



# POLYCYSTIC KIDNEY DISEASE

<sup>1</sup>AKHIL.S, <sup>2</sup> SOUMYA R.V, <sup>3</sup> GRACE N RAJU, <sup>4</sup>PRASOBH G.R,

<sup>1</sup>5th Year Doctor of Pharmacy Student, Sree Krishna College of Pharmacy and Research Centre, Parassala, Trivandrum, Kerala

<sup>2</sup>Associate Professor, Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre, Parassala, Trivandrum, Kerala

<sup>3</sup>Assistant Professor, Department of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre, Parassala, Trivandrum, Kerala

<sup>4</sup>Principal, Sree Krishna College of Pharmacy and Research Centre, Parassala, Trivandrum, Kerala

## ABSTRACT

Polycystic kidney disease (PKD) is an inherited disorder in which clusters of cysts develop primarily within the kidneys, causing the kidneys to enlarge and lose function over time. A gene mutation, or defect, causes PKD. Autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) is cilia-related disorders and the two main forms of monogenic cystic kidney diseases. Clusters of fluid-filled sacs called cysts develop in the kidneys and interfere with their ability to filter waste products from the blood. The growth of cysts causes the kidneys to become enlarged and can lead to kidney failure. PKD is caused as the result of primary cilium formation. PKD is usually diagnosed by ultrasound of the kidneys, CT scans, and MRI tests. Tolvaptan is a medication that treats ADPKD in adults. The sclerosing agents are used to shrink kidney cysts. Dialysis and kidney transplantation are the other two treatment options for PKD.

**KEYWORDS:** Autosomal dominant, Autosomal recessive, polycystic kidney disease

## INTRODUCTION

Polycystic kidney disease is a multisystem and progressive disease in which cysts (watery-filled sacs) are formed and kidney enlargement along with other organ involvement like the liver, spleen, and pancreas.<sup>1</sup>As the kidney loses the ability to filter waste products from the blood thus leading to kidney failure. PKD is caused as the result of primary cilium formation. [2] Cysts are commonly noncancerous round sacs containing fluid. The cysts vary in size, and they can grow very large. A gene mutation or defect will cause PKD. In most PKD cases, a child got the gene mutation from a parent.<sup>1</sup> In a very small number of PKD

cases, the gene mutation developed on its own, without either parent carrying a copy of the mutated gene.<sup>4</sup> Autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD) is cilia-related disorders and the two main forms of monogenic cystic kidney diseases. ADPKD is a common disease that mostly presents in adults, whereas ARPKD is a rarer and often more severe form of polycystic kidney disease (PKD) that usually presents perinatally or in early childhood. Genetic mutations in one of two genes, PKD1 or PKD2, account for most ADPKD cases.<sup>4</sup> The PKD1 gene is located on chromosome 16p13.3, and the PKD2 gene is located on chromosome 4q21. Polycystin 1 may regulate tubular epithelial cell adhesion and differentiation; polycystin 2 may function as an ion channel, with mutations causing fluid secretion into cysts Children affected by ADPKD are born with the condition, and it rarely causes any noticeable problems until the cysts grow large enough to affect the kidneys' functions.<sup>4</sup> ARPKD is often known as "infantile PKD" because signs and symptoms appear early in life, shortly after birth, or later in childhood. ARPKD is caused by a genetic alteration in the gene PKHD1, which in most cases is passed on to a child by their parents.

## ETIOLOGY

PKD is an autosomal disease so it is found in male and females equally. The acquired polycystic disease occurs in the setting of chronic, progressive renal scarring due to diabetes mellitus, chronic glomerulonephritis, or other renal disorders that lead to azotemia. Acquired cystic kidney disease (ACKD) is seen most commonly in patients undergoing dialysis (>75,000 cases) and it is discovered incidentally in most instances.<sup>8</sup>

ADPKD is an autosomal dominant disease that involves at least two genes. PKD1 accounts for most ADPKD cases and is located on 16p13.3. PKD2 accounts for 15% of ADPKD cases.

PKD1 codes for polycystin 1, a 4304 amino acid protein. Polycystin 1 interacts with polycystin 2 and is involved in cell cycle regulation and intracellular calcium transport. PKD2 codes for polycystin two, which is structurally similar to polycystin 1. It is a member of the family of voltage-activated calcium channels.

Polycystins 1 and two are located in the epithelial cells of the renal tubules and other areas of the renal cell epithelium. Both forms of heteromeric complexes are found in the primary cilium of epithelial cells in the kidneys. The primary cilium is considered a mechanical receptor that can sense changes in tubular fluid flow, and that can transduce them into intracellular calcium signaling. ADPKD1 is more severe than ADPKD2.<sup>4</sup>

ARPKD is an autosomal recessive disease caused by a DNA mutation in a gene called PKHD1, which produces a protein called fibrocystin that gives the kidney its structure. The faulty PKHD1 gene is responsible for small fluid-filled sacs and scarring developing in the kidneys.<sup>8</sup>

## CAUSES

Abnormal genes cause polycystic kidney disease, which means that in most cases, the disease runs in families. Sometimes, a genetic mutation occurs on its own (spontaneous), so that neither parent has a copy of the mutated gene.<sup>7</sup>

The two main types of polycystic kidney disease, caused by different genetic flaws, are:

(a)Autosomal dominant polycystic kidney disease (ADPKD). Signs and symptoms of ADPKD often develop between the ages of 30 and 40. In the past, this type was called adult polycystic kidney disease, but children can develop the disorder.

Only one parent needs to have the disease for it to pass to the children. If one parent has ADPKD, each child has a 50% chance of getting the disease. This form accounts for most of the cases of polycystic kidney disease.

(b)Autosomal recessive polycystic kidney disease (ARPKD). This type is far less common than ADPKD. The signs and symptoms often appear shortly after birth. Sometimes, symptoms don't appear until later in childhood or during adolescence.

Both parents must have abnormal genes to pass on this form of the disease. If both parents carry a gene for this disorder, each child has a 25% chance of getting the disease.<sup>7</sup>

## COMPLICATIONS

Complications associated with polycystic kidney disease include:<sup>8</sup>

**High blood pressure:** Elevated blood pressure is a common complication of polycystic kidney disease. Untreated, high blood pressure can cause further damage to your kidneys and increase your risk of heart disease and strokes.

**Loss of kidney function:** Progressive loss of kidney function is one of the most serious complications of polycystic kidney disease. Nearly half of those with the disease have kidney failure by age 60.

PKD can interfere with the ability of your kidneys to keep wastes from building to toxic levels, a condition called uremia. As the disease worsens, end-stage kidney (renal) disease may result, necessitating ongoing kidney dialysis or a transplant to prolong your life.

**Chronic pain:** Pain is a common symptom for people with polycystic kidney disease. It often occurs in your side or back. The pain can also be associated with a urinary tract infection, a kidney stone, or a malignancy.

**Growth of cysts in the liver:** The likelihood of developing liver cysts for someone with polycystic kidney disease increases with age. While both men and women develop cysts, women often develop larger cysts. Female hormones and multiple pregnancies might contribute to liver cyst development.

**Development of an aneurysm in the brain:** A balloon-like bulge in a blood vessel (aneurysm) in your brain can cause bleeding (hemorrhage) if it ruptures. People with polycystic kidney disease have a higher risk of aneurysms. People with a family history of aneurysms seem to be at the highest risk. Ask your doctor if screening is needed in your case. If screening reveals that you don't have an aneurysm, your doctor may

recommend repeating the screening exam in a few years or after several years as a follow-up. The timing of repeat screening depends on your risk.

**Pregnancy complications:** Pregnancy is successful for most women with polycystic kidney disease. In some cases, however, women may develop a life-threatening disorder called preeclampsia. Those most at risk have high blood pressure or a decline in kidney function before they become pregnant.

**Heart valve abnormalities:** As many as 1 in 4 adults with polycystic kidney disease develops mitral valve prolapse. When this happens, the heart valve no longer closes properly, which allows blood to leak backward.

**Colon problems:** Weaknesses and pouches or sacs in the wall of the colon (diverticulosis) may develop in people with polycystic kidney disease.

## **PATHOPHYSIOLOGY**

### **Autosomal Dominant Polycystic Kidney Disease (ADPKD)**

The disease is inherited in an autosomal dominant manner, affected family members have a 50% risk of recurrence. With an incidence of 1:400 to 1:1000 people, it is one of the most common genetic disorders. However, the disease rarely develops before middle age. It begins in middle-aged to elderly people to cause progressive renal failure as the cysts to enlarge and decrease the amount of functioning renal parenchyma.<sup>4</sup>

This form of the cystic disease rarely presents before birth or in childhood. ADPKD is associated with defects in the PKD1 gene, which encodes polycystin-1, and the PKD2 gene, which encodes polycystin-2. The former is more common. Polycystin acts at Ca<sup>2+</sup> channels and disruption of normal intracellular Ca<sup>2+</sup> homeostasis may underlie cyst formation. There are many alleles that explain differences in ADPKD onset and severity.<sup>11</sup>

Broadly speaking, ADPKD results in very large kidneys, perhaps 3 or 4 kg or more. The affected kidney is a large, fluid-filled cystic mass. Bleeding into cysts is common, so some may be filled with sullen brown organized hemorrhages, intervening normal renal parenchyma early in the disease or late in the course. There may be an intervening fibrous stroma at a later stage. When ADPKD appears in a fetus or infant, cysts may affect the glomeruli (called "glomerular cysts").<sup>18</sup>

In adults, the polycystic disease often affects all or part of the liver, and in some cases the liver can be more severely affected, leading to liver failure. Patients with ADPKD are also prone to Berry aneurysms of the cerebral arteries.

## Autosomal Recessive Polycystic Kidney Disease (ARPKD)

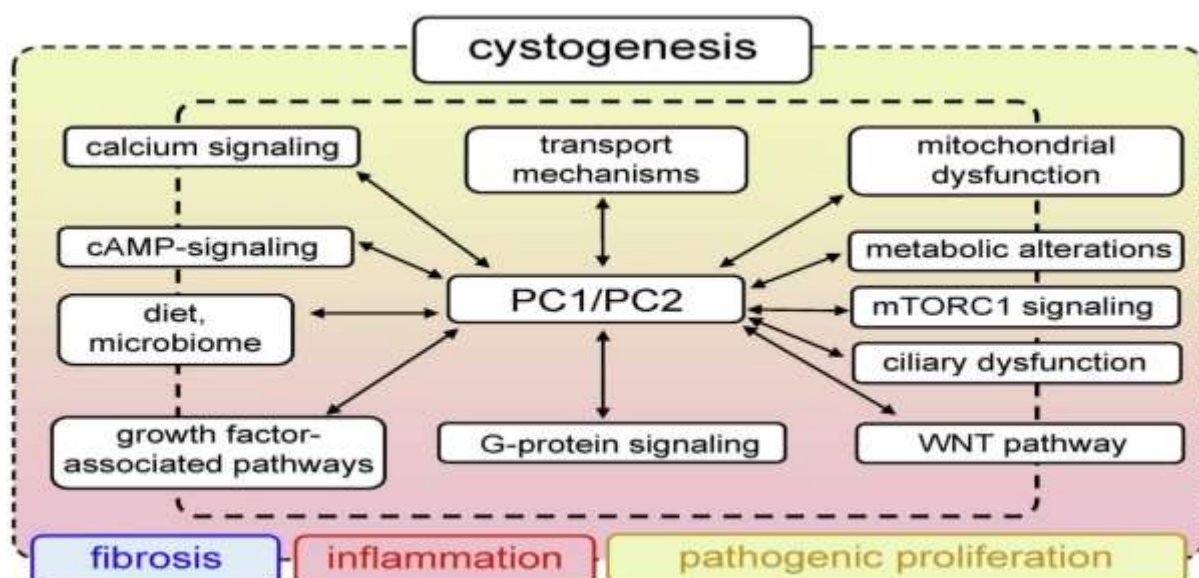
This is the condition inherited in an autosomal recessive pattern, giving a 25% recurrence risk for parents having subsequent children. The kidneys are affected bilaterally so that in utero, there is typically oligohydramnios because of poor renal function and failure to form significant amounts of fetal urine. The most significant result from oligohydramnios is pulmonary hypoplasia so newborns do not have the sufficient lung capacity to survive, irrespective of any attempt to treat renal failure.<sup>30</sup>

Grossly, the kidneys are markedly enlarged and tend to fill the retroperitoneum and displace abdominal contents. The kidneys tend to be symmetrically enlarged. The cysts are quite small and uniform, perhaps 1 to 2 mm on average.<sup>30</sup> Microscopically, the characteristic finding in the later third trimester is cystic change with the cysts elongated and radially arranged. The few remaining glomeruli are not involved by the cysts, and the intervening parenchyma is not increased. In the second trimester, the cysts may not be as well-developed.<sup>18</sup>

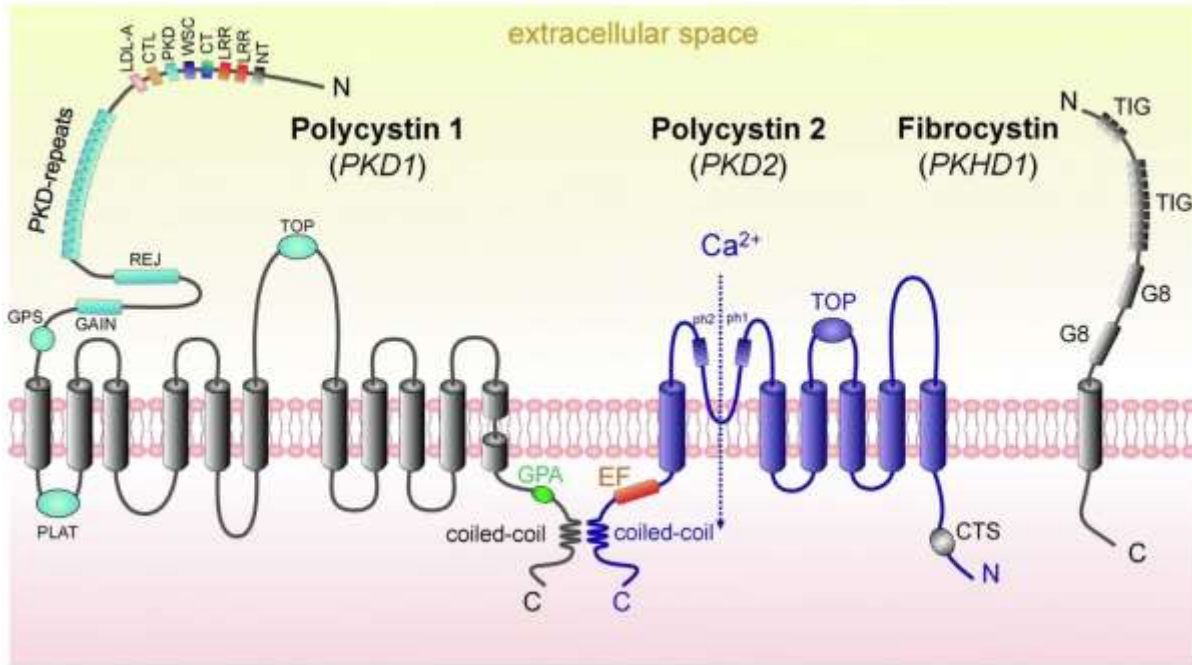
ARPKD results from mutations in the PKHD1 gene that encodes for a membrane-associated receptor-like protein called fibrocystin. This protein is involved in ciliary signaling required for the regulation of proliferation and differentiation of renal and biliary tract epithelial cells.[13] Abnormalities lead to dilation of renal collecting ducts. In the liver, there is an expansion of portal tracts from ductal plate malformation with increased numbers of dilated bile ductules in expanded fibrous connective tissue, called congenital hepatic fibrosis.<sup>19</sup>

In cases of ARPKD where a fibrocystin gene mutation leads to less severe defects, then enough renal function can be present for survival.<sup>20</sup> In those cases, over time, the hepatic abnormalities become more prominent. There is more fibrosis, and dilation of bile ducts may become apparent with imaging studies. Into adulthood, even some macroscopic hepatic cysts are possible, but by then fibrosis is the most prominent component<sup>27</sup>

**FIGURE 1.** Generalized pathways involved in PKD development. Mutations in PKD1/PKD2 lead to aberrant functionality of a variety of interconnected signaling pathways, which can result in abnormal proliferation, fibrosis, and inflammation that accompany cystogenesis.<sup>1</sup>

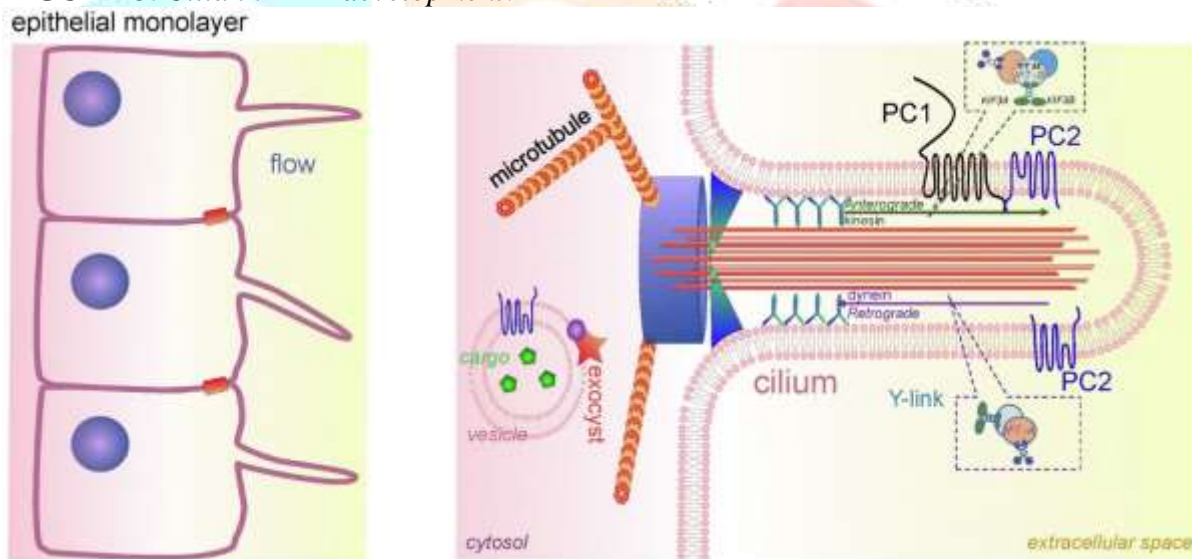


**FIGURE 2.** Domain structure of proteins causing



ARPKD and ADPKD: polycystin 1, polycystin 2, and fibrocystin.

**FIGURE 3.** Cilia in PKD development.<sup>1</sup>



**DIAGNOSIS**

For polycystic kidney disease, certain tests can detect the size and number of kidney cysts you have and evaluate the amount of healthy kidney tissue, Imaging tests can help determine whether a kidney mass is a cyst or a tumor. Kidney function tests, testing a sample of your blood may reveal whether a kidney cyst is affecting how well your kidney works, the test includes:<sup>25</sup>

• **Ultrasound:**

A transducer, which resembles a wand, is put on your body during an ultrasound. Similar to sonar, it produces sound waves that are reflected back to the transducer. The reflected sound waves are converted by a computer into pictures of your kidneys.

- **CT scan:**

You are led into a large, doughnut-shaped machine that projects thin X-ray beams through your body as you are lying on a mobile table. Your kidneys can be seen in cross-section by your doctor.

- **MRI test:**

Magnetic fields and radio waves produce cross-sectional images of your kidneys as you are lying within a sizable cylinder.

## TREATMENT

The severity of polycystic kidney disease varies from person to person, even among members of the same family. Often, people with PKD reach end-stage kidney disease between the ages of 55 to 65. But some people with PKD have mild disease and might never progress to end-stage kidney disease. Treating polycystic kidney disease involves dealing with the following signs, symptoms, and complications in their early stages:<sup>11</sup>

**Kidney cyst growth:** Adults at risk of quickly developing ADPKD benefit from tolvaptan therapy. Tolvaptan (Jynarque, Samsca) is an oral medication that works to reduce the rate of kidney cyst formation and the decline in kidney function.

Tolvaptan is a vasopressin V2 receptor competitive antagonist. Its main activity is in the renal collecting ducts, where it reduces water reabsorption and causes aquaresis without causing salt loss, increasing free water clearance and treating dilutional hyponatremia.

Tolvaptan can cause serious liver damage and may interact with any medications you are taking. When using tolvaptan, it is best to see a doctor who specializes in kidney health (nephrologist) so that any adverse effects may be monitored.

**High blood pressure:** Controlling high blood pressure can decrease disease progression and prevent further kidney damage. Combining a low-sodium, low-fat diet with moderate protein and calorie content, as well as quitting smoking, increasing exercise, and decreasing stress, may help regulate high blood pressure.<sup>1</sup>

Medication is frequently required to regulate high blood pressure. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are frequently used to treat high blood pressure.

**Declining kidney function:** Experts advocate keeping a regular body weight to keep your kidneys as healthy as possible for as long as possible (body mass index). Drinking water and fluids throughout the day may help limit the growth of kidney cysts, hence slowing the reduction in kidney function. Following a low-salt diet and consuming less protein may help kidney cysts respond better to fluid increases.

**Pain:** Over-the-counter acetaminophen drugs help to manage the pain of polycystic kidney disease. However, for some people, the pain is more acute and constant. To decrease kidney cysts, doctor propose a procedure that involves drawing out cyst fluid with a needle and injecting a medicine (sclerosing agent). If the cysts are large enough to cause pressure and pain, need surgery to remove them.

**Bladder or kidney infections:** Avoid kidney damage, infections must be treated as soon as possible with antibiotics. Doctor conduct an examination to determine if you have a simple bladder infection or a more serious cyst or kidney infection. For more complex infections, need to take antibiotics for a longer period of time. Example; Ciprofloxacin, Chloramphenicol, Clindamycin.

**Blood in the urine:** Drink plenty of fluids, particularly plain water, as soon as if observe blood in your urine to dilute it. Dilution may aid in the prevention of obstructive clots in the urinary tract. The bleeding will usually stop on its own. If it does not, should consult a doctor.

**Kidney failure:** If kidneys lose their ability to eliminate waste and excess fluids from blood, will eventually require dialysis or a kidney transplant. Seeing doctor on a frequent basis for PKD monitoring helps with the ideal timing of a kidney transplant. Could be able to get a preemptive kidney transplant, which means won't have to start dialysis but will instead have the transplant.

**Aneurysms:** If have polycystic kidney disease and a family history of ruptured brain aneurysms, may recommend regular intracranial aneurysm screening.

If an aneurysm is identified, depending on its size, surgical clipping of the aneurysm to lessen the risk of bleeding may be a possibility. Nonsurgical therapy for minor aneurysms may include lowering blood pressure and cholesterol levels, as well as quitting smoking.

Early treatment has the best chance of stopping the course of polycystic kidney disease.

## CONCLUSION

PKD is one of the most common monogenic disorders in humans. It is characterized by the formation and inevitable expansion of kidney cysts, ultimately leading to ESRD. Current therapeutic approaches focus on symptom and complication management, as well as slowing the rate of disease progression.



## REFERENCE

1. Polycystic kidney disease Carsten Bergmann,<sup>1,\*</sup> Lisa M. Guay-Woodford,<sup>2</sup> Peter C. Harris,<sup>3</sup> Shigeo Horie,<sup>4</sup> Dorien J. M. Peters,<sup>5</sup> and Vicente E. Torres<sup>3</sup>
2. Bergmann C ARPKD and early manifestations of ADPKD: the original polycystic kidney disease and phenocopies. *Pediatr. Nephrol.* 30, 15–30 (2015). [PMC free article] [PubMed] [Google Scholar]
3. Torres VE, Harris PC & Pirson Y Autosomal dominant polycystic kidney disease. *Lancet* 369, 1287–1301 (2007). [PubMed] [Google Scholar]
4. Bergmann C & Weiskirchen R It's not all in the cilium, but on the road to it: genetic interaction network in polycystic kidney and liver diseases and how trafficking and quality control matter. *J. Hepatol.* 56, 1201–1203 (2012). [PubMed] [Google Scholar]
5. Gerdes JM, Davis EE & Katsanis N The vertebrate primary cilium in development, homeostasis, and disease. *Cell* 137, 32–45 (2009). [PMC free article] [PubMed] [Google Scholar]
6. Hildebrandt F, Benzing T & Katsanis N Ciliopathies. *N. Engl. J. Med.* 364, 1533–1543 (2011). [PMC free article] [PubMed] [Google Scholar]
7. Dalgaard OZ Bilateral polycystic disease of the kidneys; a follow-up of two hundred and eighty-four patients and their families. *Acta Med. Scand. Suppl.* 328, 1–255 (1957). [PubMed] [Google Scholar]
8. Iglesias CG et al. Epidemiology of adult polycystic kidney disease, Olmsted County, Minnesota: 1935–1980. *Am. J. Kidney Dis.* 2, 630–639 (1983).
9. [PubMed] [Google Scholar] Levy M & Feingold J Estimating prevalence in single-gene kidney diseases progressing to renal failure. *Kidney Int.* 58, 925–943 (2000). [PubMed] [Google Scholar]
10. Davies F et al. Polycystic kidney disease re-evaluated: a population-based study. *Q. J. Med.* 79, 477–485 (1991). [PubMed] [Google Scholar]
11. Simon P et al. [Epidemiologic data, clinical and prognostic features of autosomal dominant polycystic kidney disease in a French region]. *Nephrologie* 17, 123–130 (1996). [PubMed] [Google Scholar]
12. Cnossen WR et al. Whole-exome sequencing reveals LRP5 mutations and canonical Wnt signaling associated with hepatic cystogenesis. *Proc. Natl Acad. Sci. USA* 111, 5343–5348 (2014). [PMC free article] [PubMed] [Google Scholar]
13. Gunay-Aygun M et al. Hepatorenal findings in obligate heterozygotes for autosomal recessive polycystic kidney disease. *Mol. Genet. Metab.* 104, 677–681 (2011). [PMC free article] [PubMed] [Google Scholar]
14. Hart TC et al. Mutations of the UMOD gene are responsible for medullary cystic kidney disease 2 and familial juvenile hyperuricaemic nephropathy. *J. Med. Genet.* 39, 882–892 (2002). [PMC free article] [PubMed] [Google Scholar]
15. Kirby A et al. Mutations causing medullary cystic kidney disease type 1 lie in a large VNTR in MUC1 missed by massively parallel sequencing. *Nat. Genet.* 45, 299–303 (2013). [PMC free article] [PubMed] [Google Scholar]
16. Chapman AB et al. Autosomal dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 88, 17–27 (2015). [PMC free article] [PubMed] [Google Scholar]
17. Bolar NA et al. Heterozygous loss-of-function SEC61A1 mutations cause autosomal-dominant tubulo-interstitial and glomerulocystic kidney disease with anemia. *Am. J. Hum. Genet.* 99, 174–187 (2016). [PMC free article] [PubMed] [Google Scholar]
18. Plaisier E et al. COL4A1 mutations and hereditary angiopathy, nephropathy, aneurysms, and muscle cramps. *N. Engl. J. Med.* 357, 2687–2695 (2007). [PubMed] [Google Scholar]
19. Bergmann C Recent advances in the molecular diagnosis of polycystic kidney disease. *Expert Rev. Mol. Diagn.* 17, 1037–1054 (2017). [PubMed] [Google Scholar]

20. Hughes J et al. The polycystic kidney disease 1 (PKD1) gene encodes a novel protein with multiple cell recognition domains. *Nat. Genet.* 10, 151–160 (1995). [PubMed] [Google Scholar]
21. Qian F et al. Cleavage of polycystin-1 requires the receptor for egg jelly domain and is disrupted by human autosomal-dominant polycystic kidney disease 1-associated mutations. *Proc. Natl Acad. Sci. USA* 99, 16981–16986 (2002). [PMC free article] [PubMed] [Google Scholar]
22. Kurbegovic A et al. Novel functional complexity of polycystin-1 by GPS cleavage in vivo: role in polycystic kidney disease. *Mol. Cell. Biol.* 34, 3341–3353 (2014). [PMC free article] [PubMed] [Google Scholar]
23. Low SH et al. Polycystin-1, STAT6, and P100 function in a pathway that transduces ciliary mechanosensation and is activated in polycystic kidney disease. *Dev. Cell* 10, 57–69 (2006). [PubMed] [Google Scholar]
24. Xu Y et al. The polycystin-1, lipoxygenase, and a-toxin domain regulates polycystin-1 trafficking. *J. Am. Soc. Nephrol.* 27, 1159–1173 (2016). [PMC free article] [PubMed] [Google Scholar]
25. Tsiokas L, Kim E, Arnould T, Sukhatme VP & Walz, G. Homo- and heterodimeric interactions between the gene products of PKD1 and PKD2. *Proc. Natl Acad. Sci. USA* 94, 6965–6970 (1997). [PMC free article] [PubMed] [Google Scholar]
26. Shen PS et al. The structure of the polycystic kidney disease channel PKD2 in lipid nanodiscs. *Cell* 167, 763–773 (2016). [PMC free article] [PubMed] [Google Scholar]
27. Grieben M et al. Structure of the polycystic kidney disease TRP channel Polycystin-2 (PC2). *Nat. Struct. Mol. Biol.* 24, 114–122 (2017). [PubMed] [Google Scholar]
28. Qian F, Watnick TJ, Onuchic LF & Germino GG The molecular basis of focal cyst formation in human autosomal dominant polycystic kidney disease type I. *Cell* 87, 979–987 (1996). [PubMed] [Google Scholar]
29. Watnick T et al. Mutations of PKD1 in ADPKD2 cysts suggest a pathogenic effect of trans-heterozygous mutations. *Nat. Genet.* 25, 143–144 (2000). [PubMed] [Google Scholar]
30. Bergmann C et al. Mutations in multiple PKD genes may explain early and severe polycystic kidney disease. *J. Am. Soc. Nephrol.* 22, 2047–2056 (2011). [PMC free article] [PubMed] [Google Scholar]