NephU™
Improving Awareness & Patient Outcomes

# Interpreting Genetic Testing in Cystic Kidney Disease

## When to perform genetic testing in a patient with suspected ADPKD

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, and imaging is the most common approach for diagnosing it. However, because of the highly genetically heterogeneous nature of ADPKD and the impact the genetic variant may have on disease progression, genetic testing is increasingly becoming a component of diagnosing and providing appropriate care to patients suspected of having ADPKD. Although not all patients will require genetic testing, it is recommended if there is no family history of PKD, if atypical imaging is present, or if the disease course varies between generations.

## What to do when you encounter VUS during genetic testing

Although genetic tests are optimized for the genes included on the panel, a disease-associated variant may be missed because not all pathogenic changes are always detected. In addition to disease causing variants, genetic testing may also identify variants of uncertain significance (VUS), a non-diagnostic category, leaving the way forward unclear.

Use the flowchart below to organize your approach to testing, including what to do if a VUS is detected. While the flowchart may help you determine when a VUS leans likely pathogenic, it is important to note that not all VUS can be reclassified. We recommend collaborating with a clinical geneticist or reaching out to your local PKD Foundation Center of Excellence to complete the later steps. Please see the next page for a detailed explanation of each step and a practical case study.

**A** Assess the clinical probability of ADPKD based on imaging, clinical presentation, and renal and extrarenal features. If there is no family history of PKD, if atypical imaging is present, or if the disease course varies between generations, then genetic testing is recommended

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**B** Perform genetic testing. Does it identify a pathogenic (P) or likely pathogenic (LP) *PKD1* or *PKD2* gene variant that can explain the clinical findings?

Yes → STOP

No ↓

**C** Is there another cystic kidney gene variant that can explain the phenotype?

Yes → STOP

No ↓

**D** Is the identified VUS in *PKD1* or *PKD2* (or other ADPKD gene) rare? Examine its frequency in the gnomAD database

No → STOP

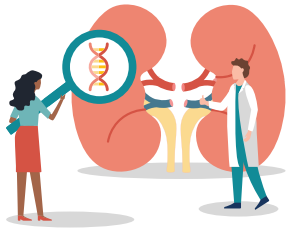
A more common variant may still cause a mild phenotype with a few cysts (hypomorphic) but is unlikely to cause clinically significant disease

Yes ↓

**E** Is the variant classified in the ADPKD Variant Database?

No → Consider consulting with a clinical geneticist or a nephrologist with genetics expertise to help guide further analysis

Yes → **F** Use the results from this additional analysis presented in the ADPKD Variant Database to see if there are sufficient data to classify the VUS as LP according to the ACMG guidelines. Moving forward, periodically check the databases to see if the VUS classification has been updated



**Mutations in genes causing an ADPKD-like phenotype include the following:**

- *GANAB*, *DNAJB11*, *ALG9*, and *IFT140*
- *COL4A1*, *COL4A3*, and *COL4A4* may lead to bilateral renal cysts and kidney disease
- *HNF1B* produces cystic kidney disease and early-onset diabetes mellitus, renal cysts and diabetes syndrome (RCAD), or maturity-onset diabetes of the young (MODY) type 5
- *PRKCSH*, *SEC63*, *GANAB*, and *ALG8* are implicated in the spectrum of autosomal dominant polycystic liver disease, but some also cause kidney cysts

Consider consulting with a clinical geneticist or reaching out to your local PKD Foundation Center of Excellence

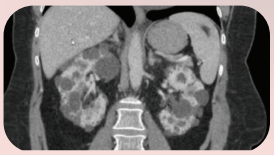
Aklilu AM, et al. The VUS challenge in cystic kidney disease: a case-based review. *Kidney360*. 2024;5(1):152-159.

## Detailed Description of Each Decision Point

## Practical Case Study for How to Assess a Patient Who Has a VUS

**A**

**Likelihood of ADPKD can be assessed based on a combination of imaging and clinical features. Bilateral kidney cysts are a requirement for an ADPKD diagnosis but other features may include the presence of hypertension, impaired kidney function, and extrarenal findings (eg, hepatic or pancreatic cysts, colonic diverticula, abdominal wall hernias).**



A 22-year-old woman has a family history of polycystic kidney disease. There was a high clinical suspicion of ADPKD due to the presence of high-risk features, including hypertension, a urologic event before 35 years of age, and a CT scan that showed multiple cysts on both kidneys.

**B**

**Genetic testing can help provide a firm diagnosis and identify the gene and specific disease causing variant. Variants can be classified as pathogenic (P), likely pathogenic (LP), or variant of uncertain significance (VUS). The clinical relevance of VUS remains unknown; therefore, additional steps should be taken to try to reassign the variant to another classification.**

A genetic test is ordered and it does not classify the variant as P or LP. The variant is a VUS.

**C**

**Other identified genes that cause an ADPKD-like phenotype include the following:**

- *GANAB, DNAJB11, ALG9,* and *IFT140*
- *COL4A1, COL4A3,* and *COL4A4* may lead to bilateral renal cysts and kidney disease
- *HNF1B* produces cystic kidney disease and early-onset diabetes mellitus, renal cysts and diabetes syndrome (RCAD), or maturity-onset diabetes of the young (MODY) type 5
- *PRKCSH, SEC63, GANAB,* and *ALG8* are implicated in the spectrum of autosomal dominant polycystic liver disease, but some also cause kidney cysts

No other disease-causing variants explained her phenotype.

**D**

**If no other disease-causing variant is identified, any detected VUS in *PKD1* or *PKD2* should be further evaluated. Pathogenic variants are expected to be very rare, with an allelic frequency lower than 3 out of 280,000. The gnomAD database can be used to determine the rarity of the variant.**

Genetic testing identified a VUS in *PKD1* (c.12406A>G, p.Arg4136Gly). The variant is absent from gnomAD; therefore, it is a rare variant.

**gnomad.broadinstitute.org**

**E**

**The ADPKD Variant Database is a repository for all known variants in *PKD1* and *PKD2* and classifies variants using research evaluation as P, LP, or VUS. Family segregation of the variant with disease and other descriptions and evaluations of the variant can move its ACMG class to LP.**

The variant is classified as LP within the ADPKD Variant Database, supporting pathogenicity, and family data provide additional evidence for an LP designation.

**pkdb.mayo.edu**

**F**

**Understanding the genotype and whether a variant is likely disease-causing can help elucidate the rate of progression and predict patient outcomes, which can be used to inform treatment decisions. Sometimes additional evaluation will not change the VUS classification, and a genetic diagnosis will not have been made. Further testing of family members (cascade testing) may be indicated. Moving forward, periodically check the databases to see if the VUS classification has been updated.**

The variant is LP; therefore, it should be interpreted as potentially disease-causing, and the patient should be managed accordingly. Since genetic testing does not detect 100% of pathogenic variants, a negative or inconclusive genetic test in a patient with clinical/imaging findings typical for ADPKD does not exclude the diagnosis. A diagnosis can be made based on clinical/imaging grounds. If criteria for rapidly progressive disease are also met, treating such a patient is also appropriate.