 16.5). Several of the BBS gene products comprise the functional BBSome that is central to the selective delivery of integral membrane proteins into cilia.[304–306] The gene products associated with NPHP, JBTS, and MKS comprise part of the transition zone gatekeeper complex at the base of cilia.[276,278,307] Within this transition zone complex, there are at least three functional subcomplexes.[307] NPHP gene products are active in apical organization and centriole/cilia integrity, MKS gene products are associated with Hh signaling,[307] and JBTS-MKS complex proteins regulate ciliary membrane composition.[278] Although functionally interrelated, the IFT, BBSome, and NPHP-JBTS-MKS complexes do not appear to interact physically, and only components of the latter two are associated with human diseases. It is possible that the absence of human disease resulting from recessive IFT mutants is due to lethality.

Relationship of Polycystic Diseases to Ciliopathies

Although it is tempting to categorize ADPKD as part of the ciliopathy spectrum of disorders, there are some important distinctions that support keeping ADPKD and diseases with close functional relation to it (ADPLD and ARPKD) in a conceptually and biologically distinct compartment. From a genetic

standpoint, the ciliopathies are all recessively inherited. It is likely that somatic second hits are affecting the normal copies of the ciliopathy genes in heterozygous carrier parents, yet these individuals do not develop clinical cystic phenotypes. This is in stark contrast to ADPLD, in which heterozygous patients still form liver cysts following second hit mutations in genes whose products only indirectly affect PC-1 and PC-2 activity.[254,255] The genetic evidence suggests that ciliopathy genes really have limited or absent functional interaction with the polycystins. These findings are also consistent with the view that the ciliopathy disorders are primarily developmental diseases with less of a role in structural homeostasis of the adult kidney than the ADPKD gene products. From a biochemical standpoint, PC-1, PC-2, and FPC are all integral membrane proteins and are notably absent from any of the complexes described for the other ciliopathy genes. Conceptually, the ciliopathy gene products function in establishing and maintaining the structural integrity and the unique molecular composition of cilia. PC-1 and PC-2 (and FPC) are part of that unique composition and form a receptor-channel signaling complex that subsumes a specific sensory signaling function within the primary cilium. The genetic and functional dichotomy between ciliopathies and polycystic diseases should raise a cautionary note in extrapolating molecular pathways defined in terms of defects in the cilia structure and function based on IFT, the transitional zone, and the BBSome mutations to disease pathogenesis in ADPKD, ADPLD, and ARPKD.

PATHOGENESIS: CELLULAR PATHWAYS AFFECTED BY THE POLYCYSTINS

Cellular Sensory Reception

The polycystins are integral membrane proteins expressed on a sensory organelle, the primary cilium. PC-1 has a structure suggestive of receptor function, and PC-2 is a member of the TRP nonselective cation on the channel family that largely serves as receptor-gated sensory signaling channels.[308] These features have been taken to indicate that PC-1 and PC-2 function as a sensory receptor-channel signaling complex, but the specific nature of the signal that the polycystins "sense" has remained elusive. The predominant hypothesis is that the polycystins comprise a mechanosensory complex within the cilia that detect luminal fluid flow or shear stress. The data to support this role come from laminar shear stress experiments performed on ciliated monolayers of cells in culture, which showed a global cytosolic calcium response that was dependent on the bending of intact cilia[309,310] and the presence of active PC-1 and PC-2.[311] Indirect in vivo evidence supporting this function came from a study examining defects in lateralized, flow-dependent calcium signaling in the embryonic node in mice.[299] The formation of the vertebrate left–right body axis requires leftward vectorial fluid flow generated by motile cilia in a transitory embryonic structure referred to as the embryonic node. Pkd2 knockout animals, which have a randomization of the left–right axis,[297] show a failure to initiate normal calcium transients along the left side of the node presumably due to the failure to sense the flow signal.[299] This flow sensor hypothesis suggests that renal tubular luminal flow per se is required for the normal homeostatic structural maintenance of the kidney, something that has not yet been directly demonstrated.

The alternative hypothesis that unknown ligands are involved in polycystin signaling remains plausible because the effects of flow or shear stress may be difficult to separate from the effects of signaling ligands that are delivered by flow. Recent evidence has shown that polycystins and FPCs are shed into the luminal space, and the ELVs in which they appear adhere to the surface of cilia.[169,210] These ELVs may be the vehicles carrying signals important in PKD. Earlier biochemical evidence supports homotypic interactions involving the extracellular domains of PC-1,[312] further posing the possible involvement of ligand binding in polycystin signaling. In the instance of flow-dependent embryonic node signaling in left–right asymmetry, shed vesicles carrying signaling molecules such as Sonic Hedgehog and retinoic acid have been shown to be essential in generating lateralized calcium signals, mentioned previously.[313] The PC-2–dependent cellular calcium response to flow stimulus was subsequently shown to require a heteromeric complex between PC-2 and transient receptor potential cation channel subfamily V member 4 (TRPV4).[314] Loss of TRPV4 abolishes the cellular calcium in response to flow in vitro yet does not result in cyst formation in the zebrafish model in vivo. This puts into question whether calcium transients resulting from ciliary flow sensing in vitro are a fundamental mechanism of cyst formation in vivo.[314] It is noteworthy that, to date, it has not been possible to document changes in local calcium within cilia in response to flow. A recent study linking the cilia-mediated flow response to regulation of the mammalian target of rapamycin (mTOR) signaling and cell size regulation showed that this was a function of the master kinase Lkb1 in cilia and specifically excluded PC-2 as the cilia sensor.[315] Finally, evidence that polycystin complex signaling is dynamically regulated by PC-1 dosage and not a binary on/off process[254] can be extrapolated to suggest that the signal sensed by PC-1 is also dynamically regulated. This should give pause to the notion that flow alone serves as the primary signal for determining kidney tubule lumen diameter. The increasing application of proteomic technologies to the analysis of signaling molecules in the urine may uncover novel signaling molecules and lead to improved understanding of the interrelationship between flow, ligands, and polycystin signaling.

Effector Pathways

A multitude of effector pathways have been proposed for the renal tubule cell response to a loss of polycystins.[58,316,317] Nonetheless, the molecular mechanism linking PC-1/PC-2 function in cilia to the extensive array of candidate cellular effector pathways has been elusive beyond a hypothesized role for calcium ions (Fig. 16.6).[58] The potential complexity of what is unknown in cilia-based signaling downstream of polycystins is best illustrated by what is known of Hedgehog

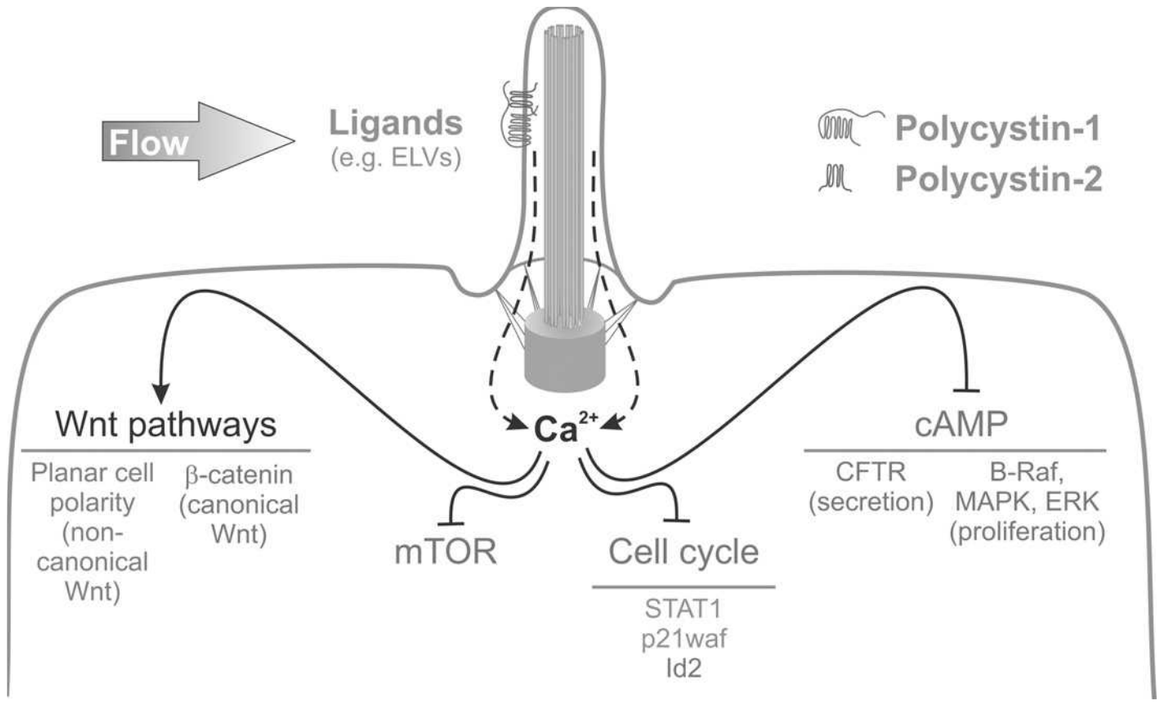


FIGURE 16.6 Polycystin (PC) signaling effector pathways. The PC-1/PC-2 receptor channel sensory complex on apical cilia on the renal tubular epithelium is activated by flow and potential ligands carried by the flow (exosome-like vesicles [ELVs]). This is thought to result in a rise in local and cellular calcium, which mediates signals to a number of effector pathways. Pathways or components shown in *blue* are activated by normal polycystin signaling, whereas those shown in *red* are inhibited by intact polycystin signals. A loss of PCs results in increased cyclic adenosine monophosphate (cAMP) production, which may increase apical secretion and the proliferation in cyst cells. The loss of PCs also increases the progression of the cell cycle, and may activate mammalian target of rapamycin (mTOR) signaling and may favor β-catenin-dependent Wnt signaling. STAT1, signal transducers and activators of transcription 1; CFTR, cystic fibrosis transmembrane conductance regulator; MAPK/ERK, mitogen-activated protein kinase/extracellular regulated kinase. (See Color Plate.)

(Hh) signaling in cilia.[281] In the absence of Hh ligand, the receptor Patched (Ptch) resides in cilia and inhibits the entry of the seven transmembrane receptor protein Smoothened (Smo) into cilia. In this state, the transcriptional repressor Gli3R inhibits Hh-responsive gene transcription, whereas the transcriptional activator Gli2 is sequestered in cilia by binding of Suppressor of Fused (SuFu). Upon binding of the Hh ligand, Ptch translocates out of cilia, thereby allowing Smo to enter the cilium. This in turn alleviates Gli3R repressor activity and promotes translocation of transcription activators Gli1 and Gli2 to the nucleus. All of the aforementioned components of the Hh signaling pathway have been found in cilia.[318,319] The lack of a comparable mechanistic understanding of polycystin signaling leaves open the possibility that many of the effector pathways identified to date represent secondary processes removed from the immediate molecular events of polycystin signaling. These secondary processes may contribute substantially to disease progression and therefore merit investigation and evaluation as potential targets for clinical therapy. In parallel, continued basic studies to identify the less understood, more proximate polycystin signaling events is essential to achieve the goal of identifying novel and specific therapeutic targets for ADPKD.

Planar Cell Polarity and Wnt Signaling

Cyst formation has been attributed to defects in a tissue organization process defined by planar cell polarity (PCP). In the case of the kidney, the developing nephron grows in the direction oriented in parallel with the lumen while not growing in the dimension perpendicular to the lumen. This asymmetric orientation of growth within the plane of the tubule epithelium is reflective of PCP (Fig. 16.7). "Convergent

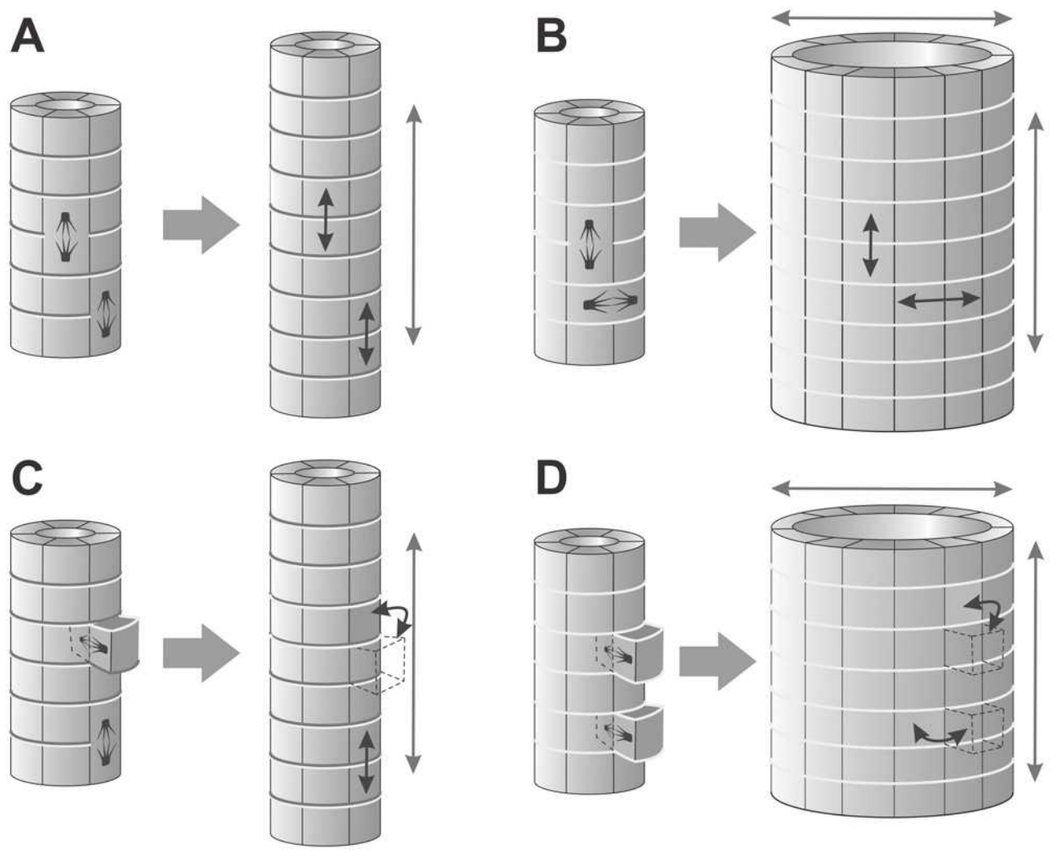


FIGURE 16.7 Planar cell polarity in the kidney. **A**: The postnatal elongating nephron shows oriented cell division (OCD) with mitotic spindle poles aligned with the long axis of the tubule within the plane of the epithelium. **B**: Randomization of the mitotic spindle axis, as may occur in recessive ciliopathies, can interfere with normal tubular elongation and give rise to dilated or cystic tubules. **C**: Planar cell polarity is also mediated by convergent extension movements whereby cells move toward a midline axis and along its length. In this schematic, a cell dividing out of the plane of the epithelium is shown entering that plane along the longitudinal axis. **D**: A loss of convergent extension movements can also result in impaired tissue polarity.

extension" movements, in which cells move toward a midline in one dimension and extend along that midline in a perpendicular direction, are one component of PCP. Another PCP component, oriented cell division (OCD), occurs when the axis of the mitotic spindle poles in anaphase and telophase align in parallel to the tubule lumen leading to cell division that is parallel to the axis of elongation and in the plane of the epithelium. Evidence linking cilia functions to PCP[320,321] has been provided by the association of Ift88 mutations with defective planar polarization of actin-based stereocilia in the inner ear[322] and by the roles in PCP processes of recessive ciliopathy genes for nephronophthisis (inversin)[323] and BBS.[324]

It has been proposed that a loss of OCD in elongating kidney tubules results in randomized orientation of mitoses, which replaces the directional tubule elongation process with cyst formation (Fig. 16.7).[325] Experimental studies have confirmed that elongating tubules in the postnatal mouse or rat kidney show OCD with mitotic spindles oriented parallel to the long axis of the tubule.[326,327] Consistent with the hypothesized pathogenic role of PCP defects in cyst formation, mice with mutations in Hnf-1β and rats with mutation in Pkhd1 show a loss of OCD in advance of the cyst formation.[326] Similarly, postnatal Ift20 mutant kidneys and injured adult Kif3a mutant kidneys, both of which have structural defects in cilia formation, also show a loss of OCD followed by cyst formation.[234,328] Finally, a loss of the PCP-related protocadherin Fat4 can result in cystic kidneys, a phenotype worsened by a reduced dosage of the core PCP protein Vangl2.[329] Although OCD is the predominant PCP mechanism in the postnatal elongating nephron in mice, convergent extension movements predominate during the embryonic phase of kidney development.[327] BBS genes (e.g., Bbs1, Bbs4, Bbs6) are required for PCP-associated convergent extension movements in zebrafish,[330] but a role for the human PKD genes (e.g., Pkhd1, Pkd1, Pkd2) in convergent extension movements has not yet been reported.

The previous data suggest that PCP-related processes are linked to cilia structure and function and are important in kidney development. The disruption of PCP processes during development can result in cyst formation. Despite this connection, the relationship of disruption of PCP to the pathogenesis of human ADPKD and ARPKD is less clear. Two mouse models of ARPKD that do not show a cystic phenotype in the collecting duct nonetheless show a loss of OCD in that segment in the postnatal kidney.[331] The same study also found that precystic tubules that had lost either PC-1 or PC-2 expression did not show a loss of OCD yet went on to form cysts.[331] The finding that mutations in Pkhd1 disrupt OCD during tubule elongation but do not lead to cysts calls into question whether a loss of OCD is sufficient for kidney cyst formation. The finding that a loss of PC-1/PC-2 can initiate cysts without the loss of OCD suggests that PCP defects are not necessary for cyst formation in ADPKD. One interpretation of these apparently discrepant results is that the mechanisms of kidney cyst formation in human ADPKD and ARPKD differ from those associated with the recessive ciliopathy diseases.

PCP is mediated by components of the noncanonical Wnt signaling pathway. Modulation of canonical Wnt signaling, which regulates cellular proliferation and differentiation, has also been associated with cystic diseases (Fig. 16.6).[332] Wnts are secreted glycoproteins that bind to Frizzled receptors, which signal through Dishevelled inside the cell. Downstream of Dishevelled, the canonical and noncanonical pathways diverge with β-catenin–dependent gene expression acting as the major effector of the canonical Wnt pathway. The nephronophthisis gene inversin modulates Dishevelled levels to determine the balance between canonical and noncanonical Wnt signaling.[323] Similarly, BBS genes are required for PCP-associated convergent extension movements in zebrafish, but suppression of these transcripts results in the activation of canonical Wnt signaling through stabilization of β-catenin.[330] These findings have led to the emergence of the concept that several ciliopathy genes function to regulate the balance between canonical and noncanonical Wnt signals. Implicit in such a hypothesis is the idea that cyst formation following the disruption of PCP pathways is fostered by the associated increase in canonical Wnt signaling.

The role of canonical Wnt signaling in cyst formation has been explored directly. The product of the JBTS gene Ahi1 supports canonical Wnt signaling by facilitating β-catenin accumulation and consequent transcriptional activation in the nucleus.[333] Loss of Ahi1 impairs the canonical Wnt response to kidney injury and results in cyst formation. Although cilia-related proteins may function in Wnt pathways, a direct role for cilia in Wnt signaling remains controversial given conflicting evidence that cilia inhibit canonical Wnt signaling[330,334] or have no role in it.[335,336] The data on the role of Wnt/β-catenin signaling in cyst formation in ADPKD is also confounded. Initial support for a role for canonical Wnt signaling in cyst formation came from studies showing that transgenic overexpression of a constitutively active β-catenin or kidney specific inactivation of the APC gene (which normally inhibits β-catenin signaling) results in cyst formation.[337,338] On the other hand, the study of Wnt9b-deficient mice that supported the role of noncanonical Wnt signaling/PCP in cyst formation did not find any evidence for β-catenin–dependent canonical Wnt signaling in the process.[339] The activity of COOH-terminal fragments of PC-1 in canonical Wnt signaling have been implicated in both activation[340–342] and repression[173,343] of the canonical Wnt pathway; the latter was also reported for PC-2.[344] Finally, a recent study using embryonic Pkd1 and adult Pkd2 mouse models of polycystic kidney disease in combination with a canonical Wnt activity reporter transgene failed to show evidence of β-catenin transcriptional activation in kidney cysts in vivo.[345] Although the absence of transgenic reporter activation in these mice does not entirely exclude a role for canonical Wnt signaling in cyst formation, it does pose a significant challenge to the model. In aggregate, the data suggest involvement of both canonical and noncanonical Wnt signaling in cystic processes, but this relationship is not universal and the direct relevance to human ADPKD remains uncertain.

Mitogen Activated Protein Kinase/ Extracellular Regulated Kinase

The mitogen activated protein kinase (MAPK)/extracellular regulated kinase (ERK) pathway is a kinase phosphorylation cascade that integrates extracellular signals received through receptor tyrosine kinases, G-protein-coupled receptors, and integrins. MAPK/ERK signaling is modulated by cAMP, protein kinase A (PKA), protein kinase C (PKC), and regulates a spectrum of cellular activities including cell cycle, gene transcription, protein translation, and epithelial morphogenesis (Fig. 16.6). Activation of the MAPK/ERK pathway is seen in cell culture models based on human ADPKD cyst lining cells that lack PC-1.[346,347] PC-2 has been implicated in providing tonic suppression of MAPK/ERK signaling.[348] MAPK/ERK activation occurs in vivo in mouse models based on nonorthologous[346,349,350] and orthologous ADPKD genes.[223] In human ADPKD cell culture models, the activation of the MAPK/ERK cascade is dependent on activation of B-Raf by cAMP—a paradoxical effect unique to PKD cells or in conditions of calcium deprivation.[346,347] Evidence for a similar mechanism of activation in vivo is lacking.[223] The presence of dysregulated MAPK/ERK activation associated with proliferation in both in vitro and in vivo models of ADPKD have identified this pathway as a potential target for therapy. To date, preclinical evaluations of inhibitors of this pathway have given mixed results. The MAPK/ERK blockade in a mouse model of NPHP reduced cyst formation,[350] but it had no effect in an early onset model of ADPKD.[223] It remains possible that an evaluation of additional agents targeting the ERK pathway in refined orthologous gene mouse models of ADPKD will identify agents suitable for human studies.

Mammalian Target of Rapamycin

The mTOR pathway integrates signaling input and nutrient availability to regulate a diverse set of processes including cell size, proliferation, metabolism, and survival. It has been implicated as an effector pathway in PKD (Fig. 16.6),[351,352] and mTOR inhibitors were evaluated in the first major randomized clinical trials for ADPKD (see the following). The earliest indication of a potential role for this pathway in PKD came from the observation that severe juvenile ADPKD was often the result of a contiguous gene deletion syndrome involving PKD1 and TSC2.[258,259] Mutations in TSC2 and TSC1 result in tuberous sclerosis complex. Together, their respective gene products have GTPase activity that inhibits Rheb, which is a master activator of the mTORC1 pathway. Experimental evidence for mTOR activation in PKD came from immunohistochemical studies showing phosphorylation of the mTORC1 target P70 ribosomal S6 kinase (S6K) in cells lining some, but not all, cysts; S6K phosphorylation was also observed in normal tubular epithelial cells in polycystic mouse models.[225,353,354]

Although there is evidence of activation of the mTOR pathway in PKD, as with the other putative effector pathways, the mechanisms of PC-1 or PC-2 to this mTOR activity remains incompletely understood. There has been a suggestion that the C-terminal tail of PC-1 interacts directly with TSC2 but the specificity of this putative interaction is uncertain given that no studies using the full-length PC-1 have been reported.[225] A functional interaction between PC-1 and mTORC1 has been suggested in cell-based studies where there was overexpression of PC-1–inhibited mTORC1 signaling, whereas cells lacking Pkd1 showed increased mTORC1 activation.[355] PC-1 inhibition of the mTORC1 cascade was dependent on its inhibition of ERK1/2 phosphorylation acting through TSC2. The mechanism of PC-1/mTOR interdependence remains unsettled because another study using just the COOH–terminus of PC-1 suggested that sequestration of TSC2 is the mechanism of mTOR repression,[356] whereas a third study found no evidence for constitutive activation of mTORC1 in cells lacking PC-1.[357] Throughout these studies, mTOR has been separately connected with cilia[315,357] and with polycystins,[225,355] but not with polycystins in cilia. In fact, a recent study of cilia-dependent Lkb1 regulation of mTOR actually excluded regulation by PC-2 signaling.[315] Given this uncertainty in the preclinical data and two negative clinical studies (see the following), consideration of the use of mTOR inhibitors in ADPKD requires further investigation.[358]

Cyclic Adenosine Monophosphate (cAMP)

Elevated levels of intracellular cAMP in polycystic kidneys are believed to promote cyst growth and disease progression (Fig. 16.6).[359,360] cAMP levels are regulated by the balance of adenylate cyclase (AC) synthetic activity and phosphodiesterase (PDE) degradation. AC activation occurs following ligand interaction with heterotrimeric GPCRs. A subset of ACs and PDEs are calcium responsive, resulting in the refinement of cAMP activity by local subcellular calcium levels. Increases in cAMP levels above a threshold results in the activation of PKA, which acts as an effector for cAMP signaling. Finally, the subcellular microdomain localization of cAMP signals is achieved by the scaffolding activity of A kinase anchoring proteins (AKAPs), which confine PKAs to regions in close proximity to AC and its GPCR receptor, as well as PDE.

Elevated cAMP levels have been found in animal models of ADPKD.[224,361] The mechanisms underlying the elevated cAMP levels are uncertain. Increased levels of circulating vasopressin as well as of the vasopressin type 2 GPCR (V2R) in the collecting duct in polycystic kidneys have been hypothesized to enhance cAMP production.[362] It is notable in this regard that the largest number and size cysts in ADPKD appear to be derived from collecting duct segments that express V2R.[224,363] In addition, the hypothesized reduction in cellular calcium resulting from the loss of the activity of the PC-1/PC-2 channel complex may result in increased activity of calcium inhibitable ACs and decreased activity of calcium-activated PDEs. Recent work may have shed additional light on the mechanistic relationship of polycystins and cilia to cAMP activity. Cilia contain an interacting protein complex comprised

of adenylate cyclase 5 (AC5), A kinase anchor protein 150 (AKAP150), phosphodiesterase-4C, and PC-2.[364,365] PC-2 is required for the ciliary location of AC5/6, which are calcium inhibitable, and the loss of either Pkd2 or of cilia through Kif3a mutation results in elevated cAMP perhaps due to the loss of AC5/6 inhibition.[364] Although the GPCR associated with this complex is unknown, V2R has been found in the cilia.[366] cAMP has also been implicated in determining cilia length and functioning in a negative feedback loop whereby longer cilia produce reduced responses to flow, which in turn decreases intracellular cAMP. This flow-mediated adaptive response is lost in the absence of polycystins.[367]

Several mechanisms have been proposed by which increased cellular cAMP fosters progression in ADPKD. In vitro, cAMP inhibits the proliferation of normal kidney epithelial cells but paradoxically increases the proliferation of ADPKD cyst cells. The latter occurs by a Ca^{2+}-dependent activation of the B-Raf/MAPK/ERK pathway.[347,368] cAMP-dependent activation of PKA and the consequent activation of the cystic fibrosis transmembrane regulator (CFTR) chloride channel is thought to be responsible for the chloride-dependent transepithelial fluid secretion that drives cyst enlargement.[369–371] In support of this, Pkd1 mutant kidney explants treated with cAMP analogs develop cysts, and this process can be blocked by inhibitors of CFTR.[372] CFTR inhibitors have also shown some efficacy in a mouse model based on Pkd1.[373] V2R antagonists that were effective in preclinical trials[224,361] and that are currently in human clinical trials are thought to act by reducing intracellular cAMP levels. The reduction of both cAMP production and cAMP-dependent fluid secretion remain attractive targets for therapeutic trials in ADPKD.

Calcium Signaling

The importance of calcium signaling in PKD was initially suggested by the identification of PC-2 as a nonselective calcium-permeable cation channel of the TRP family and by evidence that point mutations that abrogate PC-2 channel activity are pathogenic in human ADPKD.[135,179,180,374] This association was bolstered by the finding that the mechanical deflection of primary cilia result in cellular calcium transients[310,375] that are dependent on normal expression of PC-1 and PC-2 (Fig. 16.6).[311] The molecular mechanisms underlying these whole cell calcium changes have been challenging to define in large part because the local calcium effects in cilia have not been directly measured. In addition, the whole cell calcium results are confounded by the function of PC-2 as an ER calcium channel[188,311] and perhaps as a channel on the cell surface.[376,377] It has been difficult to define the precise disease-associated signaling processes because it is not known whether the polycystin-dependent calcium effects relevant to ADPKD are very localized (e.g., in cilia), or generalized in the whole cell.

A direct demonstration of the role of calcium in most of the putative ADPKD-effector signaling pathways has also been elusive. Some effector pathways have shown a response to fluid flow, and fluid flow has been associated with cellular calcium transients; therefore, a role for calcium has been inferred but not shown. For example, fluid flow in ciliated cells was implicated in modulating inversin levels, which in turn determine the balance between canonical and noncanonical Wnt signaling.[323] The inference that flow induced calcium transients in mediating inversin action remains speculative. The role of calcium in the regulation of cAMP levels through calcium-dependent AC and PDE as discussed in the previous section has remained inferential. The activation of MAPK/ERK attributed to changes in cAMP levels are linked to cellular calcium homeostasis by in vitro studies.[368] The limitations of these indirect associations are illustrated by the case of cilia and flow-dependent mTORC1 signaling in which PC-2–dependent calcium transients were specifically excluded, whereas a novel role for ciliary Lkb1/AMPK was identified.[315]

Aside from calcium changes following mechanosensitive activation of PC-1/PC-2 receptor channel complex, PC-2 functions as a calcium-activated intracellular calcium release channel.[179] The calcium sensitivity of PC-2 activity is modulated by phosphorylation at serine 812. PC-2 and PC-1 interact with and modulate the activity of the major epithelial ER calcium release channel, the inositol 1,4,5-triphosphate receptor (IP_3R).[378–380] PC-2 also regulates calcium signaling by the other major ER calcium release channel, the ryanodine receptor.[381] The ER t-SNARE protein syntaxin-5 interacts with the COOH-terminus of PC-2 and inactivates the channel to prevent calcium leak from ER stores.[188] PC-2 has also been proposed as a GPCR or receptor tyrosine kinase (RTK)–operated cell surface channel. An epidermal growth factor (EGF) treatment of epithelial cells stimulates PC-2–dependent increases in cellular calcium.[376] This response is augmented by an overexpression of PC-2 and is attenuated by the siRNA knockdown of PC-2. It has also been suggested that PC-2 is activated downstream of GPCR and PLC signaling.[377] This activity requires heterotrimeric channel formation between PC-2 and TRPC1 and is independent of PC-1.

There is compelling evidence based on the structure, function, and mutations in PC-2 that calcium ions play a central role in the pathogenesis of ADPKD. There is a general consensus that the channel activity of the polycystin complex in cilia is related to the pathogenesis of ADPKD. The relevance of polycystin channel activity in the ER and plasma membranes to the disease pathogenesis remains less certain. The difficulty in discovering the detailed mechanistic role of calcium signaling in ADPKD may rest with the fact that the bulk of PC-2 channel activity occurs at sites other than the cilia, yet it is the minute portion of the signal occurring in cilia that is central to disease progression.

Regulation of the Cell Cycle

The profound increase in the cystic cell mass in ADPKD suggests that proliferation is a central feature of the disease phenotype (Fig. 16.6). Whether this proliferative response is primarily connected to polycystin signaling or is secondary

to the multitude of changes occurring as the tissue remodels in response to the loss of polycystins is an area of active investigation. Interfering with the expansion of cystic cell mass has the potential to slow the progression of PKD. The first study to directly address the role of polycystins in cellular proliferation showed that the overexpression of full-length PC-1 in MDCK cells resulted in cell cycle arrest at the G0/G1 phase.[242] PC-1 was proposed to interact with JAK2, which increased STAT1 expression, which in turn upregulated $p21^{wafl}$ to inhibit cell cycle progression. This process is dependent on the ability of PC-1 to interact with PC-2. Although these studies were cell based, in vivo support was provided by the demonstration of the altered expression of STAT1 and $p21^{wafl}$ in $Pkd1^{-/-}$ embryos.[242] PC-2 has been proposed to interact with and sequester Id2 in the cytosol, thereby preventing translocation of the latter to the nucleus where it can stimulate proliferation.[382] The extension of this mechanism to PC-1 was suggested by the increased nuclear localization of Id2 in $Pkd1^{-/-}$ mice and by the ability of RNAi knockdown of Id2 to decrease proliferation in $Pkd1^{-/-}$ cells in culture. $Pkd2^{-/-}$ cells in culture also exhibit increased proliferation and increased propensity toward branching morphogenesis in a three-dimensional culture.[348] Additional proliferative effects from the loss of polycystins may be mediated through the activation of either the MAPK/ERK or the mTOR pathways, as discussed previously.

The proliferative response in kidney tubule cells following the loss of polycystins is likely to be highly context dependent. As discussed, the early inactivation of polycystins during postnatal development in vivo results in rapid cystic expansion, whereas adult inactivation of polycystins results in the more indolent progression of cystic disease.[220] The proliferation of cyst cells in vivo likely results from a combination of cell autonomous effects due to reduced or absent polycystin function coupled with noncell autonomous effects that can foster an enhanced proliferative milieu. The latter can result from ongoing development,[220] acute injury and regeneration,[234,236–238] or stimulation by mediators of inflammation entering the kidney.[248] The most specific agents for therapy targeting proliferation in ADPKD would be directed at the earliest cell autonomous changes resulting from the loss of polycystins. On the other hand, the earliest available therapies may in fact be targeted toward the noncell autonomous secondary processes that foster the enhanced growth of cyst lining cells and the progression of PKD.

KIDNEY DISEASE PROGRESSION AND TOTAL KIDNEY VOLUME IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

ADPKD is characterized by the development and expansion of renal cysts, resulting in increased kidney size and TKV. Combined kidney weights can exceed 10 kg once ESRD is reached. The initiation and growth of cysts over time cause increased kidney size, compression, and remodeling of normal renal architecture and vasculature resulting in inflammation, interstitial fibrosis, and renal failure.[43] Although cyst expansion results in total organ enlargement, the initiation of cyst formation and growth is restrictive and focal in nature. Microdissection studies of early stage ADPKD kidneys showed focal cyst formation involving less than 5% of nephrons and a minor subset of cells within individual tubules.[44] The increase in TKV in ADPKD can be seen in utero, is a consistent finding during childhood, and is predominant throughout adult life. ADPKD is the only hereditary cystic kidney disorder associated with an inexorable increase in kidney size. Although ARPKD is associated with increases in TKV, this is typically greatest during the early postnatal period and either plateaus or diminishes over time as renal function declines.

A striking feature of ADPKD is the prolonged oligosymptomatic period typically spanning 4 decades, during which cyst mass is expanding with an increase in TKV while kidney function remains relatively intact when measured by the glomerular filtration rate (Fig. 16.8). During this phase, all of the common signs and symptoms related to progression in ADPKD, including hypertension, chronic pain or heaviness in the flank or abdomen, hematuria and cyst hemorrhage, urinary tract infections, and nephrolithiasis occur and are directly associated with increased TKV.[62] Despite the preservation of kidney function, the size of kidneys increases from a normal size (150 to 200 mL each) in childhood to

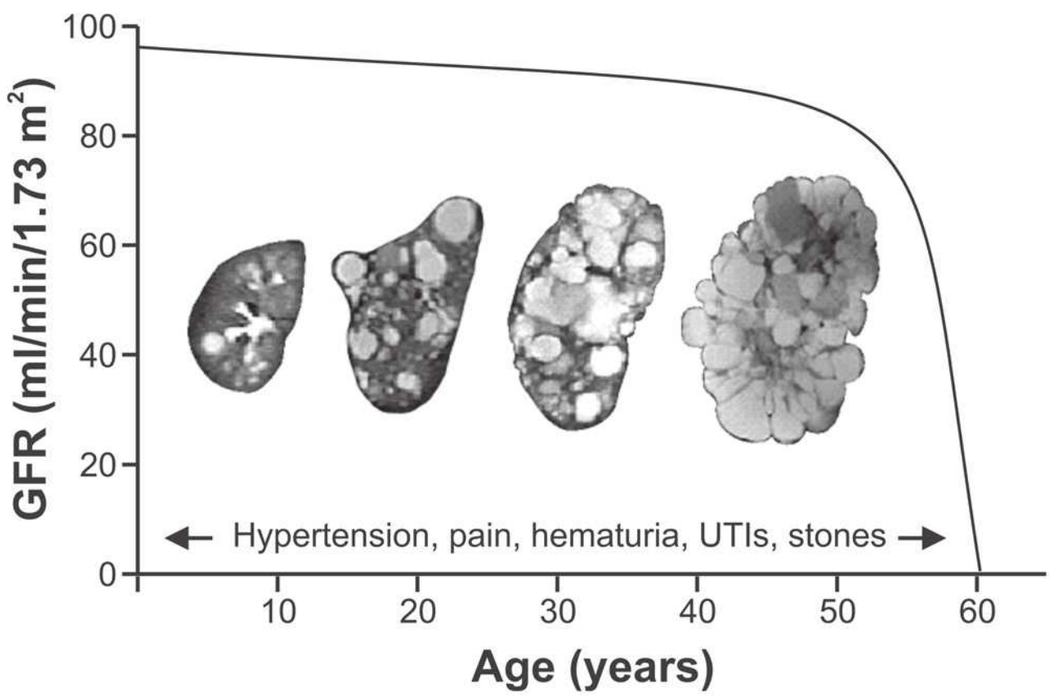


FIGURE 16.8 A proposed relationship between renal cyst burden, age, and renal function in autosomal dominant polycystic kidney disease (ADPKD). Coronal magnetic resonance imaging (MRI) of four ADPKD individuals age 9, 20, 21, and 40 with normal renal function are overlaid on a plot of glomerular filtration rate (GFR) as a function of age in ADPKD patients. Although hypertension, pain, hematuria, urinary tract infections (UTIs), and nephrolithiasis occur throughout the course of ADPKD, renal function remains largely intact until total kidney volume reaches a size where renal reserve no longer can compensate. Thereafter, renal function inexorably declines to end-stage renal disease. (Adapted with permission from Torres V, Scheinman S. Polycystic kidney diseases. *NephSAP*, Jan 2004;3(1):22.)

greater than 1500 mL by the third to fourth decade.[383] The relentless expansion of TKV due to the growth of cysts is the hallmark of ADPKD and leads inexorably to deformation of normal renal and vasculature architecture, inflammation, interstitial fibrosis, tubular atrophy, and finally, progressive kidney dysfunction.

Measurement methods using ultrasound, CT, and MRI have been developed to quantify TKV in ADPKD. Ultrasound imaging uses the formula for a modified ellipse to determine TKV [4/3π × ½(anterior–posterior diameter + width) × ½(length)].[31,384] Obtaining accurate longitudinal, axial, and depth measurements requires significant training and appropriate alignment through the cystic kidney. Ultrasound measurements are accurate in individuals with relatively small kidneys, which can be measured in a single imaging window. Significant variability occurs in individuals with extremely large kidneys, or in those with concomitant significant polycystic liver disease. Additional variability is introduced with different operators, motion artifact, and respiratory variation. Ultrasound determinations of TKV tend to underestimate TKV measurements obtained by MRI by approximately 25% in healthy controls.[384] Despite these limitations, ultrasound ellipsoid-based and MR-based stereology estimates of TKV are highly correlated (r = 0.89). The reproducibility or the coefficient of variation differs greatly with ultrasound (21% to 35%) compared to MRI (2.1% to 2.5%).[384] Importantly, kidney length is the most reproducible measurement using ultrasound. These observations indicate that ultrasound is not an appropriate imaging tool for short-term longitudinal monitoring in ADPKD, but may have a screening role for risk stratification in young individuals or could be used in individuals followed over long periods (more than 5- to 7-year intervals).

Recently, the National Institutes of Health (NIH)–sponsored CRISP has evaluated the relationship between GFR progression and TKV expansion in ADPKD. MRI acquisition methods that can accurately, reproducibly, and reliably determine TKV in ADPKD individuals have now been developed. Using both T2- and T1-weighted MRIs, interobserver and intraobserver variability, as well as day-to-day variability of TKV measurements, are all less than 2.5%.[385] Both gadolinium-enhanced and non–gadolinium-based MR measures of TKV are accurate, with a slightly greater TKV (1% to 6%) measurement seen in postgadolinium studies.[386] Given the previous reports of systemic nephrogenic fibrosis related to gadolinium exposure, CRISP no longer uses gadolinium contrast agents during image acquisition. Total cyst volume measurements in CRISP are more variable than TKV measurements, but they remain highly correlated with TKV (r = 0.99), indicating that renal cystic expansion accounts for the overwhelming majority of the increase in TKV seen in ADPKD. CRISP has now had the opportunity to prospectively follow 241 nonazotemic patients for 8 years with MRI examinations to measure the progression of kidney and cyst volumes.[385,387] The mean rate of increase in TKV over 3 and 8 years was 5.3% and 5.2% per year, respectively, which is consistent with an independent cohort from the SUISSE pre-randomization studies (5.8% per year). On average, CRISP participants increased their TKV 55% from baseline at the end of 8 years of follow-up. This rate of change is roughly equivalent to a 75 to 90 mL per year increase in TKV, which is equivalent to half of a normal adult kidney size and which is easily detectable by current imaging methodologies.

In CRISP, the overwhelming majority of ADPKD individuals demonstrated detectable increases in TKV over relatively short (6- to 12-month) periods (Fig. 16.9).[387] Men had higher rates of kidney and cyst growth than women. These differences diminish when TKV is indexed for measures of body size, including height (htTKV). In the CRISP study, baseline TKV correlated with a subsequent rate of increase in TKV, and an initial TKV above 1500 mL (approximately 5 times greater than normal) was the primary predictor of declining glomerular filtration rate in the first 3 years of study. Importantly, receiver operator characteristic curves

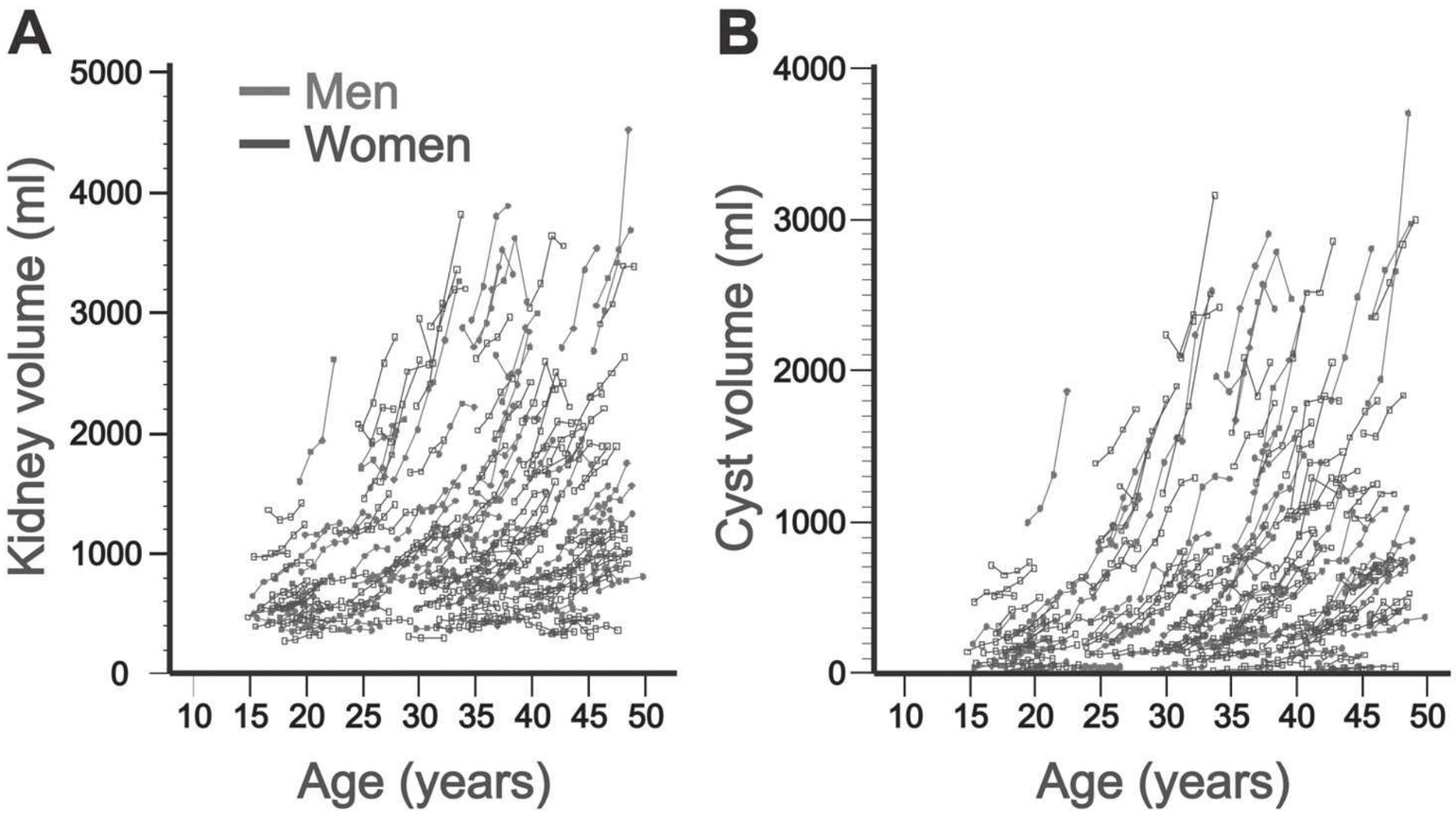


FIGURE 16.9 Total kidney volume **(A)** and total cyst volume **(B)** in relation to age in women (*blue*) and men (*red*) imaged annually over 3 years during participation in the Consortium for Radiologic Imaging studies in Polycystic Kidney Disease (CRISP). (From Grantham JJ, Torres VE, Chapman AB, et al. Volume progression in polycystic kidney disease. *N Engl J Med.* 2006;354:2122–2130. Copyright (c) 2006 Massachusetts Medical Society.) (See Color Plate.)

(ROC) demonstrated that htTKV reliably and accurately predicts the development of chronic kidney disease (CKD) stage 3 within 8 years of measurement with a cut point of 600 mL per meter (equivalent to a TKV of approximately 1200 mL). The htTKV-based prediction of CKD stage 3 was independent of variables known to associate with renal insufficiency in ADPKD, including genotype, gender, race, and age. A multivariate analysis further indicated that for each 100 mL increment of htTKV at baseline, the odds of reaching a CKD stage 3 end point within 7.9 years increases 1.48-fold.

PKD2 participants in CRISP demonstrated significantly smaller TKVs than PKD1 participants, but nonetheless showed similar rates of increase in TKV.[227] Mathematical modeling of TKV data from CRISP participants to estimate TKV at age 18 were accurate, indicating a relatively constant rate of increase in TKVs accounting for the observed exponential rate of kidney size growth.[388] Computational modeling integrating cyst surface area, volume, and an assumed overall constant rate of cyst growth (assuming variability across cysts within an individual) as shown by TKV change in the CRISP study suggested that cysts that developed early in life were the main contributors to TKV.[388] These inferred data were interpreted as showing that there are periods of accelerated cyst growth and/or that the initiation of cyst burden is mostly established by the time of birth.

The relationship between clinical symptoms of ADPKD and GFR is highly variable, which is likely due to the striking dissociation between the expansion of TKV and GFR observed early in the course of the disease. A significant time lag between the increase in TKV and the decline in GFR and an increasingly negative correlation between baseline TKV and GFR measured in subsequent years was demonstrated in CRISP.[389] The stability of GFR results from hyperfiltration of the surviving nephrons. The finding of stable GFR when ADPKD kidneys are dramatically enlarged, distorted by multiple cysts, and fibrotic provides false reassurance as to the stability of the disease progression. Once GFR begins to decline the progression is inexorable, with an average rate of decrease of approximately 4.4 to 5.9 mL per minute per year, a faster rate than in other types of progressive renal disease.[390] Currently, changes in GFR (frequently estimated from changes in serum creatinine) are considered the gold standard for quantifying the progression rate in most chronic renal diseases. However, given that these changes are seen only once the kidney architecture has been grossly and irreversibly distorted, GFR may not be suitable as a primary end point for clinical studies testing early interventions in ADPKD.[383] Risk factors associated with a worse prognosis in addition to TKV include male gender, a first episode of hematuria before the age of 30, PKD1 genotype, the onset of hypertension before the age of 35, dipstick-positive proteinuria, elevated low density lipoprotein (LDL), decreased high density lipoprotein (HDL), increased dietary sodium intake, and decreased renal blood flow.[391,392] All of these variables, with the exception of sodium intake and dyslipidemia, are specifically related to TKV. The CRISP study has shown that kidney and cyst volumes are the strongest predictors of renal functional decline,[389] and it is anticipated that this measurement will find its way into clinical practice.

RANDOMIZED CLINICAL TRIALS IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

The availability of an extensive array of orthologous and nonorthologous animal models for PKD has permitted the preclinical evaluation of a broad spectrum of potential therapeutic agents. Many of these agents have shown promising results in one or more rodent models, but only a handful have been deemed sufficiently promising to enter human clinical trials.

Vasopressin V2 Receptor Antagonists

Arginine vasopressin (AVP) increases cAMP levels in the collecting duct, and evidence for the role of cAMP in cystogenesis has provided the rationale for preclinical trials of V2R antagonists in a variety of hereditary renal cystic diseases. Inhibition of the AVP V2 receptor and the subsequent decrease in adenylyl cyclase activity may help to compensate for alterations in intracellular calcium homeostasis and may affect the normalization of intracellular cAMP levels, thereby reducing the proliferative phenotype of cystic epithelium.[393] The V2R antagonists OPC-31260 and OPC-41061 (Tolvaptan) reduce renal levels of cAMP and markedly ameliorate cyst development in models of ARPKD (pck rat), NPHP (pcy mouse), and ADPKD ($Pkd2^{WS25/-}$).[224,394] High water intake by itself, possibly by suppressing the release of vasopressin, has demonstrated a protective effect on the development of PKD in pck rats.[395] The genetic deletion of the vasopressin gene in pck rats by intercrossing them with Brattleboro rats leads to lower renal cAMP levels and an almost complete inhibition of cystogenesis.[396] The cystic phenotype can be recovered following the administration of the exogenous V2 receptor agonist, desmopressin (dDAVP). Activation of the predominant endothelin receptor subtype in the collecting tubules, the endothelin-1 endothelin B (ETB) receptor, inhibits AVP action. An antagonist of this receptor increases renal cAMP levels and aggravates renal cystic disease in a mouse model of ADPKD, presumably by interfering with the inhibition of AVP activity.[397] In aggregate, the data support the hypothesis that the pharmacologic inhibition of the V2R pathway is a logical strategy to inhibit the development and expansion of renal cysts in ADPKD.

Based on these preclinical studies, the Tolvaptan Efficacy and Safety in Management of PKD and Outcomes (TEMPO) program was initiated. Tolvaptan is an orally effective, relatively short-acting, nonpeptide arginine vasopressin V2 receptor antagonist. It is currently approved in the United States and the European Union for the treatment of hyponatremia associated with hypervolemic states (e.g., cirrhosis, congestive heart failure) and euvolemic syndrome of inappropriate

antidiuretic hormone (SIADH) states, and in Japan for the treatment of cardiac edema that is resistant to diuretics. Tolvaptan is also being studied in the United States and in Europe as an adjunct therapy for volume overload in patients with heart failure. A phase IIa dose ranging study to determine the response to increasing doses of tolvaptan in patients with normal renal function has been completed.[398,399] An international phase III clinical trial for the treatment of ADPKD is ongoing at the time of this writing (Table 16.3). A primary therapy study to delay the progression of ADPKD (NCT00428948) has enrolled over 1400 relatively young (< 50 years) ADPKD patients with preserved kidney function (creatinine clearance > 60 mL per minute) but with TKVs greater than 750 mL as measured by MRI. Based on this enrollment, regardless of the final study outcome, this trial will leave open the question of the potential role for V2R antagonists in patients with more advanced kidney disease and the potential efficacy of these drugs at lower doses, which are associated with reduced side effects of polyuria and nocturia and with improved tolerance.

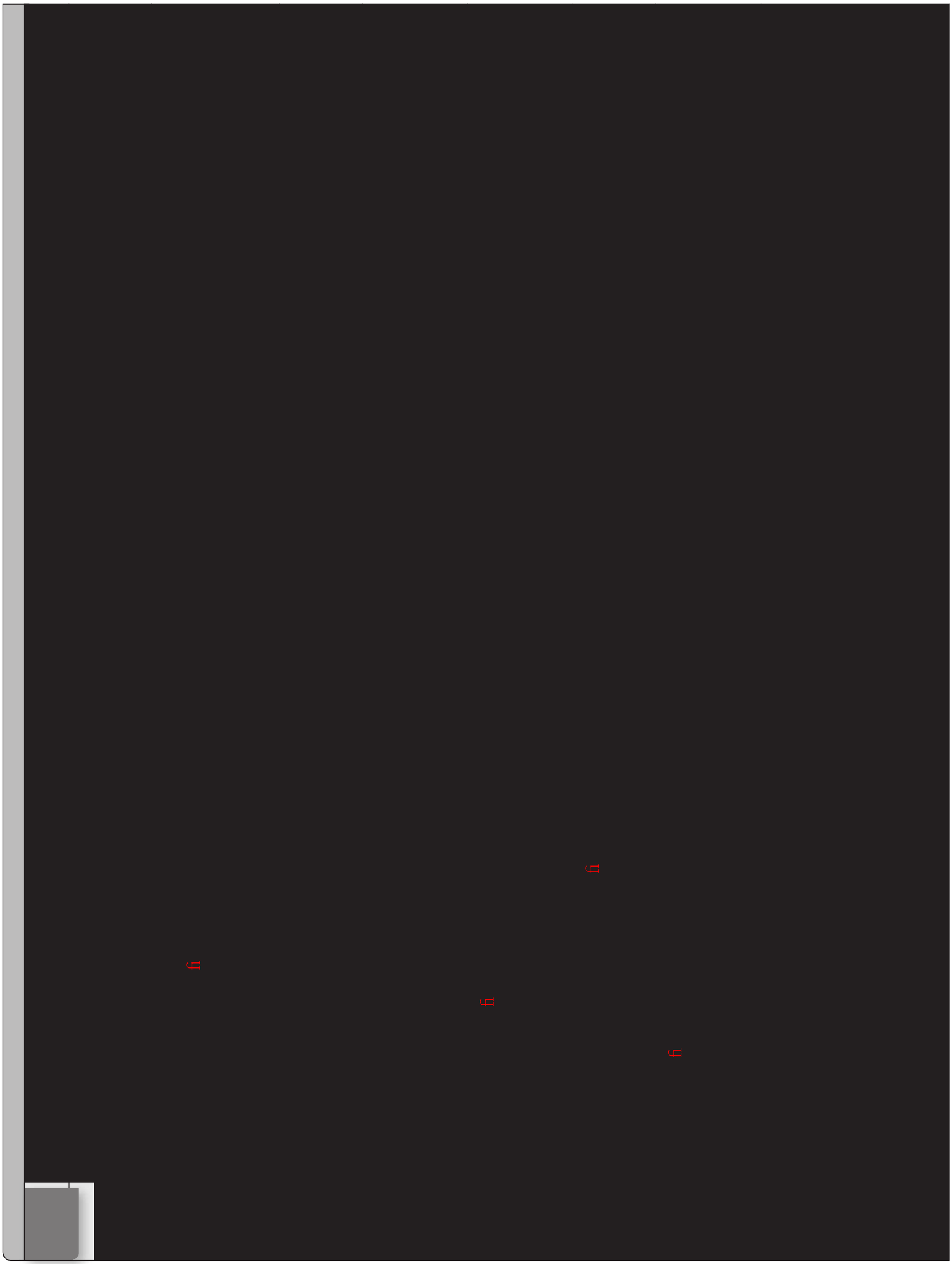
Somatostatin Analogs

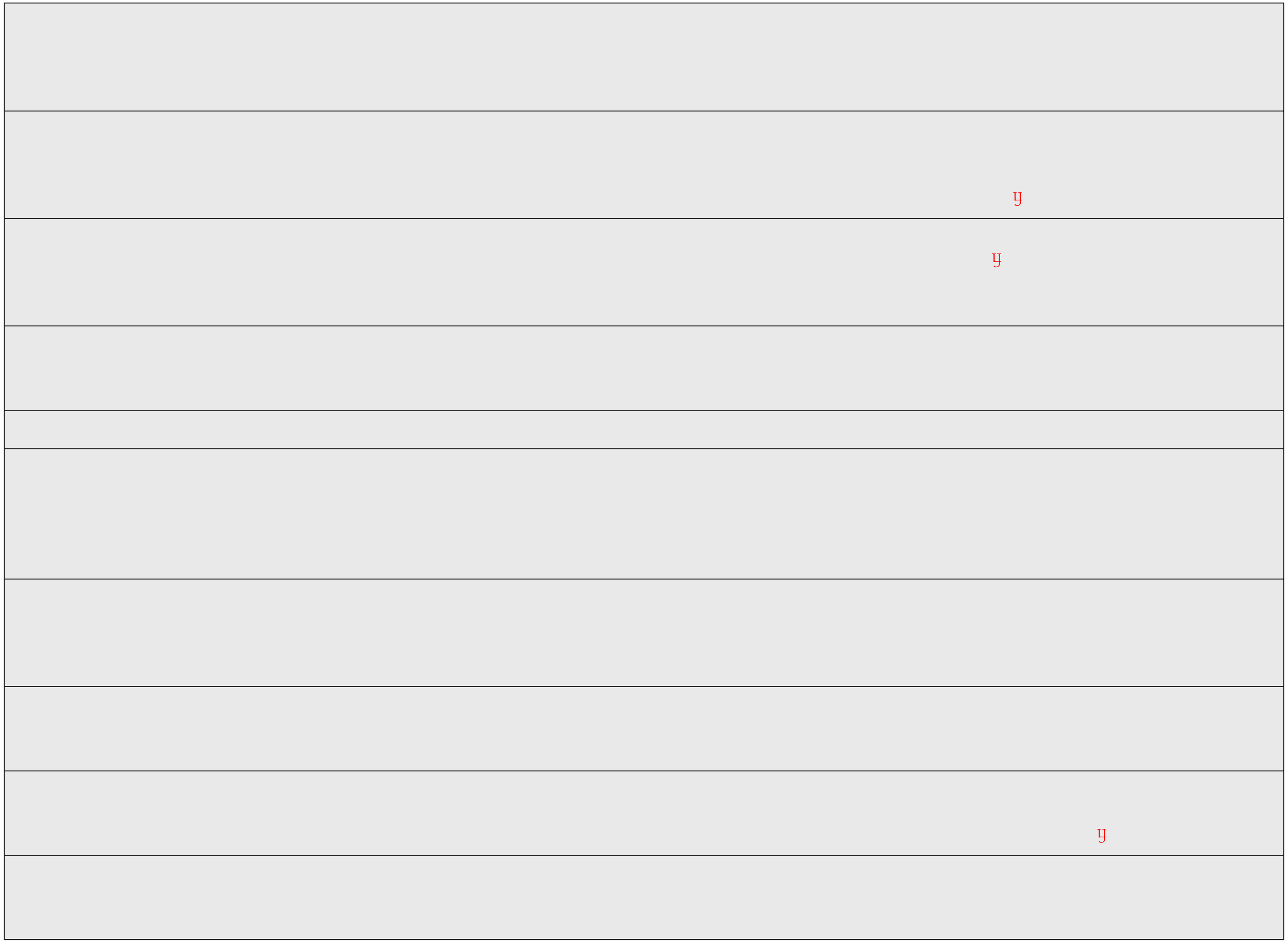
A similar pharmacologic inhibition of cAMP accumulation has been established with the administration of somatostatin, which acts on somatostatin receptor 2 (SST2) receptors in the kidney and liver.[400] Octreotide, a metabolically stable somatostatin analog, halted the expansion of hepatic and renal cysts in ARPKD model pck rats. These observations are consistent with the reduction in total kidney volume in a pilot study of long-acting octreotide for human ADPKD. Presently, there are a number of ongoing clinical trials of octreotide and lanreotide for PKD and liver disease (NCT00309283, NCT00426153, and NCT00565097). Pilot studies evaluating the feasibility of increasing the fluid intake in the form of water have also begun in ADPKD patients.[401] These are based on the assumption that decreasing the urinary osmolality to less than 300 mOsm per kilogram in the steady state will result in the deactivation or inhibition of the V2R. The tolerability of increasing fluid intake is reasonable; however, long-term compliance and 24-hour monitoring of urinary osmolality is a potential concern. Measures of disease progression under these conditions have not yet taken place.

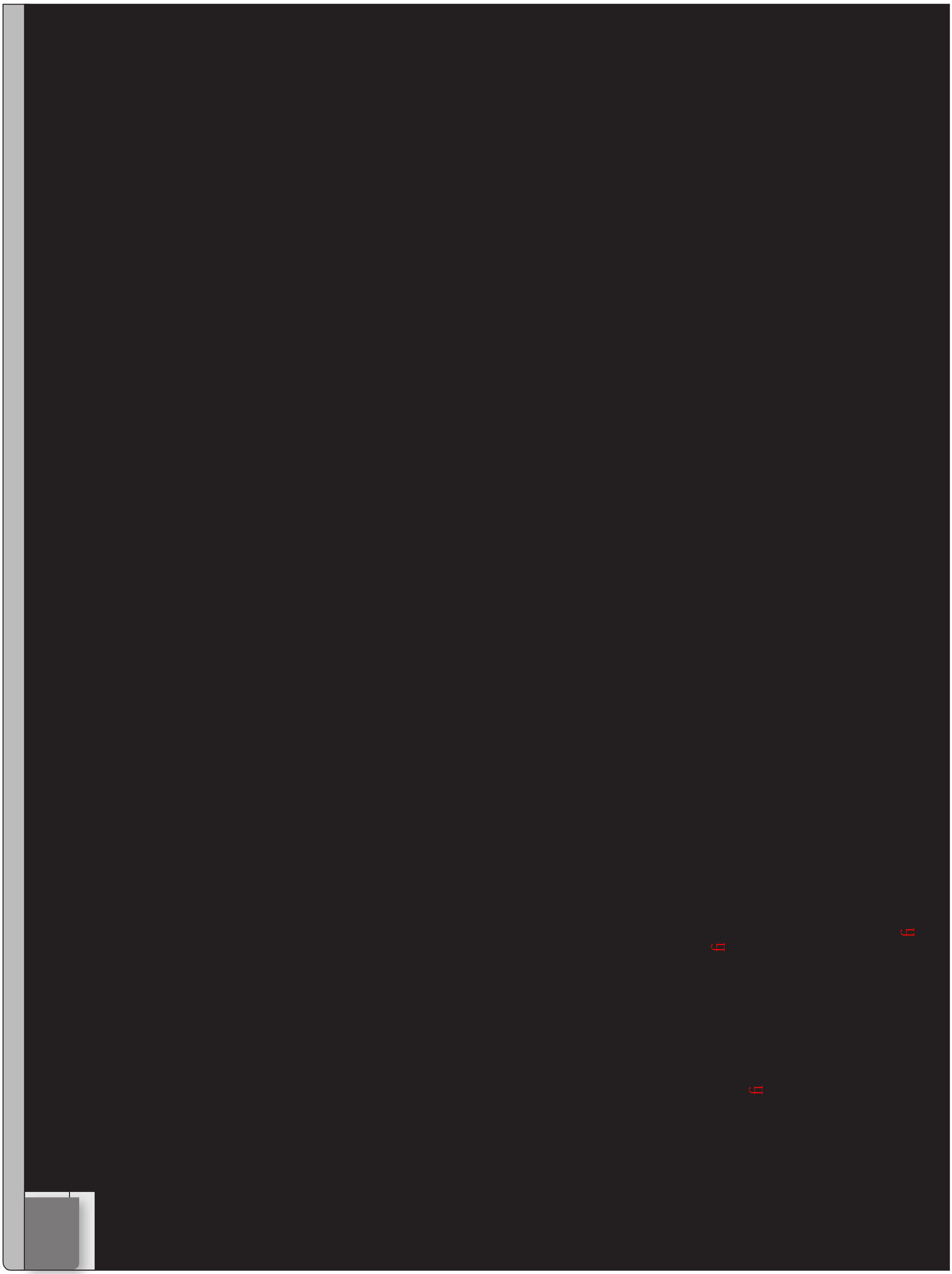
Inhibition of the Mammalian Target of Rapamycin

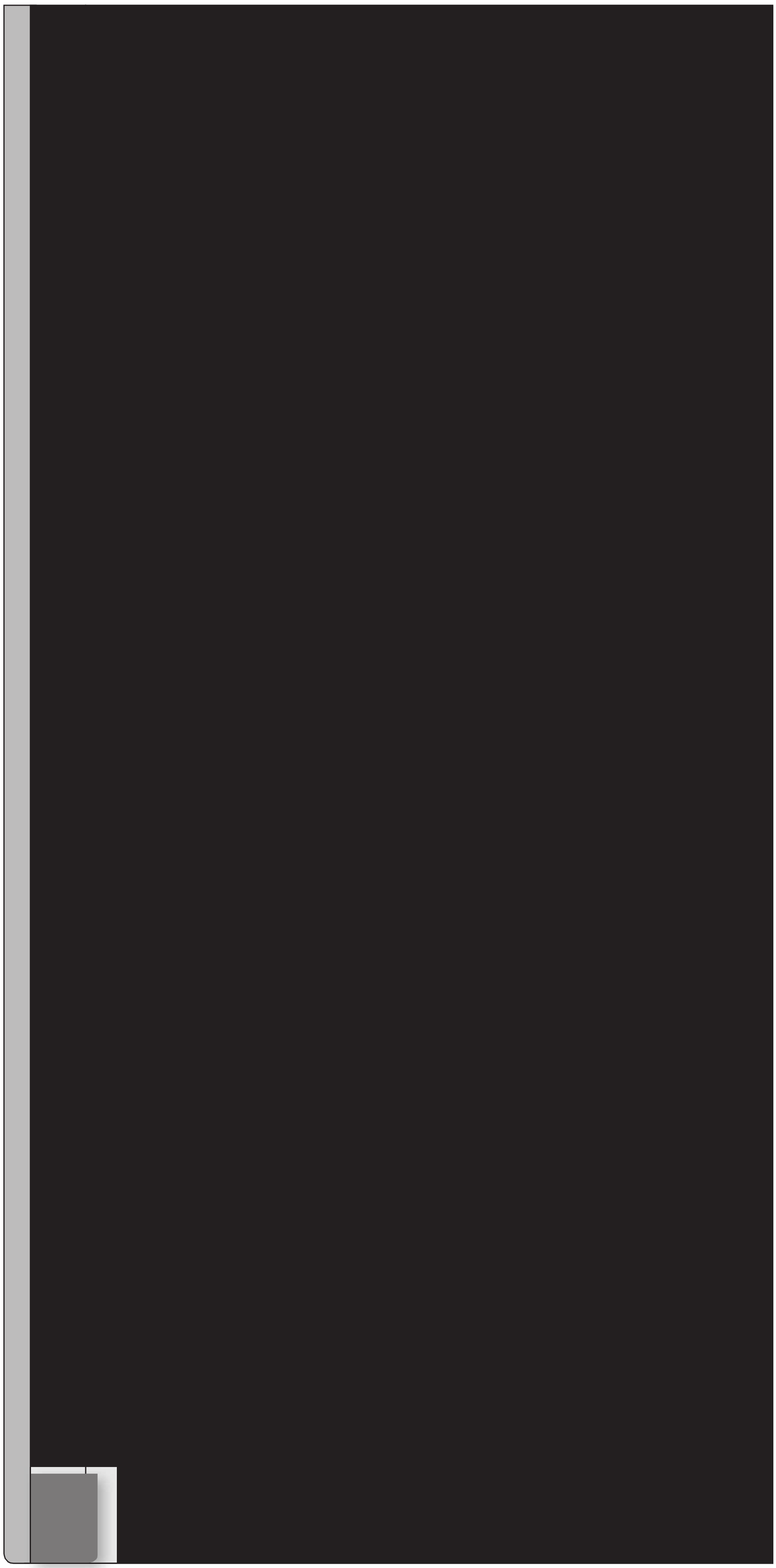
mTOR, a serine-threonine kinase that is involved in the coordination of cell growth and proliferation, is inappropriately activated in cysts lining the epithelial cells of kidneys from mice and humans with ADPKD (see previous).[225,402,403] Studies in animal models of cystic kidney disease have shown that mTOR inhibition suppresses cyst growth. Sirolimus or everolimus significantly reduced kidney volume growth in the nonorthologous Han:SPRD rat model by reducing cyst expansion with a sustained effect with prolonged treatment.[404,405] Sirolimus also had some effect in an animal model of NPHP and in an orthologous mouse model with the conditional inactivation of Pkd1.[354,406] These studies used higher doses of mTOR inhibitors than can be achieved in humans and only tested their preclinical potential in early onset, rapidly progressive orthologous gene mouse models of Pkd1.[354] A small scale, 6-month, randomized trial comparing eight patients on sirolimus with eight control patients showed reduced kidney volume growth in the sirolimus-treated group.[407] Collectively, these preclinical and clinical observations offered a rationale for clinical trials of mTOR inhibitors in ADPKD.

Two major prospective randomized clinical trials using sirolimus or everolimus have since been completed (Table 16.3). The studies differed with respect to patient number, subject characteristics, and dose range. The two studies reported negative results. Walz et al.[408] randomly assigned 433 patients aged 18 to 65 years with ADPKD and an estimated GFR > 30 mL per min per 1.73 square meter (chronic kidney disease stage II/III) to receive either placebo or the mTOR inhibitor everolimus (2.5 mg twice daily) for 2 years. Everolimus treatment was associated with a marginal slowing of the increase in TKV, reaching statistical significance at 1 year and marginal significance at 2 years. The finding that increases in TKV were persistently lower in the everolimus group suggests that everolimus may be able to limit the growth of cysts in patients with ADPKD. The perceived lack of a positive effect on glomerular filtration rate and the progression of chronic kidney disease may be due to the reduced power of the trial resulting from the fact that approximately one-third of the patients dropped out, largely because of drug-related adverse effects. In a complementary trial, the SUISSE ADPKD study treated 100 patients aged 18 to 40 years with preserved renal function with sirolimus (2 mg per day) for 18 months.[409] At the end of the study period, the median increase in TKV was similar in the placebo group to the sirolimus group (97 mL versus 99 mL, respectively). The study used a relatively low target dose of sirolimus, and the dose delivered was approximately 25% lower than the intended dose because of adverse effects. The average sirolimus dose normalized by mean patient body weight was approximately 0.020 mg per kilogram. ROC curve analyses of dose finding studies identified 0.049 mg per kilogram of body weight as the cut-off threshold for sirolimus dosage that predicted a reduction or reversal of total cyst volume growth. The negative findings from these studies contrast the positive results from preclinical studies and the results from smaller clinical studies of shorter duration.[407] Taken together, mTOR inhibitors require further investigation to determine any potential to favorably impact changes in TKV in ADPKD individuals. Efficacy is limited by their toxicity, and the impact of mTOR inhibitors appears to be greatest during the most proliferative stages of disease type. It remains to be seen if this class of agent can still be used in patients during the more aggressive phases of cyst growth and expansion, potentially in concert with other disease modifying agents.









3-Hydroxy-3-Methyl-Glutaryl-CoA (HMG-CoA) Reductase Inhibitors

Lovastatin therapy in the heterozygous male (but not the female) Han:SPRD rats resulted in decreased cystic kidney size and improved renal function.[410] These effects may be due to the decreased formation of farnesyl pyrophosphate, an intermediate in the conversion of acetyl-coenzyme A (CoA) to cholesterol that is also required for the activation of Ras, which in turn may be an important factor in cell proliferation. Three clinical trials of statins lasting from 4 weeks to 2 years in small numbers of ADPKD patients have shown improved renal hemodynamics, including increased GFR and effective renal plasma flow, improved endothelial function, and longer term kidney function and urinary protein excretion.[411–413] Currently, a phase III randomized trial comparing pravastatin to placebo over 5 years is under way in 107 children and young adults aged 8 to 22 years and treated with angiotensin-converting enzyme inhibitors. The end points in this trial include TKV, renal function, and urinary protein excretion levels.[414]

Triptolide

Triptolide is a natural compound derived from the Chinese herb Thunder God Vine. It is a potent inhibitor of nuclear factor-kappa B (NF-κB) and nuclear factor of activated T cells (NFAT)-mediated transcription, which thereby decreases inflammatory and proliferative cellular responses. Triptolide also promotes increased PC-2–mediated calcium release and reduces cyst formation in Pkd1 mouse models.[415–417] Current clinical trials using triptolide are under way in approximately 300 patients at the University of Nanjing to evaluate its effects on kidney function and TKV.

Epidermal Growth Factor Receptors and Src Inhibitors

Epidermal growth factor receptor (EGFR) inactivation has been shown to slow cyst growth in nonorthologous recessive models of polycystic kidney disease,[418,419] but not in a rat model orthologous to human ARPKD.[224] EGFR tyrosine kinase inhibitors, one of which is an Src inhibitor, play an intermediary role in cAMP pathways.[420] Src activity has been shown to be associated with the progression of disease in bpk mice and pck rats.[421] A truncated EGFR-like protein, Bosutinib, which is a Src inhibitor, has been valuable in treating breast cancer.[422] Most of the EGF receptor tyrosine kinase inhibitors are relatively nonspecific and have significant side effects, which suggest that long-term use at normal antineoplastic doses will not be feasible in ADPKD individuals. However, they may be extremely useful at a reduced dosage level with other disease modifying agents in appropriate subsets of ADPKD individuals. A clinical trial of 400 ADPKD individuals is under way using the receptor kinase inhibitor Bosutinib SKI606 (NCT01233869). This trial is designed to inhibit Src and to increase MAPK activation. Both renal function and TKVs are being evaluated in this study.

HALT Polycystic Kidney Disease

Substantial evidence has implicated the RAAS in the pathogenesis of ADPKD and associated hypertension. However, evidence that treatments inhibiting the RAAS are superior to other treatment strategies or are at all beneficial are, to date, inconclusive. Limitations of previous studies due to small sample size, short periods of follow-up, and the study of patients at relatively late stages of the disease without a complete blockade of the RAAS have hampered the development of evidence-based guidelines for the treatment of hypertension in ADPKD. Because of the importance of hypertension in ADPKD and the uncertainties surrounding its treatment, the NIH/National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has funded two distinct, multicenter, double-blind, randomized clinical trials adequately powered to assess the effect of RAAS blockade on renal progression in early and late stages of the disease (NCT00283686). HALT PKD consists of two ongoing randomized trials with the largest cohort of systematically studied patients with ADPKD to date. Study A is designed to compare the combined treatment with an angiotensin-converting inhibitor and receptor blocker to the inhibitor alone at standard compared to low blood pressure targets. There are 558 ADPKD early stage patients with an eGFR over 60 mL per min per 1.73 square meters. Study B is comparing angiotensin-converting enzyme inhibitors and receptor blockers to the inhibitor alone at standard blood pressure level in 486 patients with more progressive renal disease and an eGFR between 25 and 60 mL per minute per 1.73 square meters. An initial evaluation of this study population[95,423] demonstrates a significant association between eGFR, urinary albumin excretion, body surface area, and TKV. These studies are due to be completed in 2014.

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