Polycystic Kidney Disease Panel

Test code: KI2101

Is ideal for patients suspected to have autosomal dominant or autosomal recessive polycystic kidney disease.

The panel covers genes associated with autosomal recessive and autosomal dominant forms of the disease.

About Polycystic Kidney Disease

Polycystic kidney disease (PKD) is inherited in an autosomal dominant (ADPKD) or recessive (ARPKD) fashion. It is characterized by the presence of multiple cysts, primarily in the kidneys and liver and can present both in the neonatal period as well as in adulthood. Typically, ADPKD is diagnosed in the second and third decades of life, while ARPKD frequently presents in utero or in the neonatal period with bilateral enlarged kidneys. Most families with ADPKD have a defect in the PKD1 gene (85%) and a smaller proportion in the PKD2 gene (15%). Antenatal ultrasonography can show enlarged hyperechogenic kidneys or macrocysts. Renal cyst infection represents a difficult problem and requires aggressive antibiotic therapy. ARPKD is frequently associated with hepatic involvement. Histologically, ARPKD has a characteristic radial pattern of fusiform cysts present in the dilated collecting ducts. Childhood-onset end-stage renal disease (ESRD) is characteristic of ARPKD, with up to 30% requiring kidney transplantation. However, ESRD rarely occurs before the age of 15 years. ADPKD is the most common form of polycystic kidney disease, the prevalence being estimated at 1:400–1:1,000, thus it is not a rare disease. ARPKD is rare, with an estimated incidence ranging between 1:20,000-1:40,000. Its prevalence in the general population is 1:85,000.

Availability

Results in 3-4 weeks

Gene set description

Genes in the Polycystic Kidney Disease Panel and their clinical significance

<table>
<thead>
<tr>
<th>Gene</th>
<th>Associated phenotypes</th>
<th>Inheritance</th>
<th>ClinVar</th>
<th>HGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNAJB11</td>
<td>Autosomal dominant polycystic kidney disease</td>
<td>AD</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>DZIP1L</td>
<td>Polycystic kidney disease 5</td>
<td>AR</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>GANAB</td>
<td>Polycystic kidney and/or polycystic liver disease 3</td>
<td>AD</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>HNF1B</td>
<td>Renal cell carcinoma, nonpapillary chromophobe, Renal cysts and diabetes syndrome</td>
<td>AD</td>
<td>35</td>
<td>234</td>
</tr>
<tr>
<td>JAG1</td>
<td>Alagille syndrome</td>
<td>AD</td>
<td>131</td>
<td>610</td>
</tr>
<tr>
<td>LRP5*</td>
<td>Van Buchem disease, Osteoporosis-pseudo吉lia syndrome, Hyperostosis, endosteal, Osteosclerosis, Exudative vitreoretinopathy, Osteopetrosis late-onset form type 1, LRP5 primary osteoporosis</td>
<td>AD/AR/Digenic</td>
<td>57</td>
<td>196</td>
</tr>
<tr>
<td>NOTCH2*</td>
<td>Alagille syndrome, Hajdu-Cheney syndrome</td>
<td>AD</td>
<td>37</td>
<td>70</td>
</tr>
<tr>
<td>PKD1*</td>
<td>Polycystic kidney disease</td>
<td>AD</td>
<td>237</td>
<td>1923</td>
</tr>
<tr>
<td>PKD2</td>
<td>Polycystic kidney disease</td>
<td>AD</td>
<td>55</td>
<td>333</td>
</tr>
<tr>
<td>PKHD1</td>
<td>Polycystic kidney disease</td>
<td>AR</td>
<td>249</td>
<td>557</td>
</tr>
</tbody>
</table>
Some regions of the gene are duplicated in the genome leading to limited sensitivity within the regions. Thus, low-quality variants are filtered out from the duplicated regions and only high-quality variants confirmed by other methods are reported out. Read more.

Gene, refers to HGNC approved gene symbol; Inheritance to inheritance patterns such as autosomal dominant (AD), autosomal recessive (AR) and X-linked (XL); ClinVar, refers to a number of variants in the gene classified as pathogenic or likely pathogenic in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/); HGMD, refers to a number of variants with possible disease association in the gene listed in Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/). The list of associated (gene specific) phenotypes are generated from CDG (http://research.nhgri.nih.gov/CGD/) or Orphanet (http://www.orpha.net/) databases.

**Non-coding disease causing variants covered by the panel**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genomic location HG19</th>
<th>HGVS</th>
<th>RefSeq</th>
<th>RS-number</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAG1</td>
<td>Chr20:10629767</td>
<td>c.1349-12T&gt;G</td>
<td>NM_000214.2</td>
<td></td>
</tr>
<tr>
<td>PKD1</td>
<td>Chr16:2140209</td>
<td>c.12445-14T&gt;C</td>
<td>NM_001009944.2</td>
<td></td>
</tr>
<tr>
<td>PKD1</td>
<td>Chr16:2147825</td>
<td>c.10167+25_10167+43delGGCTGGGCTGGGGGTCCTG</td>
<td>NM_001009944.2</td>
<td>rs1197421698</td>
</tr>
<tr>
<td>PKD1</td>
<td>Chr16:2152273</td>
<td>c.9202-16G&gt;A</td>
<td>NM_001009944.2</td>
<td>rs1389523126</td>
</tr>
<tr>
<td>PKD2</td>
<td>Chr4:88940551</td>
<td>c.596-59A&gt;G</td>
<td>NM_000297.3</td>
<td>rs750504141</td>
</tr>
<tr>
<td>PKHD1</td>
<td>Chr6:51618610</td>
<td>c.8798-459C&gt;A</td>
<td>NM_138694.3</td>
<td></td>
</tr>
<tr>
<td>PKHD1</td>
<td>Chr6:51747238</td>
<td>c.7350+653A&gt;G</td>
<td>NM_138694.3</td>
<td></td>
</tr>
</tbody>
</table>

**Test performance**

The Blueprint Genetics polycystic kidney disease panel covers classical genes associated with autosomal recessive polycystic kidney disease, cystic kidney disease and autosomal dominant polycystic kidney disease. The genes on the panel have been carefully selected based on scientific literature, mutation databases and our experience.

Our panels are sliced from our high-quality whole exome sequencing data. Please see our sequencing and detection performance table for different types of alterations at the whole exome level (Table).

Assays have been validated for different starting materials including EDTA-blood, isolated DNA (no FFPE), saliva and dry blood spots (filter card) and all provide high-quality results. The diagnostic yield varies substantially depending on the assay used, referring healthcare professional, hospital and country. Blueprint Genetics’ Plus Analysis (Seq+Del/Dup) maximizes the chance to find a molecular genetic diagnosis for your patient although Sequence Analysis or Del/Dup Analysis may be a cost-effective first line test if your patient’s phenotype is suggestive of a specific mutation type.

**Bioinformatics**

The target region for each gene includes coding exons and ±20 base pairs from the exon-intron boundary. In addition, the panel includes non-coding variants if listed above (Non-coding variants covered by the panel). Some regions of the gene(s) may be removed from the panel if specifically mentioned in the “Test limitations” section above. The sequencing data generated in our laboratory is analyzed with our proprietary data analysis and annotation pipeline, integrating state-of-the art
algorithms and industry-standard software solutions. Incorporation of rigorous quality control steps throughout the workflow of the pipeline ensures the consistency, validity and accuracy of results. Our pipeline is streamlined to maximize sensitivity without sacrificing specificity. We have incorporated a number of reference population databases and mutation databases such as, but not limited, to 1000 Genomes Project, gnomAD, ClinVar and HGMD into our clinical interpretation software to make the process effective and efficient. For missense variants, *in silico* variant prediction tools such as SIFT, PolyPhen, MutationTaster are used to assist with variant classification. Through our online ordering and statement reporting system, Nucleus, the customer has an access to details of the analysis, including patient specific sequencing metrics, a gene level coverage plot and a list of regions with inadequate coverage if present. This reflects our mission to build fully transparent diagnostics where customers have easy access to crucial details of the analysis process.

**Clinical interpretation**

We provide customers with the most comprehensive clinical report available on the market. Clinical interpretation requires a fundamental understanding of clinical genetics and genetic principles. At Blueprint Genetics, our PhD molecular geneticists, medical geneticists and clinical consultants prepare the clinical statement together by evaluating the identified variants in the context of the phenotypic information provided in the requisition form. Our goal is to provide clinically meaningful statements that are understandable for all medical professionals regardless of whether they have formal training in genetics.

Variant classification is the cornerstone of clinical interpretation and resulting patient management decisions. Our classifications follow the Blueprint Genetics Variant Classification Schemes based on the ACMG guideline 2015. Minor modifications were made to increase reproducibility of the variant classification and improve the clinical validity of the report. Our experience with tens of thousands of clinical cases analyzed at our laboratory allowed us to further develop the industry standard.

The final step in the analysis of sequence variants is confirmation of variants classified as pathogenic or likely pathogenic using bi-directional Sanger sequencing. Variant(s) fulfilling the following criteria are not Sanger confirmed: the variant quality score is above the internal threshold for a true positive call, and visual check-up of the variant at IGV is in-line with the variant call. Reported variants of uncertain significance are confirmed with bi-directional Sanger sequencing only if the quality score is below our internally defined quality score for true positive call. Reported copy number variations with a size <10 exons are confirmed by orthogonal methods such as qPCR if the specific CNV has been seen less than three times at Blueprint Genetics.

Our clinical statement includes tables for sequencing and copy number variants that include basic variant information (genomic coordinates, HGVS nomenclature, zygosity, allele frequencies, *in silico* predictions, OMIM phenotypes and classification of the variant). In addition, the statement includes detailed descriptions of the variant, gene and phenotype(s) including the role of the specific gene in human disease, the mutation profile, information about the gene’s variation in population cohorts and detailed information about related phenotypes. We also provide links to the references used, congress abstracts and mutation databases to help our customers further evaluate the reported findings if desired. The conclusion summarizes all of the existing information and provides our rationale for the classification of the variant.

Identification of pathogenic or likely pathogenic variants in dominant disorders or their combinations in different alleles in recessive disorders are considered molecular confirmation of the clinical diagnosis. In these cases, family member testing can be used for risk stratification within the family. In the case of variants of uncertain significance (VUS), we do not recommend family member risk stratification based on the VUS result. Furthermore, in the case of VUS, we do not recommend the use of genetic information in patient management or genetic counseling.

Our interpretation team analyzes millions of variants from thousands of individuals with rare diseases. Thus, our database, and our understanding of variants and related phenotypes, is growing by leaps and bounds. Our laboratory is therefore well positioned to re-classify previously reported variants as new information becomes available. If a variant previously reported by Blueprint Genetics is re-classified, our laboratory will issue a follow-up statement to the original ordering health care provider at no additional cost.

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ICD-10 | Disease
--- | ---
Q61.19 | Autosomal recessive polycystic kidney disease
Q61.9 | Cystic kidney disease
Q61.2 | Autosomal dominant polycystic kidney disease

**Accepted sample types**

- EDTA blood, min. 1 ml
- Purified DNA, min. 3μg*
- Saliva (Oragene DNA OG-500 kit)

Label the sample tube with your patient’s name, date of birth and the date of sample collection.

Note that we do not accept DNA samples isolated from formalin-fixed paraffin-embedded (FFPE) tissue.

**Resources**

- ARPKD/CHF Alliance
- ARegPKD
- GeneReviews - Autosomal Dominant Polycystic Kidney Disease
- GeneReviews - Autosomal Recessive Polycystic Kidney Disease
- NORD - Autosomal Dominant Polycystic Kidney Disease
- NORD - Autosomal Recessive Polycystic Kidney Disease
- PKD Charity
- PKD Foundation
- PKD Foundation Australia
- PKD International