Polycystic Kidney Disease, Autosomal Dominant (PKD1 and PKD2) Sequencing and Deletion/Duplication
ARUP test code 2012250

ADPKD Seq and Del/Dup Specimen | Whole Blood

ADPKD Seq, Del/Dup Interp | Positive *
TEST PERFORMED - 2012250
TEST DESCRIPTION - Polycystic Kidney Disease, Autosomal Dominant (PKD1 and PKD2) Sequencing and Deletion/Duplication
INDICATION FOR TEST - Not Provided

RESULT
One pathogenic variant was detected in the PKD1 gene. No pathogenic variants were detected in the PKD2 gene.

DNA VARIANT
Classification: Pathogenic
Gene: PKD1
Nucleic Acid Change: c.5890delC; Heterozygous
Amino Acid Alteration: p.Arg1964fs

INTERPRETATION
One copy of a pathogenic variant, c.5890delC; p.Arg1964fs, was detected in the PKD1 gene by sequencing; no additional pathogenic variants were detected by sequencing the PKD2 gene and deletion/duplication analysis of the PKD1 and PKD2 genes. This result is consistent with a diagnosis of autosomal dominant polycystic kidney disease (ADPKD); clinical manifestations are variable and age-dependent. This individual's offspring have a 50 percent chance of inheriting the causative variant.

Evidence for variant classification: The PKD1 c.5890delC; p.Arg1964fs variant, to our knowledge, is not reported in the medical literature or gene-specific databases. This variant is also absent from general population databases (Exome Variant Server, Genome Aggregation Database), indicating it is not a common polymorphism. This variant causes a frameshift by deleting a single nucleotide, so it is predicted to result in a truncated protein or mRNA subject to nonsense-mediated decay. Additionally, numerous downstream truncating variants have been described in individuals affected with autosomal dominant polycystic kidney disease (ADPKD; Audrezet 2012, Rossetti 2007). Based on available information, the c.5890delC variant is considered to be pathogenic.

RECOMMENDATIONS
Genetic consultation is indicated, including a discussion of medical screening and management. Renal imaging is recommended for at-risk adult family members. If imaging results are equivocal, targeted testing for the identified PKD1 variant should be considered (Familial Mutation, Targeted Sequencing, ARUP test code 2001961).

COMMENTS
Reference Sequences: GenBank # NM_001009944.2 (PKD1), NM_000297.3 (PKD2)
Nucleotide numbering begins at the "A" of the ATG initiation codon.

Likely benign and benign variants are not reported.

REFERENCES


This result has been reviewed and approved by Steven Steinberg, Ph.D.
BACKGROUND INFORMATION: Polycystic Kidney Disease, Autosomal Dominant (PKD1 and PKD2) Sequencing and Deletion/Duplication

CHARACTERISTICS: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is typically an adult-onset, multisystem disorder. Renal findings include: bilateral renal cysts, renal insufficiency, renal pain, hypertension, dilated renal tubules, enlarged kidneys, and end-stage renal disease (ESRD). Extra-renal findings include cysts in other organs, including liver, pancreas, seminal vesicles, and arachnoid membrane. Connective tissue findings include intracranial aneurysms, dolichoectasia, dilation of the aortic root, aortic dissections, mitral valve prolapse, and abdominal wall hernias. Fifty percent of individuals with ADPKD will develop ESRD by age 60.

PREVALENCE: 1:500-1:1,000 in the U.S.

INHERITANCE: Autosomal dominant; 5-10 percent of cases are de novo.

PENETRANCE: Age-dependent; nearly all older adults develop multiple renal cysts. The average age of onset for ESRD in individuals with PKD1 and PKD2 mutations is 54 and 74 years, respectively.

CAUSE: Pathogenic PKD1 or PKD2 gene mutations. In cases with an identifiable molecular cause, 85 percent are attributed to PKD1 and 15 percent are attributed to PKD2.

CLINICAL SENSITIVITY: 90 percent for ADPKD. Approximately 87 percent of cases are due to sequence variants and up to 3 percent of cases result from large deletions/duplications in PKD1 or PKD2.

METHODOLOGY: Bidirectional sequencing of the entire coding region and intron/exon boundaries of the PKD1 and PKD2 genes. A large region of PKD1, including exons 1-33, is duplicated six times on the same chromosome; therefore, to distinguish the PKD1 gene from the PKD1-like pseudogenes, long range PCR followed by site-specific PCR is used to sequence PKD1 exons 1-33. Multiplex ligation-dependent probe amplification (MLPA) is used to detect large exonic deletions/duplications of PKD1 or PKD2.

ANALYTICAL SENSITIVITY AND SPECIFICITY: 99 percent.

LIMITATIONS: Diagnostic errors can occur due to rare sequence variations. Regulatory region mutations and deep intronic mutations in PKD1 or PKD2 will not be detected. Large deletions/duplications of PKD1 exons 1, 2, 4, 8, 17, 24, 28, 32, 34, and 45 will not be detected. Mosaic mutations in PKD1 or PKD2 may not be detected. Breakpoints for large deletions/duplications will not be determined. Mutations in genes other than PKD1 and PKD2 are not assessed by this assay.
## VERIFIED/REPORTED DATES

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**END OF CHART**

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**H=High, L=Low, *=Abnormal, C=Critical**