

Polycystic Kidney Disease

Polycystic kidney disease, or PKD, is the fourth leading cause of kidney failure in the U.S.¹ Fluid-filled cysts form in the kidneys and other organs and can, as they grow over time, compromise kidney function. Patients with the disease typically have high blood pressure, urinary tract infections, and chronic pain. There is no primary treatment for PKD, and patients generally receive drugs to control their blood pressure and manage their pain. However, knowledge of the causes of PKD has increased dramatically in the past 20 years due to NIDDK-supported research. Scientists have a better understanding of the genetic causes of PKD, and are studying the use of new technologies to improve disease detection and monitoring. Because of the efforts of many dedicated scientists, there is hope for the future for people with PKD and their families.

What is Polycystic Kidney Disease?

Polycystic kidney disease (PKD) is a genetic disorder characterized by the growth of numerous fluid-filled cysts. These cysts develop primarily in the kidneys, but also can appear in organs such as the liver, pancreas, spleen, and thyroid. In the kidneys, these cysts can slowly replace much of the mass of the kidneys, reducing kidney function and leading to kidney failure. About half of people with the most common form of PKD progress to irreversible kidney failure, also called end-stage renal disease (ESRD). When this occurs, usually in the fifth or sixth decade of life, patients require either a kidney transplant or dialysis to survive. In the United States, an estimated 600,000 people have PKD, and it is the fourth leading cause of kidney failure. While there is no effective treatment for the underlying causes of PKD, patients are usually prescribed pain-relieving drugs, antibiotics to treat infections, as well as medications to control blood pressure that are aimed at preserving or slowing the decline in kidney function.

There are two major inherited forms of PKD, called autosomal dominant and autosomal recessive. Autosomal Dominant PKD, or ADPKD, accounts for about 90 percent of all cases. People with ADPKD usually develop symptoms between the ages of 30 and 40, but symptoms can appear earlier, even in childhood. The genetically recessive form of PKD, Autosomal Recessive PKD, or ARPKD, is a rare inherited form of the disease that displays symptoms in the earliest months of life, even in the womb.

Past Treatment for PKD

About 30 years ago, knowledge about the causes and progression of PKD was limited. The details of the genetics of the dominant form of PKD were unknown. Doctors knew that, on average, half of children born to an affected parent would develop the disease, and that it could be transmitted by either the mother or the father. The mechanism by which the disease caused cysts to form and grow in the kidneys was not known. Diagnosis of well-established disease in adults was relatively straightforward using the imaging techniques that were available at the time, such as ultrasound. However, diagnosis of earlier stages of disease in children and young adults was much more difficult. By the time most people were diagnosed, their kidneys were so damaged that kidney function had begun to decline.

Treatment options for people with chronic kidney disease in general, and ADPKD in particular, were also inadequate. No specific therapy was available. The importance of controlling blood pressure and dietary protein intake in patients with chronic kidney disease was not recognized. Two life-saving kidney function replacement therapies—hemodialysis and kidney transplantation—were developed through fundamental NIH research in the 1960s. Although they were increasingly available, neither was ideal.

STORY OF DISCOVERY

Genetic Underpinnings of PKD and Insights from Animal Models

The emergence of molecular biology and modern biotechnology in the late 1970s and early 1980s permitted researchers for the first time to examine in detail the genetic underpinnings of a number of diseases. Scientists have identified two genes associated with ADPKD. The first was found in 1985 on chromosome 16 and was named *PKD1*. The second gene, *PKD2*, was localized to chromosome 4 in 1993. Within 3 years, scientists had isolated the proteins these two genes produce—polycystin-1 and polycystin-2. Most cases of the dominant form of PKD can be traced back to mutations in one of these two genes. However, evidence suggests that the disease development also requires other factors. Normally, polycystin-1 and polycystin-2 form an ion channel on the surface of kidney cells. This channel regulates the flow of calcium into and out of the cell. Mutation of either gene inhibits the activity of the channel, thus disrupting calcium-dependent intracellular signaling pathways.

This ion channel is part of a complex of proteins located on the cell surface at the site where tiny, hair-like projections called cilia emerge from the cell into the renal tubule, where waste products are filtered into what will become urine. Under normal conditions, the cilia on the surface of these renal tubule cells detect changes in urine flow, and transmit this information inside the cell through the activation of various molecular signaling pathways. One signaling mechanism is the opening of the ion channel formed by polycystin-1 and -2. The opening allows calcium ions to enter the cell, setting off a cascade of signaling events. However, when one or both are mutated, the channel does not function properly. As a result, calcium does not enter the cell, and the metabolic response to changes in urine flow is disrupted. This abnormality in calcium signaling may result in cells that grow abnormally and retain fluid, ultimately giving rise to multiple, fluid-filled cysts characteristic of PKD.

Disruptions in cilia signaling have been found to underlie a number of diseases of the kidney, as well as other organs. Many genes encode proteins that localize to the cilia, and mutations in these genes often produce similar clinical manifestations. These observations have given rise to the hypothesis that many cystic kidney diseases may arise from defects in primary cilia signaling. Future efforts will be devoted to improved understanding of cilia signaling and identifying potential new therapeutic targets. Because cilia are found on the surface of almost all cells in the body, insights gained from these studies may also benefit people suffering from a number of diseases in which cilia signaling is impaired.

Researchers have also identified the gene associated with ARPKD, called *PKHD1*. The protein encoded by this gene, known as fibrocystin or polyductin, is present in fetal and adult kidney cells, and is also present at low levels in the liver and pancreas. Its precise biological function is unknown.

Current Clinical Management and Research Studies of PKD

Advances in knowledge about cyst formation and disease progression have been complemented by improvements in the early detection and treatment of the most common form of PKD. The NIDDK supports a number of clinical studies aimed at furthering our knowledge about the origins, progression, and optimal treatment of this disease.

The NIDDK-supported Consortium for Radiologic Imaging Studies of PKD (CRISP) was established to develop innovative imaging techniques and analyses to follow disease progression or to evaluate treatments for the common form of the disease. Importantly, the CRISP study demonstrated that magnetic resonance imaging (MRI) could accurately track structural changes in the kidneys, and that such methods may be able to predict functional changes earlier than standard blood and urine tests in people with the common form of PKD.

STORY OF DISCOVERY

The respective roles of *PKD1* and *PKD2* in disease progression, as indicated by ultrasound analysis, have remained unclear. The CRISP investigators, using a more sensitive MRI method, reported that patients with the *PKD1* gene have more cysts and significantly larger kidneys than those with the *PKD2* gene. Data from the CRISP study suggest that this difference results from earlier development of cysts, not from a faster growth of cysts, in patients with *PKD1* mutations. These clinically important results will inform the development of targeted therapies for patients with this form of the disease.

To expand and follow-up on the important insights gained in the CRISP study, the NIDDK has funded an extension, CRISP II, to continue to monitor this valuable cohort of patients. The extension will enable researchers to determine the extent to which changes in kidney volume do in fact predict changes in kidney function.

The NIDDK, with co-funding from the PKD Foundation, is also conducting two clinical trials of people with the most common form of PKD—one in patients with early kidney disease and another in patients with more advanced disease. These two trials are the largest multi-center studies of PKD conducted to date, and are collectively termed HALT-PKD. These studies are testing whether optimum blood pressure management, in combination with drugs—either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers—will slow the progression of this disease. The NIDDK is also funding an investigator-initiated interventional trial of optimum blood pressure therapy in children and young adults. These interventional studies are the first clinical trials to implement and formally validate the imaging surrogate marker of PKD progression that was developed by the CRISP study.

Hope for the Future

Investigators are continuing to pursue basic biologic studies of the causes of PKD, as well as new avenues for therapies, in the hope that diagnosis and treatment can be improved. As scientists' understanding of the genetics and progression increases, it is hoped that there will be a decrease in the number of patients with the disease who progress to ESRD. Because PKD can affect patients very differently, even within the same family, the NIH is assembling a large genetic sample collection for future investigations. Studies of these samples may help to identify genetic markers that might predict who will develop more rapidly progressive kidney disease. These genetic studies could also provide new information on identifying key disease pathways and aid in the design of new drug treatment strategies. The studies also could yield clues about how to intervene earlier, more precisely, and more effectively in these patients. Earlier intervention, more intensive management of high blood pressure, and use of drugs that target kidney fibrosis may delay progression to ESRD and give patients additional years of life without the need for dialysis or a kidney transplant. For patients who eventually do need dialysis, the NIH is conducting a trial to determine whether more frequent dialysis improves their quality of life.

Although there have been advances in the knowledge base about dialysis and improvements in technology, a functioning kidney transplant remains a patient's best hope of living a more normal life. However, normal life expectancy and health-related quality of life are rarely, if ever, restored by organ transplantation. Furthermore, despite the best immunosuppressive therapies, many patients with kidney transplants still lose their transplanted kidneys due to rejection of the transplant by the body's immune system. Better strategies to maintain the

STORY OF DISCOVERY

function of transplanted kidneys and prevent chronic scarring are likely to emerge from ongoing basic research and improved imaging methods. The NIDDK and NIH will continue to support research into kidney disease in general, and PKD in particular, working across Institutes and joining with other partners to better understand, monitor, and treat this disease.

¹ *U.S. Renal Data System, USRDS 2007 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2007.*