

## Polycystic Kidney Disease

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**P**olycystic kidney disease (PKD) is the most common genetic cause of kidney failure in adults and children. PKD is characterized by progressive cystic dilation of the renal tubules, which results in nephromegaly and often culminates in end-stage renal disease. PKD can be inherited as either an autosomal dominant trait (ADPKD) or autosomal recessive trait (ARPKD). Since our last review on this subject in 2002 (1), there have been tremendous advances in the understanding of the genetics and pathogenesis of PKD. The localization of the PKD proteins polycystin-1, polycystin-2, and fibrocystin in the primary cilium has renewed attention on this neglected organelle and rejuvenated an entire field of cell biology. The elucidation of the signaling pathways that are disrupted in cyst epithelial cells has provided new targets for therapeutic intervention. The generation of orthologous animal models, especially knockout mice, has enabled preclinical evaluation of drugs that target these pathways and accelerated their use in clinical studies of patients with PKD. Concomitant with the discoveries in basic science research, there have also been major advances on the clinical research front. The National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) has sponsored several major clinical studies on PKD. One recently completed study, the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) study, has provided new insights into disease progression and measurement.

The purpose of this Frontiers miniseries is to review some recent basic and clinical research on PKD. Because of the broad ongoing investigations in this field, it is not possible to provide a comprehensive review. Rather, two articles will discuss basic research on molecular pathogenesis, focusing on the roles of primary cilia, Wnt signaling, and planar cell polarity. Two more articles will summarize clinical research on genotype-phenotype correlations, diagnosis, and emerging therapies.

ADPKD is caused by mutations of *PKD1* or *PKD2*, which



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produce similar clinical manifestations, although kidney failure and other clinical symptoms occur earlier in patients with mutations of *PKD1*. All cases of ARPKD appear to arise from mutations of *PKHD1*. Since the original cloning of the PKD genes, many different mutations have been identified in affected individuals. In the first article (2), Drs Rossetti and Harris at the Mayo Clinic review what has been learned about genotype-phenotype correlations in PKD. These investigators and their collaborators have compiled large databases of DNA samples from PKD patients and have attempted to correlate the mutations with various clinical features of the disease. The goal of this work is to find better prognostic indicators and to identify regions of the proteins that are critical for function. For example, Rossetti *et al.* found that mutations located toward the 5' end of the *PKD1* gene are associated with earlier onset of end-stage renal disease and increased risk of ruptured intracranial aneurysms (3). In the case of ARPKD, the presence of two truncating mutations in *PKHD1* produces a severe and lethal

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neonatal form of the disease, whereas patients with at least one missense mutation may survive to adolescence or even adulthood when they present with hepatic fibrosis as the primary manifestation (4). The review by Rossetti and Harris emphasizes the great variability in the severity and manifestations of PKD even between individuals from the same family who carry identical germline mutations. Recent work has begun to identify the genetic modifier and environmental factors that may contribute to this heterogeneity.

A major insight into the pathophysiology of PKD was revealed by the discovery that the proteins encoded by the PKD genes are located in primary cilia. In the second article (5), Dr Yoder at the University of Alabama at Birmingham reviews the structure and function of primary cilia. Primary cilia are solitary hair-like sensory organelles that project from the cell surface. Studies first performed in *C. elegans* showed that homologs of polycystin-1 and polycystin-2 are located in sensory cilia (6). This surprising finding was subsequently verified by Dr Yoder and others in kidney epithelial cells. In the kidney, primary cilia project into the tubule lumen and may have a mechanosensory function. The loss of polycystin-1 or polycystin-2 in cilia is believed to disrupt a calcium-dependent signaling pathway that leads to dysregulated cell proliferation and structure and/or increased fluid secretion. Similarly, Dr Yoder and others found that fibrocystin, the protein mutated in ARPKD, is also located in primary cilia, which raises the possibility of a common cystogenic mechanism in ADPKD and ARPKD. Moreover, several proteins involved in other diseases that manifest renal cysts, such as nephronophthisis and Bardet-Biedl syndrome, have also been found in the primary cilium and/or the basal body that anchors the cilium to the cell. Although these results lend considerable support to the ciliary hypothesis of cyst pathogenesis, it should be remembered that the polycystins and fibrocystin are also located at other sites in the cell, such as the plasma membrane and endoplasmic reticulum, and expression at these sites may be as important, or more important, in cyst formation.

Polycystin-1 has been shown to regulate a large number of intracellular signaling pathways involving intracellular calcium, G-proteins, cAMP, JNK, mitogen-activated protein kinase/extracellular signal-regulated kinase, JAK-STAT, and mammalian target of rapamycin. Indeed, a challenge in the field has been to distinguish signaling pathways that are primarily mediated by polycystin-1 from those that are affected secondarily. One of the first signaling pathways to be investigated was the Wnt signaling pathway. In the third article (7), Drs. Benzing, Simons, and Walz discuss the role of Wnt signaling in PKD. Wnts are secreted glycoproteins that play essential roles in embryonic development, differentiation, and growth. Dr. Walz' group was the first to show that the C-terminal domain of polycystin-1 can activate canonical ( $\beta$ -catenin-dependent) Wnt signaling. Interest in Wnt signaling has recently been renewed by the discovery of alterations of planar cell polarity (PCP) in some forms of PKD. PCP refers to polarity within the plane of the epithelial monolayer, which is important in morphogenesis. Dr. Fischer and her colleagues at the Pasteur Institute showed that renal epithelial cells normally

divide along an axis that is parallel to the orientation of the tubule, which results in vectorial tubular elongation (8). In two different animal models of PKD, the orientation of cell division was randomized, which would instead result in tubular dilation and cyst formation (8). These studies identify an abnormality in PCP in PKD. In lower vertebrates, the establishment of PCP requires noncanonical Wnt signaling. Recent findings from Dr. Walz's laboratory suggest that an altered balance between canonical and noncanonical Wnt signaling could underlie the abnormality in PCP in renal cystic diseases (9).

The progress in understanding the molecular pathogenesis of PKD has been paralleled by advances in clinical research. For example, the finding of increased cAMP-dependent signaling in cystic kidneys has led to the trial of vasopressin receptor antagonists as potential treatment of ADPKD. Tolvaptan, the first drug in this class to be studied, was already in clinical trials for congestive heart failure. Successful preclinical trials in orthologous animal models of PKD helped it receive US Food and Drug Administration Fast Track approval for studies in humans with PKD. In the last article of this miniseries, Dr Chapman at Emory University discusses tolvaptan and other new promising therapeutic approaches in PKD, including inhibitors of the renin-angiotensin system, rapamycin, and somatostatin (10). The emergence of new potential therapies has underscored the necessity of a reliable test to follow disease progression. Dr Chapman notes that the traditional measure of kidney function, serum creatinine, is an insensitive indicator of disease severity. Recently, she and other participants in the NIDDK-sponsored CRISP study showed that kidney volume measured with magnetic resonance imaging (MRI) can be used to predict disease progression (11). Using serial MRI, it was possible to detect significant changes in cyst volume over a relatively short period of time (3 yr) and to correlate changes in cyst volume with decline in GFR. Dr Chapman suggests that by incorporating kidney volume measurements into clinical trials, such as the ongoing Halt Progression of Polycystic Kidney Disease (HALT-PKD) study, the potential effects of therapies may be recognized sooner. However, because the cost of MRI makes its widespread application impractical, the search continues for other biomarkers of PKD that can provide prognostic information.

As the articles in this Frontiers series demonstrate, there have been considerable advances in our understanding of the molecular basis for PKD that have led to promising new therapeutic approaches. The challenges in the future are to understand the biologic functions of polycystins and fibrocystin, distinguish primary cellular abnormalities from secondary effects of mutations, identify disease biomarkers, and find safe and effective treatments that will slow cyst enlargement in patients with PKD.

## Disclosures.

None.

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