Polycystic Kidney Disease (PKD) Panel

Panel Gene List

*GANAB, HNF1B, PKD1, PKD2, PKHD1, PRKCSH, TSC2***

**Test is designed to identify a contiguous gene deletion involving *PKD1* and *TSC2*, not to identify sequencing and exon-level copy number variants of *TSC2*.

Clinical Features

Polycystic kidney disease is a multisystem disorder characterized by the development of multiple cysts in the kidney and other extrarenal features. Autosomal dominant polycystic kidney disease (ADPKD) is characterized by renal cysts that lead to hypertension, renal insufficiency and end-stage renal disease (ESRD). Onset ranges from the antenatal period to late adulthood and the severity of disease varies, even within the same family.[1,2] Penetrance is believed to be very high with most affected adults eventually developing bilateral renal cysts. While cysts may form in other organs, hepatic cysts are the most common extrarenal feature of ADPKD.[2] Individuals with ADPKD may also have vascular abnormalities including intracranial aneurysms, subarachnoid hemorrhage, and/or dilation of the aortic root.[1,2] The majority of ADPKD cases are caused by variants in *PKD1* and *PKD2*.[3] Pathogenic variants in *PKD1* and *PKD2* cause overlapping phenotypes; however, *PKD1* variants tend to be associated with more severe disease, as well as an earlier age of onset and progression to end-stage renalfailure.[4] Rarely, pathogenic biallelic variants in *PKD1* have been reported in individuals presenting with features similar to autosomal recessive PKD (ARPKD). In these cases, affected individuals have inherited a *PKD1* pathogenic variant from each of their unaffected parents.[5,6] Finally, a subset of individuals have presented with polycystic kidney disease as well as phenotypic features of tuberous sclerosis complex due to a contiguous gene deletion involving *PKD1* and the adjacent *TSC2* gene.[7] In regards to other genes tested in this panel, a small number of individuals is expected to have ADPKD due to pathogenic variants in the *GANAB* gene, and those individuals may or may not show liver disease manifestation.[8] Renal cysts following autosomal dominant inheritance have also been reported in patients with *HNF1B* and *PRKCSH* variants, although renal cysts are not the main clinical feature. Variants in *PRKCSH* are found in AD polycystic liver disease (PLD), which may present with occasional renal cysts.[9] Variants in *HNF1B* cause maturity-onset diabetes of the young type 5 (MODY5), which is characterized by renal cysts and diabetes (RCAD) syndrome.[10,11] Bi-genic variants in *HNF1B* and *PKD1* have been reported in individuals with severe PKD.[12] Autosomal recessive polycystic kidney disease (ARPKD) is characterized by bilateral renal cystic disease and congenital hepatic fibrosis, typically presenting in the developing fetus with oligohydramnios, enlarged echogenic kidneys and liver abnormalities.[13,14] Other symptoms may include nephromegaly, hypertension and renal dysfunction, often with onset of ESRD within the first decade of life. While features may be seen already in utero, peak age of onset ranges from birth into young adulthood. A subset of patients have a Caroli phenotype, which presents with cystic dilatation of the intrahepatic bile ducts.[14] ARPKD is a significant cause of renal and liver related morbidity and mortality in children, with severe cases leading to neonatal lethality.[13] The majority of cases of ARPKD are caused by bi-allelic pathogenic variants in the *PKHD1* gene.[12,15]

Genetics

Polycystic kidney disease is a genetically heterogeneous disorder that may be inherited in an autosomal dominant or autosomal recessive pattern. ADPKD is a common disorder usually presenting in adulthood, while ARPKD is a rare disorder that frequently presents in the prenatal, neonatal, or early childhood period.

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The majority of ADPKD cases are due to pathogenic variants in *PKD1* and *PKD2* (~95%) while most ARPKD cases are due to pathogenic variants in *PKHD1* (~75%). Multiple types of pathogenic variants have been reported in *PKD1* and *PKD2* and are disseminated across the genes without apparent mutation clusters. Large copy number changes, including intragenic or whole gene deletions/duplications or rearrangements account for approximately 4% of pathogenic variants in *PKD1* and <1% of variants in PKD2.[5] Rarely, ADPKD may be caused by gene conversion events between the PKD1 gene and one of its pseudogenes, which may not be detectable by this test.[16-21] Additionally, copy number variants encompassing multiple exons or the entire *HNF1B* gene, and more rarely, copy number variants affecting multiple exons of the *PKHD1* gene have been reported.[22-24]

Test Methods

Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. Sequence variants are reported according to the Human Genome Variation Society (HGVS) guidelines. Copy number variants are reported based on coordinates of involved exons, precise breakpoints or probe coordinates when partial exons are involved. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size. Sequencing of the *PKD1* gene is known to be particularly challenging since more than half of the gene (exons 1-33 out of 46 exons) shares high homology with its six known pseudogenes, all located on the same chromosome as *PKD1* (chromosome 16).[25,26] Accordingly, gene-specific long-range PCR analysis followed by nested amplification of each exon will be used for sequencing of exons 1-33. Multiplex ligation-dependent probe amplification (MLPA) is used to determine the copy number of the *PKD1* and *PKD2* genes, as well as evaluate for the presence of a contiguous gene deletion involving the *TSC2* gene. Deletions/duplications involving exons 31-46 of the *PKD1* gene and exons 1, 29, and 38-42 of the *TSC2* gene may not be reliably detected.

Clinical Sensitivity

Polycystic kidney disease is a genetically heterogeneous disorder. The clinical sensitivity of sequencing and deletion/duplication analysis of the genes included in this panel depends in part on the patient's clinical phenotype and family history. Although ADPKD and ARPKD are usually regarded as clinically distinct disorders, overlapping features and presentation, as well as lack of family history may lead to confusion.

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Panel testing including genes for both AD and ARPKD provides a solution for questionable diagnosis and is essential for genetic counseling. Additional information about the general clinical sensitivity of each gene is included in the table below.

Gene	Protein	Inheritance	Disease Association	Sensitivity
GANAB	Glucosidase II Alpha Subunit	AD	PKD3, with or without PLD	<1% of individuals with ADPKD[8]
HNF1B	HNF1 Homeobox B	AD	Renal cysts and diabetes syndrome (RCAD/MODY5)	40-70%of individuals with RCAD (MODY5)[23, 27]
PKD1	Polycystin 1	AD	PKD1	~80% of individuals with ADPKD[3,28]
PKD2	Polycystin 2	AD	PKD2	~15% of individuals with ADPKD[3,28]
PKHD1	Fibrocystin	AR	PKD4, with or without hepatic disease	~75% of individuals with ARPKD[6,29]
PRKCSH	Hepatocystin	AD	PLD1	15-33% of individuals with polycystic liver disease[30-32]
TSC2 (contiguous deletion with PKD1)	Tuberin	AD	Tuberous sclerosis2	Rare in individuals with ADPKD[7]

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