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Autosomal Dominant Polycystic Kidney Disease

York Pei, MD and

8N838, 585 University Avenue, University Health Network, Toronto, Ontario, Canada M5G2N2,
Phone: 416-340-4257, Fax: 416-340-4999, york.pei@uhn.on.ca

Terry Watnick, MD

Division of Nephrology, Johns Hopkins School of Medicine, 855 North Wolfe Street, Rangos 552,
Baltimore, MD 21287, twatnick@jhmi.edu

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic form of kidney disease and affects 1 in 500 to 1,000 individuals worldwide, regardless of ethnicity. It is characterized by progressive renal cyst formation, which distorts normal kidney architecture and ultimately causes 5% of all cases of end-stage renal disease (ESRD) in developed countries. Renal complications such as hypertension, cyst hemorrhage, and pain occur frequently, particularly in patients with large kidneys. Extra-renal manifestations of ADPKD are common although most of them are not serious. However, severe liver cystic involvement and ruptured intracranial aneurysms can result in significant morbidity and mortality in some patients. Currently, there are limited options for the clinical management of ADPKD. Therapy is primarily directed at blood pressure control and symptomatic relief of pain in pre-ESRD patients and dialysis or transplantation in patients with ESRD. Given the clinical importance of this disease, there has been much emphasis placed by funding agencies, including the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) and the Polycystic Kidney Disease Foundation, on research efforts to improve our understanding of the basic pathobiology of ADPKD with a view towards developing better diagnostic tests and novel therapies that target key mechanisms of disease progression. Gratifyingly, the resources devoted to these efforts have paid off handsomely by any measure and have generated a remarkable number of important scientific insights. The purpose of this edition of *Advances in Chronic Kidney Disease* is to highlight the basic and clinical research advances that are poised to significantly improve the clinical management of patients with ADPKD.

The first critical step in unraveling the pathophysiology of ADPKD was to identify the causative disease genes. Although the chromosomal location of the polycystic kidney disease type 1 gene, *PKD1*, was reported in 1985, it took nearly 10 years to identify the gene^{1, 2}. The breakthrough came by way of an astute clinician who identified a family with members who had classic ADPKD as well as one child with features of tuberous sclerosis and ADPKD. Cytogenetic studies of the family revealed a balanced translocation that allowed researchers to clone the disease gene bisected by the breakpoint. Identification of the *PKD2* followed shortly thereafter, in 1996³. These seminal discoveries set the stage for the “warp speed” of research that has ensued. Over the last 15 years, researchers have applied the breadth of modern

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Corresponding Author: Terry Watnick, MD, Division of Nephrology, Johns Hopkins School of Medicine, 855 North Wolfe Street, Rangos 552, Baltimore, MD 21287, twatnick@jhmi.edu.

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scientific methodologies to elucidate our understanding of ADPKD at both basic and clinical levels.

Researchers quickly determined that the protein products encoded by *PKD1* and *PKD2*, polycystin-1 and -2, respectively, are components of a novel multi-functional signaling pathway that regulates key cellular processes including growth, differentiation, and orientation of tubular epithelial cells⁴. In addition, identification of *PKD1* and *PKD2* provided the critical genetic reagents to unravel the molecular basis of individual cyst formation. Detailed molecular genetic analysis of the cyst lining epithelia revealed that individual cysts were monoclonal in origin, and in many instances resulted from somatic mutation of the copy of *PKD1* or *PKD2* inherited from the unaffected parent. Thus, a “two-hit” cellular recessive mechanism appears to underpin the initiation of a majority of renal and liver cysts in ADPKD⁵. Based on these observations, researchers were able to explain the observation that cyst formation was a focal process occurring in a relatively small subset of cells. More recent studies from orthologous murine models of ADPKD have extended this model since it appears that complete loss of polycystin signaling may not be necessary to trigger cyst formation. These findings have suggested a “threshold” model whereby reduced effective polycystin signaling below a critical threshold may be sufficient to produce the cellular derangements that promote cyst formation⁴.

The era of genomic research validated the use of genetically tractable model organisms such as *C. elegans* (worms) and *Drosophila melanogaster* (flies) to study human diseases. A large number of human disease genes including *PKD1* and *PKD2* are conserved in model organisms^{6, 7}. The PKD field took a serendipitous turn when it was discovered that homologues of *PKD* genes are required in the ciliated neurons of male worms where they are required for proper mating. Similarly, it turned out that polycystin-1 and polycystin-2 were associated with the primary cilia of numerous vertebrate cell types, including renal epithelial cells. A plethora of subsequent studies confirmed that many of the genes implicated in renal cystic diseases were associated with cilia and/or centrioles, suggesting a potential unifying mechanism for renal cystic disease. These discoveries spawned a broad new scientific field focused on the role cilia and centrosomes in diverse processes including cell signaling, development and human diseases⁸. The precise role of polycystins in cilia continues to be an area of intense investigation.

PKD science has also benefited from modern gene targeting strategies that led to the generation of various orthologous murine models of ADPKD. These models have been used to validate the importance of several key pathways implicated in cyst growth including calcium and cAMP (cyclic AMP) and the mTOR (mammalian target of rapamycin) pathway, among others⁹⁻¹¹. In addition, orthologous murine models mimicking human disease have become invaluable in the pre-clinical testing of targeted therapies, and these have been instrumental in translating these discoveries to the bedside.

Remarkable advances on the basic science front have synergized with breakthroughs in the clinical arena. We now have simple clinical predictors of the ADPKD genotype based on family history of renal disease severity and unified renal ultrasound diagnostic criteria for screening at-risk subjects when the ADPKD gene type is unknown^{12, 13}. At the same time, molecular diagnostics of ADPKD via direct sequencing of the two disease genes are available and can be used for evaluation of at-risk individuals with equivocal imaging results, younger at-risk individuals being evaluated for living kidney donation and individuals with atypical or *de novo* renal cystic disease^{14, 15}. As therapies for ADPKD are contemplated, it is clear that standard endpoints such as doubling of serum creatinine are impractical in ADPKD because of the slow decline in GFR. However, the National Institute of Diabetes and Digestive and Kidney-funded CRISP (Consortium for Radiologic Imaging Studies of Polycystic Kidney

Disease) study has recently demonstrated that renal size increases early during the course of disease and is a predictor of a decline in renal function¹⁶. CRISP has had a major impact on clinical trial design and most intervention studies currently underway are employing MRI assessments of renal volume as a surrogate endpoint of disease progression. Whether therapies that decrease renal size ultimately slow the inexorable progression to renal failure will likely be determined in the next several years.

We expect that the rapid pace of research in the PKD field will continue in the years to come as the research community continues to address the unique challenges of treating this disorder. ADPKD progresses slowly over decades and has a variable prognosis with a significant number of individuals exhibiting relatively mild disease. The side effect profile of any targeted therapy will need to be matched with the anticipated disease severity. Achieving this goal will require a refined understanding of the polycystin signaling nexus and how it interacts with modifier pathways. In addition, we anticipate that large clinical trials will bring new opportunities to identify genetic modifiers, disease biomarkers and genetic predictors of therapeutic response. Yes, the future is indeed promising for patients with ADPKD. Warp Speed Ahead!

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