Autosomal Dominant Polycystic Kidney Disease

Indications for Ordering

- Confirm clinical diagnosis of autosomal dominant polycystic kidney disease (ADPKD)
- Confirm diagnosis in individuals with equivocal renal imaging results
- Predictive testing for younger at-risk individuals being evaluated as potential living related kidney donors

Test Description

- Polymerase chain reaction followed by bidirectional sequencing of entire coding region and intron/exon boundaries of \( PKD1 \) and \( PKD2 \) genes
- Long-range PCR followed by site-specific PCR is used to sequence \( PKD1 \) exons 1-33
  - Distinguishes \( PDK1 \) gene from \( PDK1 \)-like pseudogenes
- Multiplex ligation-dependent probe amplification detects large exonic deletions/duplications of \( PKD1 \) or \( PKD2 \)

Tests to Consider

Primary test

**Polycystic Kidney Disease, Autosomal Dominant (\( PKD1 \) and \( PKD2 \)) Sequencing and Deletion/Duplication 2012250**

- Preferred test for molecular confirmation of suspected clinical diagnosis of ADPKD

**Polycystic Kidney Disease, Autosomal Dominant (\( PKD1 \) and \( PKD2 \)) Sequencing 2012255**

- Acceptable test for molecular confirmation of suspected clinical diagnosis of ADPKD

Related tests

**Familial Mutation, Targeted Sequencing 2001961**

- Useful when a pathogenic familial variant identifiable by sequencing is known

Disease Overview

**Prevalence** – 1/500-1,000 in the U.S.

**Age of onset** – usually adult onset of symptoms

Symptoms

- Kidneys
  - Bilateral renal cysts
  - Cysts in the kidneys can be present from birth
  - Renal pain
  - Renal insufficiency
  - Hypertension
  - Dilated renal tubules
  - Enlarged kidneys
  - End stage renal disease (ESRD)
    - 50% of individuals with ADPKD will develop ESRD by age 60
- Cysts can appear in other organs
  - Liver
  - Pancreas
  - Seminal vesicles
  - Arachnoid membrane
- Connective tissue
  - Intracranial aneurysms and/or hemorrhaging
    - ~10% of individuals with ADPKD
  - Prevalence is higher in those with family history of intracranial hemorrhage (22%) than those with no family history (6%)
  - Dolichoectasia
  - Dilation of aortic root
  - Aortic dissections
  - Mitral valve prolapse
    - 25% of cases
  - Abdominal wall hernias

Diagnostic criteria/Issues

- Renal imaging to identify
  - Enlarged kidneys
  - Cysts on kidneys
  - Cysts on other organs
- Positive predictive value (PPV) of imaging is 100% when following criteria for at-risk individuals with a first-degree family member with ADPKD
- Sensitivity of criteria depends on genotype and age of individual at time of evaluation
- Criteria
  - ≥3 renal cysts (unilateral or bilateral) in individuals aged 15-39 years
  - ≥2 cysts in each kidney in individuals aged 40-59 years
  - Large echogenic kidneys without distinct macroscopic cysts in an infant/child – 50% risk for ADPKD
Pathophysiology

- Variants in PKD1 or PKD2 cause abnormal or absent expression of proteins
  - Polycystin-1 (PKD1)
  - Polycystin-2 (PKD2)
- These two proteins form a complex responsible for intracellular calcium level regulation in the primary cilia of renal tubular cells
  - Because of the complex formed by these two proteins, variants in either gene will result in a clinically indistinguishable phenotype
- Polycystins are also expressed during renal development
  - Including during development of renal tubules and medullary collecting ducts
- Altered/abnormal expression of polycystins during development leads to dilation in the renal tubules
  - Leads to formation of fluid-filled cysts characteristic of this condition

Genetics

Genes – PKD1, PKD2

Structure

- A large region of PKD1, including exons 1-33, is duplicated six times on the same chromosome

Inheritance – autosomal dominant

Penetrance – age-dependent

- Nearly all older adults develop multiple renal cysts
- Average ages of onset for ESRD in individuals with PKD1 and PKD2 variants are 54 and 74 years, respectively

De novo rate – 5-10%

Variants causing ADPKD

- Up to 90% of individuals with ADPKD will have an identifiable variant in PKD1 or PKD2
  - 85% of cases attributed to variants in PKD1
  - 15% of cases attributed to variants in PKD2
- Variants in PKD1 (compared to variants in PKD2)
  - More severe disease
  - Earlier age of diagnosis
  - Earlier mean age of onset of ESRD
- Sequence variants account for majority of causative variants
  - >70% of known pathogenic variants are truncating variants
- Large deletions/duplications in PKD1 or PKD2 are a rare cause of ADPKD
  - ~4% of PKD1 variants and <1% of PKD2 variants
  - Large deletions involving PKD1/TSC2 result in contiguous gene deletion syndrome
    - Early onset PKD as well as features of tuberous sclerosis

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity – 90% for ADPKD (Consugar, 2008; Rossetti, 2007)
  - ~87% of cases are due to sequence variants
  - Up to 3% of cases result from large deletions/duplications
- Analytical sensitivity – 99%
- Analytical specificity – 99%

Results

- Positive
  - At least one pathogenic variant detected in PKD1 or PKD2
    - Confirms diagnosis of ADPKD
- Negative
  - No pathogenic variants detected in either PKD1 or PKD2
    - Reduces the likelihood of, but does not exclude, a diagnosis of ADPKD
  - Inconclusive
    - Variant detected, but clinical significance is unknown

Limitations

- Presymptomatic testing in minors is not recommended
- Not detected
  - Regulatory region or deep intronic variants
  - Large deletions or duplications in exons 1, 2, 4, 8, 17, 24, 28, 32, 34, and 45 in PKD1 gene
  - Variants in genes other than PKD1 and PKD2
- Mosaic variants in PKD1 or PKD2 may not be detected
- Breakpoints for large deletions/duplications will not be determined
- Diagnostic errors can occur due to rare sequence variations

References