

# AUTSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE (ARPKD)

Comprehensive Test - **Test 1**

- updated -8-10-09 -

## DESCRIPTION

Mendelian Inheritance in Man number: [\\*606702](#)

Click here for [Gene Reviews](#) Clinical Summary.

Autosomal Recessive Polycystic Kidney Disease (ARPKD) is characterized by enlarged cystic kidneys and hepatic fibrosis. The diagnosis is often made pre- or neonatally, but some patients are still diagnosed later in life. The severity varies widely, with a high mortality rate in the first months of life. ARPKD is one of the more common hereditary childhood nephropathies with an estimated incidence of 1:20,000-1:40,000. The carrier frequency in the general population is estimated to be 1 in 70 to 1 in 100. Mutations in *PKHD1* are scattered throughout the gene. Most families carry their own "private" mutations. For more information on the condition please refer to the review on the [GeneTests](#) website and [Online Mendelian Inheritance in Man](#).

## Genetics of ARPKD

The gene for ARPKD, *PKHD1* (*Polycystic Kidney and Hepatic Disease 1*), resides on chromosome 6p21-p12, spans 470 kb of genomic DNA and is the only gene known to be associated with the wide clinical spectrum of autosomal recessive polycystic kidney disease. 86 exons have been identified and multiple alternative transcripts are known. Over 300 mutations have been reported. Missense, nonsense, frameshift, splicing and multi-exon deletions can occur and the mutations are located throughout the length of the gene, with no major mutational hotspots known, as shown in the [PKHD1 mutation database](#).

## INDICATIONS FOR DIRECT TESTING

- Diagnostic testing: confirmation of diagnosis by direct sequence analysis of longest open reading frame in patients with symptoms indicative/suspicious of a diagnosis of ARPKD;
- Carrier testing by direct sequence analysis of longest open reading frame in partners of known *PKHD1* carriers.

## TESTING METHODOLOGY

By amplification and bidirectional sequencing of all exons constituting the longest open reading frame of the *PKHD1* gene, our group has identified mutations in >82% of alleles of patients with confirmed clinical diagnosis of ARPKD. Hence, in ~96% of families, at least one mutation is identified after bidirectional sequencing of all exons constituting the longest open reading frame.

We offer a **three tiered approach** to testing. First (**Tier 1**), the exons 3, 5, 9, 14, 16, 20, 21, 22, 30, 32-34, 36, 37, 39, 43, 50, 54, 55, 57-59 and 61 are analyzed. These 23

exons contain as many as 80% of identifiable pathogenic mutations in the cohorts studied so far.

If less than two clearly pathogenic mutations are identified in the first tier of testing, the remaining exons of the entire longest open reading frame are further analyzed by bidirectional sequencing (**Tier 2**).

**New: The Medical Genomics now offers copy number analysis of the *PKHD1* gene by MLPA and quantitative PCR (Tier 3).** Copy number analysis by MLPA and qPCR will detect deletions/duplications of one or multiple exons. If less than two clearly pathogenic mutations are identified in the first two tiers of testing, copy number analysis (**Tier 3**) by MLPA and quantitative PCR is recommended as the next step. All copy number alterations identified by MLPA are confirmed using an independent method, being qPCR and/or aCGH.

If 2 pathogenic mutations are identified in the proband, parental testing is mandatory to determine that the mutations reside on two different alleles. **Parental testing is performed free of charge, if parental samples are submitted the same week as the sample of the proband.** Parental testing will be performed at charge if parental samples are submitted at a later date.

If only 1 clearly pathogenic mutation is identified in a proband with clinically evident ARPKD (as per pathology report and completed phenotypic checklist), additional haplotype testing can be performed, which will allow prenatal testing in the future, if desired.

## **SPECIMEN REQUIREMENTS**

We require either a minimum of 5 milliliters of whole EDTA blood (diagnostic or carrier testing) or a biopsy fragment from skin/liver/spleen (fresh or frozen) or cultured cells (diagnostic testing).

For those families with no family history of ARPKD that have a fetus suspected to have ARPKD based on ultrasound results, we can perform comprehensive analysis starting from T25 flasks of either cultured CVS or cultured amniocytes (>70% confluent), sent at ambient temperature. Please also send 1-5 ml of blood or buccal swab sample from the mother for maternal contamination studies.

Please contact the lab prior to amniocentesis or chorion villi sampling if you wish to pursue comprehensive analysis starting from a fetal sample.

## **TRANSPORT**

If the specimen is from clinics within UAB or Kirklin Clinic, please call 934-5562 for pickup. If specimens are being sent from some other location, please ship via UPS or Federal Express.

1. Be sure that the shipping air bill is marked "**Priority**", either Domestic or International.
2. Specimens must be packaged to prevent breakage and absorbent material must be included in the package to absorb liquids in the event that breakage occurs. Also, the package must be shipped in double watertight containers (e.g. a specimen pouch + the shipping companies Diagnostic Envelope). **You can use our collection kits, which we**

**will send to physicians directly upon request.**

3. Please contact us (Email – [mgl@genetics.uab.edu](mailto:mgl@genetics.uab.edu), Phone – 205-934-5562) prior to sample shipment and provide us with the **date of shipment** and the **tracking number** of the package, so that we can better ensure receipt of the samples

## **TURN AROUND TIME**

Normal service: maximum 4 weeks

RUSH testing: 8 working days. No RUSH testing is currently available for copy number analysis (Tier 3).

## **CPT CODES AND PRICES**

**Please note that prices listed correspond to institutional rates; please contact the lab for insurance rates.**

**Tier 1 followed by Tier 2 and Tier 3** (if necessary):

\$3350, - USD ([currency converter](#))

83891 (x1), 83896 (x6), 83898 (x86), 83904 (x160), 83909 (x6), 83912 (x1)

**Tier 1 only:**

\$1200, - USD ([currency converter](#))

83891 (x1), 83898 (x32), 83904 (x64), 83912 (x1)

**Tier 1 followed by Tier 2** (if necessary):

\$2800, - USD ([currency converter](#))

83891 (x1), 83898 (x80), 83904 (x160), 83912 (x1)

**Copy number analysis by MLPA (Tier 3):**

\$600, - USD ([currency converter](#))

83891 (x1), 83909 (x6), 83896 (x6), 83898 (x6), 83912 (x1)

**Test 1 RUSH (Tier 1 + Tier 2 only):**

\$3500, - USD ([currency converter](#))

83891 (x1), 83898 (x80), 83904 (x160), 83912 (x1)

For RUSH testing, please be aware that the RUSH fee is not reimbursable by insurance and in cases of private pay, patient is responsible for paying the test fee plus the RUSH fee up front. For listings of contracted insurance companies, please see our [billing information page](#)

## **REQUIRED FORMS**

[ARPKD Test Requisition including the phenotypic data form.](#)

**Note:** Requests for Molecular Genetic testing for ARPKD will **not** be accepted for the following reasons:

- No label (patients full name and date of collection) on the specimens
- No referring physician's or genetic counselor's names and addresses
- No billing information

- No informed consent
- **No phenotypic checklist**

**For more information, test requisition forms, or sample collection and mailing kits, please call: 205-934-5562.**

## REFERENCES

Bergmann C, Senderek J, Kupper F, Schneider F, Dornia C, Windelen E, Eggermann T, Rudnik-Schoneborn S, Kirfel J, Furu L, Onuchic LF, Rossetti S, Harris PC, Somlo S, Guay-Woodford L, Germino GG, Moser M, Buttner R, Zerres K. (2004) PKHD1 mutations in autosomal recessive polycystic kidney disease (ARPKD). *Hum Mutat.* 2004 May;23(5):453-63 [\(pubmed\)](#)

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