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

- Consugar MB, Wong WC, et al. Characterization of large rearrangements associated in autosomal dominant polycystic kidney disease and the PKD1/TSC2 contiguous gene syndrome. Kidney Int. 2008;74(11):1468-1479
- Paul BM, Vanden Heuvel GB. Kidney: polycystic kidney disease. Wiley Interdiscip Rev Dev Biol. 2014;3(6):465-487
- Rossetti S, Consugar MB, et al. Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2007;18:2143-2160