

# Renal Failure Due to Autosomal Dominant Polycystic Kidney Disease

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## Key Points

- Autosomal dominant polycystic kidney disease (ADPKD) is a genetic condition that can result in end-stage renal disease.
- Approximately 50% of individuals with ADPKD have end-stage renal failure by age 60.
- Testing for mutations in the causative genes, *PKD1* and *PKD2*, is clinically available, but has limited sensitivity.
- Siblings of an affected individual who are considering kidney donation should be evaluated for ADPKD.

## Learning Objectives

Participants will be able to:

- Identify the clinical manifestations of ADPKD;
- Outline the optimal strategy for evaluating family members at risk for ADPKD;
- Understand the issues raised by evaluation for ADPKD in an asymptomatic at-risk individual.

## Family History Issues

ADPKD is inherited in an autosomal dominant manner. Affected individuals have a 50% chance of passing this condition on to each child (offspring). Usually, affected individuals have a family history of the disease, but new mutations occur in about 10% of affected families.

## Red Flags



Indicators of a potential diagnosis of ADPKD include the incidental finding of renal or hepatic cysts on a radiological examination; the diagnosis of a cerebral aneurysm; or hematuria secondary to a renal cyst. Common

symptoms of ADPKD include pain in the back and the flanks. The kidneys may be large enough to palpate.

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## Case 33. Renal Failure in a 38-Year-Old Woman

Mrs. Y, age 38 years, has progressively worsening renal failure, due to polycystic kidney disease. Multiple bilateral renal cysts and renal failure were diagnosed about five years ago, after an episode of hematuria. She also has two cysts in her liver, and mild hypertension that is controlled with medication. She has no other health problems. She is likely to require dialysis soon and has been advised to consider renal transplantation.

Mrs. Y's father died of cerebral hemorrhage at age 45 years. Her mother is 55 years old and in good health, and has had a normal renal ultrasound study. Mrs. Y has two younger sisters and a younger brother, and has three children, ages three, six, and ten years. Of the family members who are potential kidney donors, only her youngest sister, age 25 years, is a good tissue match.

## Clinical Care Issues

### **Polycystic kidney disease**

When bilateral renal cysts are identified in a young or middle-aged adult, autosomal dominant polycystic kidney disease (ADPKD) is the leading diagnostic consideration. However, other renal cystic diseases may mimic ADPKD and need to be considered in the workup. These include acquired renal cystic disease (which may occur as a complication of end-stage renal disease), autosomal recessive polycystic kidney disease, and several rare genetic disorders that include renal cysts as one of their manifestations, but also have other characteristic clinical manifestations that assist in diagnosis. An example of the latter is [von Hippel-Lindau disease](#), which is characterized by cerebral hemangiomas, retinal lesions, renal cysts and renal cell carcinoma. See further discussion in [GeneReview: ADPKD, Differential Diagnosis](#). [Autosomal recessive polycystic kidney disease](#) usually has onset early in life, and usually includes congenital hepatic fibrosis or biliary dysgenesis.

ADPKD is characterized by progressive cyst development and bilaterally enlarged polycystic kidneys. Mutations in two different genes, *PKD1* and *PKD2*, can cause ADPKD: *PKD1* mutations are the cause in about 85% of patients, and *PKD2* mutations are the cause in about 15%. Mutations in the *PKD1* gene are associated with more severe disease and an earlier age of onset (mean of 54.3 years for *PKD1* versus 74 years for *PKD2*).

The renal problems associated with ADPKD include renal function abnormalities, hypertension, kidney stones, cyst infection and hemorrhage, and flank pain. Malignancy (renal cell carcinoma) does not occur more frequently in people with ADPKD than in the general population, but may be difficult to diagnose in the setting of polycystic kidneys. About half of patients with ADPKD have end-stage renal disease by age 60 years. However, the severity of renal disease and other complications of ADPKD varies among affected individuals, even within the same family. Other complications of ADPKD include the following [[Harris & Torres 2004](#)]:

- Polycystic liver disease is the most common extrarenal manifestation of ADPKD; it is present in 20% of affected individuals by age 30 and 75% of affected individuals above age 60. Most liver cysts are asymptomatic and require no treatment.
- Mitral valve prolapse is present in up to 25% of individuals with ADPKD. Dilatation of the aortic root and dissection of the thoracic aorta may also occur.
- Intracranial aneurysms are present in 10% of individuals with ADPKD. The prevalence is higher (22%) in individuals with a family history of aneurysms or subarachnoid hemorrhage, compared to those without (6%).
- Cysts may also occur in the seminal vesicles, pancreas, and arachnoid membrane. Abdominal wall hernias may occur.

### **ADPKD in Mrs. Y: Inherited or de novo?**

Mrs. Y's clinical history supports a diagnosis of ADPKD, because she has multiple kidney cysts bilaterally, liver cysts, and renal failure, and does not have other clinical findings pointing to alternate causes for her cysts or renal failure [[Harris & Torres 2004](#)]. However, we cannot be sure whether she inherited this condition or whether it is the result of a de novo mutation. Most individuals with ADPKD (90%) inherit the condition from an affected parent. In Mrs. Y's case, her mother is healthy and has no renal cysts on ultrasound examination. However, Mrs. Y's father's death from cerebral hemorrhage could reflect ADPKD. Further investigation of his medical records

could provide evidence for this diagnosis. Key considerations would be whether his cerebral bleed was due to a ruptured cerebral aneurysm, a known complication of ADPKD; and whether any renal imaging results were available. If Mrs. Y's father had renal studies demonstrating at least two cysts in each kidney, the diagnosis of ADPKD would be confirmed.

### **Consideration of Mrs. Y's sister as a kidney donor**

Normally, a living relative with a good tissue match represents the best kidney donor for a patient with renal failure. However, when renal failure is due to ADPKD, the relative may also have ADPKD. In this case, if the medical records of Mrs. Y's father confirm ADPKD, her sister has a 50% likelihood of having inherited ADPKD as well. Even if the medical records are inconclusive, her sister is still at risk. Before being considered as a potential donor, Mrs. Y's sister would need to be evaluated for ADPKD.

### **Risk Assessment**

Many people with ADPKD remain asymptomatic until middle age. However, renal cysts can usually be seen on renal imaging studies by the mid-twenties.

For individuals at 50% risk for ADPKD, diagnostic criteria based on renal ultrasound findings include at least two unilateral or bilateral cysts in patients younger than age 30 years, two cysts in each kidney in patients age 30-59 years, and four cysts in each kidney in patients age 60 years or older [Ravine et al 1994]. The sensitivity of these criteria approaches 100% for individuals with ADPKD who are 30 years or older; however, the criteria are only 67% sensitive for individuals who are younger than age 30 years [Nicolau et al 1999].

Therefore, if Mrs. Y's sister is willing to undergo an evaluation for ADPKD, the first step is a renal ultrasound. If renal imaging reveals no evidence of polycystic kidneys, molecular genetic testing looking for the mutation causing ADPKD in Mrs. Y would be recommended.

### **Genetic Counseling and Testing**

#### **Genetic testing options**

Genetic testing in this case is complex. Multiple mutations have been

identified in both *PKD1* and *PKD2*. Sequence analysis of both genes is available but sensitivity is estimated to be only 50-70%.

Therefore, the optimal approach to testing is to start by testing an affected family member. If a specific causative *PKD1* or *PKD2* mutation can be found, asymptomatic family members can be tested to see whether they inherited the mutation. However, if no mutation is found in an affected family member, further testing of family members will not be informative.

## Linkage analysis

In families with multiple affected family members, a family linkage study may be possible. In this approach, several affected and unaffected family members are tested for DNA markers (small segments of variable DNA sequence) adjacent to the two known ADPKD genes. The purpose of the study is to determine whether there is an association between ADPKD and particular DNA markers among family members. The testing is positive if a consistent relationship is demonstrated between certain DNA markers and the presence or absence of disease in family members. This type of study requires participation of both affected family members and family members who are known to be unaffected — that is, thoroughly evaluated older family members, whose genetic status can be established unequivocally by renal imaging. If linkage is established between ADPKD and specific DNA markers, the markers can then be used to test young at-risk family members, to determine whether they have inherited the markers associated with ADPKD in the family.

Linkage analysis is not available to Mrs. Y's family because she is the only known affected family member.

## What is the optimal testing strategy for the family?

If Mrs. Y's sister agrees to be evaluated, the first step is a renal ultrasound. If this reveals no renal cysts, genetic testing may be helpful. Initially, Mrs. Y, who is affected with ADPKD, would be offered genetic testing of the *PKD1* and *PKD2* genes, by sequence analysis, to determine if her mutation can be identified. If a mutation is found in one of these genes, her sister can then be offered testing for that specific mutation. If Mrs. Y's sister has this mutation, she will develop ADPKD in the future and therefore should NOT serve as a kidney donor. If Mrs. Y's sister does not have the mutation, she is not at increased risk for ADPKD and can serve as a kidney donor.

If Mrs. Y's genetic test results do not reveal a *PKD1* or *PKD2* mutation, no further testing is possible, because Mrs. Y's family does not include enough affected family members for linkage analysis. Mrs. Y's sister must be considered at risk for ADPKD, because a negative ultrasound does rule out ADPKD in a 25 year old. Therefore, in this circumstance, she should NOT serve as a kidney donor for her sister.

## Interventions

See [GeneReview: ADPKD](#) for detailed discussion of interventions for ADPKD. Most interventions are based on accepted clinical management of specific complications, such as treatment of hypertension, urinary tract infection, kidney stones, and renal failure.

Several measures have been proposed to delay progression of renal failure in ADPKD, including careful control of hypertension and elevated lipids; restriction of dietary protein; control of acidosis; and prevention of hyperphosphatemia [[GeneReview: ADPKD, Management](#)]. Definitive evidence on the outcome of such interventions is not yet available.

Consideration of screening for intracranial aneurysms is recommended in certain circumstances, particularly for an affected individual 20 to 50 years old who has a family history of intracranial aneurysm or subarachnoid hemorrhage or history of previous aneurysmal bleed; or will be having a surgery involving potential hemodynamic instability; or is in a high-risk occupation [[GeneReview: ADPKD, Management](#)]. Screening by magnetic resonance imaging (MRI) is preferred. Surgery is usually recommended, if feasible, for asymptomatic aneurysms larger than 10 mm. Non-surgical management techniques are under investigation.

Although delay or prevention of renal failure might be possible in asymptomatic persons, using measures such as blood pressure control and low-protein diet, outcome data are lacking. As a result, the medical benefit of presymptomatic diagnosis of ADPKD is unknown.

## Ethical/Legal/Social/Cultural Issues

Mrs. Y's sister faces a complicated decision. If she chooses to serve as a kidney donor for her sister, she must first undergo an evaluation for ADPKD. This evaluation might reveal that she herself has ADPKD.

Thus, she faces two different medical decisions, both with significant personal implications. She may have mixed feelings about serving as a kidney donor, experiencing both the desire to help her sister and fear about the medical procedures she would need to undergo and the implications of losing a kidney. In addition, she may feel uncertain about pursuing the workup to determine whether she has ADPKD. A diagnosis of ADPKD would potentially expose her to difficulties in obtaining health or other insurance; would inform her about a significant future health risk for which no specific preventive treatment is yet available; and would identify a genetic risk for future children. Taking in this information about the implications of a diagnosis of ADPKD, while at the same time considering serving as a kidney donor, may be difficult. Her decision-making process could also be complicated by family pressures, if she is the only potential related donor for her sister.

These issues underscore the importance of providing Mrs. Y's sister with appropriate counseling, allowing her to work through her decision-making process in a way that addresses all her questions and concerns. This is likely to be best accomplished by carefully separating Mrs. Y's health care from that of her sister, even though her sister's medical care issues are being raised by Mrs. Y's health problem. In this way, Mrs. Y's sister can receive counseling and health care from a provider focused on her needs.

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## Resources

- **PKD Foundation** (formerly the Polycystic Kidney Research Foundation)  
9221 Ward Parkway  
Suite 400  
Kansas City, MO 64114-3367  
**Phone:** 800-PKD-CURE  
**Fax:** 816-931-8655  
**Email:** pkdcure@pkdcure.org
- **National Kidney Foundation**  
30 East 33rd Street  
Suite 1100  
New York, NY 10016  
**Phone:** 800-622-9010; 212-889-2210  
**Fax:** 212-689-9261

**Email:** [info@kidney.org](mailto:info@kidney.org)

- **NCBI Genes and Disease Webpage:** [APKD](#)
- **National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC), National Institute of Diabetes and Digestive and Kidney Diseases:** [Polycystic Kidney Disease](#)
- [GeneTests Online Medical Genetics Information Resource](#)
- [GeneReviews, GeneTests Online Medical Genetics Information Resource](#)

## References

Harris PC and Torres VE (Updated 2004) [Autosomal Dominant Polycystic Kidney Disease](#). In: *GeneReviews* at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2005. Available at <http://www.genetests.org>. Accessed 4-4-05.

Nicolau C, Torra R, Badenas C, Vilana R, Bianchi L, Gilabert R, Darnell A, Bru C (1999) Autosomal dominant polycystic kidney disease types 1 and 2: assessment of US sensitivity for diagnosis. *Radiology* 213:273-6 [[Medline](#)]

Ravine D, Gibson RN, Walker RG, Sheffield LJ, Kincaid-Smith P, Danks DM (1994) Evaluation of ultrasonographic diagnostic criteria for autosomal dominant polycystic kidney disease 1. *Lancet* 343:824-7 [[Medline](#)]