



## Polycystic Kidney Disease - A Review

Shabana Bowsiya\*

Saveetha Dental College and Hospitals, Saveetha University, Chennai, Tamilnadu, India.

\*Corresponding author's E-mail: [shabanafouziya97@yahoo.com](mailto:shabanafouziya97@yahoo.com)

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### ABSTRACT

Polycystic Kidney Disease (PKD) is the most common genetic disorder of the kidney characterised by the presence of fluid-filled cysts primarily in the kidneys. PKD is inherited as autosomal dominant (ADPKD) or as autosomal recessive (ARPKD) traits. Mutations are either in the PKD1 or PKD2 genes, which encode polycystin1 or polycystin2, are the underlying cause of the disease. ADPKD is characterized by renal cysts, haematuria and flank pain. ARPKD is characterised by cystic dilation of the renal collecting ducts and congenital hepatic fibrosis. Both the kidneys are enlarged because of multiple progressive cystic dilation of the renal tubules that, results to renal failure. External manifestation includes hypertension, kidney stones and urinary tract infection. The management of these patients includes the use of imaging and genetic diagnosis, management of hypertension, pain and cyst infections and bleeding, extra-renal involvement including polycystic liver disease and cranial aneurysms, management of chronic kidney disease and management of children with ADPKD. Several clinical trials are being performed and studied for the treatment of this life-threatening disease. This review presents a better understanding about PKD.

**Keywords:** ADPKD, ARPKD, Polycystin-1, Polycystin- 2, Cysts.

### INTRODUCTION

Polycystic kidney disease (PKD) is an inherited disorder characterised by the formation of multiple cysts on the surface of the kidneys resulting in kidney enlargements and renal insufficiency, in addition to external manifestations<sup>1</sup>. The kidneys are two organs, about the size of a fist situated in the upper abdomen, towards the back. The function of the kidney is to regulate the hydrogen ion and electrolyte concentration. When cysts form in the kidneys, they are filled with fluid. The cysts enlarge the kidneys while replacing much of the normal structure. The progressive enlargement of the cysts compromise the normal parenchyma, often leading to renal failure.

The most common types of inheritance for PKD are autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD). ADPKD and ARPKD are caused by mutations in two different genes, but both the diseases results in the formation of multiple cysts in the kidneys. Hence, the name Polycystic Kidney Disease. ADPKD is caused by mutations in one of the two genes i.e., PKD1 or PKD2. The disease is largely related to the kidney. ARPKD is caused by the mutations in PKDH1. The manifestation of ARPKD is related to the kidney and liver. ADPKD is most common inherited form. The symptoms of the disease usually develop between the ages of 30-40 years, but they can also begin earlier, even in childhood.

PKD can also cause cysts and problems in other organs as well, such as liver, blood vessels in the brain and heart. The number of cysts and the complication involved helps to distinguish PKD from the usual simple harmless cysts formed in the kidney.

### Autosomal Dominant Polycystic Kidney Disease

ADPKD is most common inherited form. The disease occurs in approximately 1:400-1000 people<sup>2</sup>. Patients with ADPKD live for several decades without developing symptoms. For this reason, ADPKD is often called "adult polycystic kidney disease". The most common manifestation of ADPKD is hypertension, which has been found to be present in as many as 60% of patients before the impairment of renal function<sup>3</sup>. The disease is characterised by the progressive, bilateral, development and enlargement of focal cysts that in many cases ultimately results in end-stage renal disease (ESRD).ADPKD is a systemic disease, with cysts occurring in the liver, pancreas, seminal vesicles and arachnoid. Other notable phenotype in ADPKD involve vasculature, with intracranial aneurysms approximately five times more common than in general population<sup>4</sup>.



**Figure 1** Kidney from a patient with end-stage ADPKD showing multiple cysts<sup>3</sup>.

## Molecular basis

ADPKD is caused by mutations in one of the two genes (PKD1 and PKD2) expressing the interacting protein polycystin-1(PC-1) and polycystin-2(PC-2). Mutations in PKD1 accounts for approximately 85% cases in clinically identified patients. The PKD1 protein, polycystin-1, is a large (4303 amino acids) integral membrane protein with 11 transmembrane domains and an extra cellular region consisting of a variety of domains, including 12PKD domains (an immunoglobulin-like fold), which in other proteins are associated with protein-protein and protein-carbohydrate interactions<sup>5</sup>. Polycystin-1 has a structure of a receptor molecule. Polycystin-2 is a non selective cation channel that transports calcium<sup>6</sup>. The polycystins form a distinct sub-family of transient receptor potential (TRP) channels. Polycystin-2 shows homology with the final six-transmembrane region of polycystin-1. Polycystin-1 is cleaved at the G protein-coupled receptor proteolytic site (GSP) domain, which may be important to activate the protein<sup>7</sup>. Polycystin-2 regulates proliferation and differentiation by controlling progression through the cell cycle<sup>8</sup>.

## Clinical Presentation of ADPKD

Majority of patients with ADPKD have few or no symptoms at the time of diagnosis. The symptoms begin to appear at the age of 30-50 years. The most common symptoms are flank pain and or acute abdominal pain<sup>9</sup>. The most common clinical manifestation is hypertension, which has been found to be present in at least 60% of all patients before the impairment of renal function, and nearly all patients by the time they progress to ESRD<sup>10</sup>. Other signs and symptoms include palpable kidneys, microscopic or gross haematuria, recurrent urinary tract infections, lower back discomfort, shortness of breath and satiety<sup>11</sup>.

The most common external manifestation of the disease includes development of hepatic, pancreatic, thyroid, subarachnoid and seminal vesicle cysts. The most common lethal manifestation of ADPKD is intracranial aneurysms. These aneurysms can rupture, causing intracranial haemorrhage. Additional vascular findings in ADPKD include cardiac valvular disease, and less commonly, thoracic, iliac and abdominal aortic aneurysms, coronary artery aneurysms, intracranial arterial dissection, intracranial arterial dolichoectasia and megadolichobasilar artery<sup>12</sup>. Formation of renal calculus should be suspected in any ADPKD patient with an acute onset of pain, haematuria, or deteriorating kidney function.

## Diagnosis of ADPKD

ADPKD can be diagnosed by imaging of the kidney by ultrasound, CT or MRI which shows multiple cysts generally visible that increase in size and number with age. The most common method followed for the diagnosis of ADPKD is computerised tomography (CT). In autosomal dominant PKD, the onset of kidney damage

and how quickly the disease progresses can vary. Hence, the findings can also vary depending on the patient's age.

Diagnosis can also be done based on the mutation in the dominant genes PKD1 and PKD2. This test is not commonly performed; however, the ability to detect definitive mutations is only 41%-63%<sup>13</sup>.

## Treatment

No specific treatment exists for PKD, and management of patients with PKD consists of supportive measures, such as analgesics for pain, antibiotics for cyst infections, blood pressure control and avoidance of caffeine and oestrogen. Several promising investigational drugs such as the use of ACE inhibitors have been shown to increase the renal blood flow and proteinuria in ADPKD patients<sup>14</sup>.

Urinary tract infections should be treated with suitable antibiotics. Patients suffering from urinary tract infections must seek treatment immediately because the infection can spread to the cysts in the kidney. Cyst infections are difficult to treat because most antibiotics cannot penetrate the cysts.

Dialysis is a common method adopted for renal replacement treatment. This involves both haemodialysis as well as peritoneal dialysis<sup>15</sup>. Increase in the abdominal pressure can make peritoneal dialysis more difficult. Studies shows that haemodialysis is an effective and safe means of renal replacement in ADPKD patients, with a 5-year survival 10%-15% higher than non-ADPKD controls. Haemodialysis is more likely to decrease cardiac mortality in patients with ADPKD<sup>16</sup>.

## Autosomal Recessive Polycystic Kidney Disease

ARPKD is the most common heritable diseases manifested during infancy and childhood. The incidence of the disease is 1: 20,000 births with a frequency of carriers of the responsible gene in a general population of 1:70<sup>17</sup>.

ARPKD has been categorised into 4 distinct subgroups - perinatal, neonatal, infantile and juvenile forms.

The most severe involvement occurs in **perinatal** form. In these patients the disease is diagnosed at the time of delivery. The characteristics of the perinatal form of ARPKD are the presence of extremely large kidneys with severe respiratory and renal problems. All infants die within the 1st week of infancy. Microscopically, approximately 90% of the ducts are affected. The **neonatal** form has slightly milder characteristics. It is present in the 1st month of life. 60% of the ducts are impacted. The **infantile** form represents the age of 3-6 months and is characterised by both portal hypertension and renal failure. 25% of the ducts are affected. In the **juvenile** form, the patients have renal impairment along with portal hypertension between the ages of 6 months - 5 years. Approximately, 10% of the ducts are affected<sup>18</sup>.





**Figure 2** Both kidneys occupied whole kidney<sup>18</sup>.

### Molecular basis

ARPKD is caused by mutations in PKHD1 (Polycystic kidney and hepatic disease 1). It exhibits 303 mutations. Among these, approximately, 40% of the mutations are predicted to be truncating and 60% are missense. The relation between ARPKD genotypes and phenotypes are limited, but studies show that genotypes consisting of two truncating mutations to be lethal, and those with at least one missense mutations to be compatible with life, through production of a practically-functioning protein product<sup>19</sup>.

Fibrocystin, the PKHD1 protein, has 4047 amino acids and is attached to the membrane via a single transmembrane domain<sup>20</sup>. The function of fibrocystin is so far unknown.

### Clinical presentation of ARPKD

ARPKD presents bilaterally but the kidney pathology depends on the disease severity. The major clinical presentation in ARPKD is congenital hepatic fibrosis. The liver disease consists of portal fibrosis and biliary dysgenesis which increases in severity with age.

### Diagnosis of ARPKD

Ultrasonography of ARPKD reveals large and echogenic kidney and oligohydramnios. The majority of severely affected neonates die of respiratory hypoplasia. Other complications include respiratory distress, retardation of growth, electrolytic imbalance, manifestation of the liver and acute and chronic renal insufficiency<sup>21</sup>.

### Treatment

Medicines can be used for controlling hypertension in ARPKD and antibiotics to control infections. Respiratory problems may require mechanical ventilation<sup>22</sup>. Electrolytic imbalance requires change in water and sodium intake<sup>23</sup>. Renal transplantation can be adopted for ESRD.

### CONCLUSION

PKD is a life-threatening disease. The incidence of ADPKD is 10 times that of sickle cell diseases and 15 times that of cystic fibrosis<sup>14</sup>. Studies are now focused on the molecular and genetic basis of the disease. Several therapeutic

targets are now being tested in preclinical and clinical trials. Understanding that pathophysiology of the disease is the best hope for developing rational therapies in the future.

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