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Review Article

## Diagnosis and Treatment Status and Progress of Autosomal Dominant Polycystic Kidney Disease - ③

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## ABSTRACT

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common inherited kidney disease in the clinic. The incidence of ADPKD is approximately 1/2500 according to the report of latest European study, and almost 10% of the disease patient eventually requires Renal Replacement Therapy (RRT). Bilateral and progressive cyst formation in the kidneys, impaired renal parenchyma and End-Stage Renal Disease (ESRD) are the main clinical manifestation. Although ADPKD predominately affects the kidney, cystic phenotypes or disease lesions also can be seen in other organs and tissues, including the cystic liver, cardiovascular defects and brain aneurysm. ADPKD is a heterogenic disease which is resulted from the mutations of *PKD1* and *PKD2* genes. Although both disease causal genes have been identified and cloned for decades, lack of effective and less side-effect treatment still challenge vast clinicians. This review will center on current advances of ADPKD treatment in which several potential therapies for delaying or halting the disease progression have been discussed. These recent achievements of translational researches will bring hope to cure the disease in the clinic.

**Keywords:** ADPKD; Molecular diagnosis; Surgical options; Drug therapy

## INTRODUCTION

The human Polycystic Kidney Diseases (PKD) are common genetic renal disorders that follow either dominant or recessive inheritance [1,2]. ADPKD is characterized by numerous progressive, bilateral, fluid-filled cysts in the kidneys and other duct/tubule-contained organs [3,4]. ADPKD usually appears in adulthood with an incidence of 1:400-1000, and is the fourth most common single cause of end-stage renal failure worldwide [5]. Extra-renal manifestations are often prominent in individuals with ADPKD. Liver cysts occur in 83% of ADPKD patients overall, and in 94% of those older than 35 years of age [6]. 16% of patients suffer from cerebral aneurysms [7,8]. Other phenotypes include aortic root and thoracic aorta abnormalities [9], mitral valve prolapsed [10,11], and abdominal wall hernias [12,13].

ADPKD results from mutations in either *PKD1* or *PKD2*, two identified causal genes. Approximately 85% of ADPKD patients have mutations in *PKD1*. The remaining 15% of ADPKD patients have mutations in *PKD2*. ESRD in patients with *PKD1* mutations occurs 10 years earlier than patients with *PKD2* mutations [14].

*PKD1* encodes a 14-kb transcript containing 46 exons and lies in a ~53-kb genomic region on chromosome 16p13.3 [15]. The *PKD1* gene product, polycystin-1 (PC1), is a 4302-amino acid integral membrane protein, widely expressed in all tissues and organs, with a predicted molecular mass of ~462 kDa and 11 putative transmembrane domains. The N-terminal region contains an extracellular portion of > 3000 amino acids, and sequentially includes leucine-rich repeats, a C-type lectin domain, an LDL-A-like domain, multiple Ig-like PKD domains, a receptor for sea urchin egg jelly (suREJ) homology domain, and a G Protein-Coupled Receptor Proteolytic Site (GPS). This N-terminal region is predicted to serve as a site of protein-protein or receptor-ligand interactions [2,16], and may also be considered as a ligand for other proteins through cleavage at the GSP site [17]. The cytoplasmic C-terminal region of PC1 contains a putative coiled-coil domain that interacts with the *PKD2* gene product, Polycystin-2 (PC2) [18].

*PKD2* gene spans 68 kb in genome and localized at chromosome 4q21. It also encodes a 968-amino-acids integral membrane protein, named Polycystin-2 (PC2) [19]. *PKD2* spans the membrane six times with intracellular amino- and carboxyl-termini. The carboxyl-terminal domain also contains a coiled-coil motif, and an EF hand domain which can bind calcium. PC2 is therefore deemed to be a nonselective cation channel that transports calcium. Because PC2 has the similar amino acids and shares structural features with Transient Receptor Potential (TRP) channels as well as voltage-activated calcium and sodium channels, it is thought to be a member of TRP family [20,21].

Previous studies reported that PC1 physically interacted with PC2 in primary cilium of the epithelial cells [22] and demonstrated that the PC1 and PC2 can form a molecular complex through the coiled-coil domain in the C-termini of both protein [18,23,24]. These results suggest that the extracellular domain of PC1 could be the receptor, whereas its intracellularly cytoplasmic domain can interact with PC2 to form TRP channel complex [25,26]. Loss of polycystins dysregulates multiple cell signaling pathways [27] and therefore lead to aberrant ionic transportation, polarity, and proliferation/apoptosis in renal epithelia, and eventually cause renal cyst formation.

### Clinical features of ADPKD

The main manifestation of ADPKD is the formation of multiple renal cysts in both kidneys eventually leading to renal failure. Besides renal phenotypes, complications of ADPKD includes liver and pancreatic cysts, dilatation of the bile duct and the pancreatic duct, mitral valve prolapse of the heart [11,28], intracranial aneurysms [29], aortic and other aneurysms [30], abdominal wall hernias [12,13] and other systemic pathological changes. In ADPKD patients, significant cyst burden occurs after age 30 and as the lesion progresses, renal parenchyma decreases and more than half of patients develop end-stage renal disease at the age of 60 [31]. The high risk factors that affects the progression ESRD include *PKD1* mutation [31], bigger Total Kidney Volume (TKV) [32], younger diagnosed age, early onset of hypertension [33], proteinuria and microalbuminuria [34,35]. Disease progression is much faster with *PKD1*, and end-stage renal disease usually occurs before age 56. The disease course of *PKD2* tends to be slower. End-stage renal disease might not develop in the patient's lifetime, since it typically develops when the patient is more than 70 years old [36]. Although the growth rate of renal cysts is similar between the two types, patients with *PKD1* develop about twice as many cysts as those with *PKD2*, and their cyst development starts at a younger age [31]. Previous studies have showed hypertension, the major complication, occur before the significant decline in renal function in patients with ADPKD. The average onset age is about 30 years of age [37]. There is no obvious symptoms and rarely cause liver failure in ADPKD-associated hepatic cysts [38]. The prevalence of intracranial aneurysms among ADPKD patients is about 8%. This prevalence rises to 16% if patients have family history of intracranial hemorrhage [39]. Therefore, Inspection of other disease affected organs is as important as kidney.

### Clinical diagnosis and screening of ADPKD

Diagnosis of ADPKD includes family history, imaging studies and gene expression analysis. Although more than 90% of ADPKD patients have positive family history, some patients are still at risk



of a new mutation [40]. Hence, no family history is not sufficient to completely be exclude the diagnosis of the disease. At present, ultrasound, CT, MRI and other imaging studies are still the main method of diagnosis of PKD, of which ultrasound is the most preferred method for patients due to its safety, effectiveness, widely use, and low cost [41]. Ravine, et al. [42] firstly proposed the diagnostic criteria for ADPKD ultrasound. However, because patients with *PKD2* mutation exhibit less disease severity that patients harbor *PKD1* mutation, false-negative results more likely appear when using this standard. Therefore, some scholars established the screening criteria for ADPKD patients with a family history but mutation is unknown [41,42].

However, compared to MRI and ultrasound, CT had an advantage on identification of kidney cancer, hydronephrosis and other disease. In addition, MRI is the best way to measure the kidney volume that can be used to monitor the progression of the disease before renal impairment occurs [32]. Moreover, the identification of diagnostic markers of ADPKD is also on going. Kawano et al demonstrated that neutrophil gelatinase-related Lipocalin (NGAL), macrophage colony-stimulating factor (M-CSF) and monocyte chemoattractant protein-1 (MCP-1) may be potential diagnostic markers for ADPKD based on their study on urine of ADPKD patients and DBA/2FG-pcy mouse models. These findings will provide new method for noninvasive diagnosis and follow-up of prognosis for ADPKD.

### Molecular diagnosis of ADPKD

ADPKD results from mutations in genes, *PKD1* (16p13.3) and *PKD2* (4q22) [43]. *PKD1* gene is about 50 kb in length and has 46 exons. Its transcript contains an open reading frame of up to 12909 bp. However, there are six *PKD1* pseudogenes at the same position on chromosome 16 where *PKD1* is located, which is highly consistent with the sequence from 5'UTR to exon 33. Due to this high similarity, the detection of *PKD1* mutations is much more difficult. *PKD2* gene is relatively simple. It contains 68 kb in size, with 15 exons and 2904 bp open reading frame of its transcripts. Genetic linkage analysis in European ADPKD pedigrees indicated that mutations in *PKD2* account for about 15% of ADPKD [40], while a Canadian study showed a slightly higher *PKD2* mutation ratio of 26% [36]. According to the latest ADPKD mutation database (PKDB), a total of 2323 *PKD1* mutations were identified in 2,080 families, while a total of 278 *PKD2* mutations were found in 463 families [44]. A regional study of China showed that 42 out of 44 familial patients were *PKD1* mutations (95%), whereas only 2 familial patients were *PKD2* mutation (5%) [45]. In these ADPKD mutations, most of mutation were truncated mutation (70%), non-truncated mutations such as missense mutation accounted for 25%, and some individuals had in-frame deletions or atypical splicing mutations [40].

In the past, due to the high cost of genetic testing and the difficulty in detecting *PKD1* mutations in the presence of multiple *PKD1* pseudogenes, molecular detection of genes was not routinely used as a diagnostic method for ADPKD. However, with the progress of science and technology and the updating of equipment, genetic testing has become very common in clinic [46]. Because genotypes are closely associated with the age at which end-stage renal disease occurs, genetic testing is of great value in prognostic evaluation [47]. Therefore, it is now considered that the molecular diagnosis obtained from genetic testing will have an irreplaceable effect on the prognosis and the characteristics of the disease in ADPKD patients. Clinically genetic testing must be applied to the following populations: Kidney

transplant donors with a normal phenotype from the polycystic kidney family [48], neonates with very early onset of disease [49], and atypical patients, especially those ADPKD patients with no family history. In recent years, with the advent of third-generation sequencing technology, overcoming the difficulty of detecting complex genes such as pseudogenes, the high efficiency and low cost of genetic testing will make this detection a routine method for the diagnosis of ADPKD in the future.

## NON-DRUG THERAPY OF ADPKD

### Palliative treatment

Renal cyst decortication has the exact effect of treating ADPKD-induced pain [50] and laparoscopic surgery is the current recommendation. When accompanied by infection in cyst infection, decortication and focal lesions removal also exhibit good effect. Retroperitoneal laparoscopic renal cyst decortication take more advantages to avoid the occurrence of abdominal infection [51]. One group found that treatment of ADPKD by renal cyst decortication with pedicled omental packing not only significantly relieve pain, but also play a role in absorption of cystic fluid and reducing the size of the kidney as well as preventing infection [52]. However, these renal cyst decortications do not actually improve renal function in patients with ADPKD, and surgery may increase the risk of postoperative renal impairment, even when the patient with poor renal function. Therefore, surgical indications of these renal cyst decortications as palliative treatment should be carefully handled.

### Nephrectomy of ADPKD

Surgical indications for ADPKD nephrectomy include pain, persistent hematuria, recurrent infections, malignant lesions, gastrointestinal symptoms and respiratory compression, as well as providing room for kidney transplantation [53,54]. Recent studies have shown that approximately 20% of patients undergoing kidney transplantation need unilateral or bilateral polycystic nephrectomy [53]. Main nephrectomy of ADPKD is laparoscopic surgery and open surgery. Laparoscopic surgery has advantages such as shorter length of hospital stay, reduced mortality, and faster recovery than open surgery. However, it should be noted that laparoscopic kidney volume was significantly smaller than the open group [55]. Laparoscopic surgery is a preferred option when technical conditions are appropriate and the subject is well chosen [56].

### Kidney transplantation of ADPKD

Prior to the advent of drugs that would safely and effectively prevent the progression of the disease, the end result of ADPKD was end-stage renal disease requiring Renal Replacement Therapy (RRT). Kidney transplantation is the best RRT method for patients with ADPKD [57,58]. Transplantation of living kidney sources is associated with a better prognosis after surgery [59]. Preoperative assessment of renal transplant recipients in ADPKD focuses on whether or not to have their polycystic kidney resection, polycystic liver disease, intracranial aneurysm examination and relative donor kidney screening. Due to the limited number of donors, peritoneal dialysis and hemodialysis are also the options of RRT. Previous studies have shown that ADPKD patients undergoing peritoneal dialysis have a better prognosis than ESRD patients caused by other causes [60]. However, owing to the large size of the kidneys and liver, the lack of peritoneal exchange and numerous complications in some patients with advanced ADPKD, the usage of peritoneal dialysis

is limited, making hemodialysis a more common and appropriate approach [61].

## CLINICAL DRUG TREATMENT OF ADPKD

The aim of drug treatment of ADPKD is to delay cystogenesis and rescue kidney function. According to increasing understanding of pathogenesis and the large number of preclinical animal trials results [4,62-67], some drugs that have potential effects on ADPKD continue to emerge and show promise for the treatment of ADPKD. At present, main drugs that completed the Randomized Controlled Trials (RCTs) used in the clinical trials of ADPKD include vasopressin V2 receptor antagonist (tolvaptan), mTOR inhibitor (sirolimus and everolimus), somatostatin analogues (octreotide, lanreotide, pasireotide). However, some of them in clinical trials, these promising drugs including mTOR inhibitors [68,69], somatostatin analogues [70,71] and ACEI/ARB [72,73], did not prevent the decline of eGFR in the ADPKD patients. Only tolvaptan, a vasopressin V2 receptor inhibitor, currently show to both reduce the formation of renal cysts and improve renal function [74,75], but the impairment of liver function and other side effects have been challenged to be widely used in clinic [76,77]. Thus, there is still an urgent need for new drugs that can suppress cystogenesis in ADPKD patients.

### Perspective of ADPKD treatment

Currently, usage of conventional surgical treatment of ADPKD patients can only be achieved for the purpose of symptomatic treatment. It cannot delay the progression of the disease to end-stage renal disease. Most of ADPKD patients eventually need the implementation of alternative renal treatment. Kidney transplantation cannot be widely used in ADPKD patients due to the nature of ADPKD genetic disease, lack of donors from relatives and higher post-transplant mortality and costs. Therefore, the drug treatment for ADPKD is highly desired. With the in-depth study of the pathogenesis of ADPKD, more drugs targeting to different molecular pathways continue to emerge. However, these potential

**Table 1:** Ultrasound screening criteria for ADPKD patients (with a family history but mutation is unknown).

Age (Years)	Cyst Number
15-39	Unilateral or bilateral, total number $\geq 3$
40-59	Bilateral and each kidney $\geq 2$
$\geq 60$	Bilateral and each kidney $\geq 4$
$\geq 40$	Total number $\leq 2$ ( non-ADPKD)

drugs did not achieved the desired clinical effects after clinical trials. To this end, clinicians have to try to seek for new drugs and therapy with low toxicity and high efficiency for ADPKD patients.

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