Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is a genetic condition that leads to the development of renal cysts and end-stage renal disease (ESRD) by the age of 60 years in 50% of affected individuals; it is the fourth leading cause of ESRD. ADPKD is caused by pathogenic variants in *PKD1* or *PKD2*. Genetic testing can be used to confirm a diagnosis of ADPKD in those with a confirmed or suspected clinical diagnosis, especially for individuals with equivocal renal imaging results, or as predictive testing for younger at-risk individuals being evaluated as potential living related kidney donors. Presymptomatic testing in minors is not recommended.

Disease Overview

Prevalence

1/500-1,000 in the U.S.[1]

Age of onset: usually adult onset of symptoms

Symptoms

- Kidneys
  - Bilateral renal cysts (may be present from birth)
  - Renal pain
  - Renal insufficiency (leading to hypertension)
  - Dilated renal tubules
  - Enlarged kidneys
  - ESRD
- Connective tissue
  - Intracranial aneurysms and/or hemorrhaging
  - Dolichoectasia
  - Dilation of aortic root
  - Aortic dissections
  - Mitral valve prolapse
  - Abdominal wall hernias
- Cysts may appear in other organs
  - Liver
  - Pancreas
  - Seminal vesicles
  - Arachnoid membrane

Diagnostic Criteria

Renal imaging can be used in at-risk individuals to identify renal cysts and diagnose ADPKD. The positive predictive value (PPV) of imaging is nearly 100% when following the Demetriou criteria below for at-risk individuals with a first-degree family member affected with ADPKD.[2]

Age (Yrs)	Number of Cysts
15-39	>3 in 1 or 2 kidneys
40-59	>4, with ≥2 in each kidney

Tests to Consider

Polycystic Kidney Disease, Autosomal Dominant (PKD1 and PKD2) Sequencing and Deletion/Duplication (Temporary Referral as of 06/09/20) 2012250

Method: Polymerase Chain Reaction/Sequencing/Multiplex Ligation-dependent Probe Amplification

Preferred test for molecular confirmation of suspected clinical diagnosis of ADPKD

Polycystic Kidney Disease, Autosomal Dominant (PKD1 and PKD2) Sequencing (Temporary Referral as of 06/09/20) 2012255

Method: Polymerase Chain Reaction/Sequencing

Acceptable test for molecular confirmation of suspected clinical diagnosis of ADPKD

Related Tests

Familial Mutation, Targeted Sequencing 2001961

Method: Polymerase Chain Reaction/Sequencing

- Useful for confirming a diagnosis when a pathogenic sequence variant has been identified in a family member
- A copy of the family member's lab report documenting the familial variant is REQUIRED

Deletion/Duplication Analysis by MLPA 3003144

Method: Multiplex Ligation-dependent Probe Amplification

- Useful for confirming a diagnosis when a pathogenic deletion/duplication variant has been identified in family member
- A copy of the family member's lab report documenting the familial variant is REQUIRED

Age (Yrs)	Number of Cysts
≥60	>8, with ≥4 in each kidney

Genetics

Genes

PKD1, *PKD2*[1]

Inheritance

- Autosomal dominant
- De novo rate: ~10%[3]

Penetrance

- Penetrance is age and genotype dependent
- Nearly all older adults develop multiple renal cysts
- Average age of onset for ERSD[4]
  - Individuals with *PKD1* variants: 54 years
  - Individuals with *PKD2* variants: 74 years

Test Interpretation

Sensitivity/Specificity

- Clinical sensitivity
  - Greater than 90% of individuals with ADPKD will have an identifiable variant in *PKD1* or *PKD2*[5]
    - 85% of cases are attributed to variants in *PKD1*[1,5]
    - Variants in *PKD1* are associated with more severe disease, including earlier age of diagnosis and onset of ESRD
    - 15% of cases are attributed to variants in *PKD2*[1,5]
  - Sequence variants account for majority of pathogenic variants (~97%)[4]
  - Large deletions/duplications in *PKD1* or *PKD2* account for a small percent of ADPKD cases (~3%)[5]
    - Large deletions involving *PKD1*/*TSC2* result in contiguous gene deletion syndrome with early-onset PKD and features of tuberous sclerosis
- Analytical sensitivity: 99%
- Analytical specificity: 99%

Results

Results	Variant(s) Detected	Clinical Significance
Positive	At least 1 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 of unknown clinical significance	Unknown if disease causing or benign

Limitations

- A negative result does not exclude a diagnosis of ADPKD
- Not detected:
  - Large deletions/duplications in *PKD1* (exons 1, 2, 4, 8, 17, 24, 28, 32, 34, and 45)
  - Regulatory region or deep intronic variants
- 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

1. Paul BM, Vanden Heuvel GB. Kidney: polycystic kidney disease. Wiley Interdiscip Rev Dev Biol. 2014;3(6):465-487. PubMed

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3. Harris PC, Torres VE. Polycystic kidney disease, autosomal dominant. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews, University of Washington; 1993-2020. [Last update: Jul 2018; Accessed: Sep 2020]

4. Rossetti S, Consugar MB, Chapman AB, et al. Comprehensive molecular diagnostics in autosomal dominant polycystic kidney disease. J Am Soc Nephrol. 2007;18(7):2143-2160. PubMed

5. Consugar MB, Wong WC, Lundquist PA, et al. Characterization of large rearrangements in autosomal dominant polycystic kidney disease and the PKD1/TSC2 contiguous gene syndrome. Kidney Int. 2008;74(11):1468-1479. PubMed

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