Cystic Kidney and Liver Disease (CKLD) Panel

Panel Gene List (49 genes): ***AHI1, ALG8, ALG9, ANKS6, BICC1, CC2D2A, CEP120, CEP290, CEP83, COL4A1, CRB2, CSPP1, GANAB, GLIS2, GLIS3, HNF1B, IFT172, INVS, IQCB1, JAG1, LRP5, MKKS, MKS1, NEK8, NOTCH2, NPHP1, NPHP3, OFD1, PAX2, PKD1, PKD2, PKHD1, PMM2, PRKCSH, RMND1, RPGRIP1L, SEC61A1, SEC63, TMEM138, TMEM216, TMEM231, TMEM237, TMEM67, TSC1, TSC2, TTC21B, UMOD, VHL, WDR35***

CLINICAL FEATURES AND GENETICS:

Cystic kidney and liver diseases are a collection of multisystem disorders that present with development of cysts in the kidney and/or liver as well as other organ systems. These diseases can be categorized by underlying etiology (ciliopathies or phakomatoses) or by morphology (size, location, and complexity of cysts).[1,2]

Hepatorenal ciliopathic disorders include polycystic kidney disease (PKD), polycystic liver disease (PLD), nephronophthisis (NPHP), and medullary cystic kidney disease (MCKD). Polycystic kidney disease has two major forms, autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD). ADPKD is characterized by renal cysts that lead to hypertension, renal insufficiency, and end-stage renal disease (ESRD).[3,4] While cysts may form in other organs, hepatic cysts are the most common extrarenal feature of ADPKD.[4] The majority of ADPKD cases are caused by variants in the PKD1 and PKD2 genes, while a small number of individuals may have ADPKD due to variants in the GANAB gene.[5,6] ARPKD is characterized by bilateral renal cystic disease and congenital hepatic fibrosis, typically already presenting in the developing fetus with oligohydramnios and enlarged echogenic kidneys and liver.[7,8] The majority of cases of ARPKD are caused by homozygous or compound heterozygous pathogenic variants in the PKHD1 gene.[9,10] Polycystic liver disease (PLD) is characterized by progressive development of multiple liver cysts, with or without kidney cyst presentation.[11] PLD patients are usually asymptomatic with normal hepatic function prior to disease manifestation between the age of 40 and 60 years old.[12] The most common complication in symptomatic patients is extensive hepatomegaly, which may lead to malnutrition and can be lethal.[13] Isolated PLD is an autosomal dominant disorder (ADPLD) which is caused by pathogenic variants in the PRKCSH, SEC63, LRP5, ALG8, or GANAB genes; however, PRKCSH and SEC63 collectively account for at least 35% of cases.[14] Nephronophthisis (NPHP) is characterized by cystic kidney disease, reduced renal concentrating ability, chronic inflammation of the renal tubules and ESRD before the age of 30 years old.[15-17] Clinically, NPHP can be subdivided based on ESRD onset into infantile, juveline and adult NPHP. NPHP-related ciliopathies (NPHP-RC) are a group of heterogenous disorders that present with extrarenal features and share a wide variety of phenotype overlap due to multi-organ involvement and include Bardet-Biedl syndrome, COACH syndrome, Jeune syndrome and related skeletal disorders, Joubert syndrome, Meckel syndrome (also known as Meckel-Gruber syndrome), Senior-Loken syndrome and others.[18] NPHP-RC are inherited in a recessive manner. Medullary cystic kidney disease (MCKD), also known as autosomal dominant tubulointerstitial kidney disease (ADTKD), is characterized by fibrosis or scarring of the kidney tubules, which leads to slowly progressive chronic kidney disease.[19] Variants in several genes including MUC1, UMOD, REN

and SEC61A1 have been associated with various subtypes of ADTKD. The UMOD and SEC61A1 genes are included in this panel.
Phakomatoses are a group of hereditary neurocutaneous disorders that present with multi-system features, and commonly affected tissues include the central nervous system, eyes, and skin. While the clinical presentation may vary, these patients may also manifest with renal cysts.[1] Tuberous sclerosis complex (TSC) is an autosomal dominant disorder characterized by abnormalities of the skin, brain, kidney, heart, and lungs. Individuals with TSC, which is caused by pathogenic variants in the tumor suppressor TSC1 or TSC2 genes, have a significantly increased risk for neurodevelopmental disorders.[20] Rarely, individuals with TSC may also exhibit multiple renal cysts often leading to ESRD and an increased risk for Berry aneurysms and cysts in other organs. Individuals with features of both TSC and PKD typically have a contiguous gene deletion syndrome involving the neighboring TSC2 and PKD1 genes.[21] Another type of phakomatosis is Von Hippel-Lindau syndrome (VHL), an autosomal dominant hereditary cancer predisposition syndrome caused by germline variants in the VHL tumor suppressor gene. VHL is characterized by an increased risk for central nervous system hemangioblastomas (60–80%), retinal capillary hemangiomas (also referred to as retinal angiomas) (50–60%), renal cysts and carcinomas (30–60%), pancreatic cysts (30–65%), pheochromocytomas (11–19%), epididymal cystadenomas (26%), and endolymphatic sac tumors (2–10%).[22,23] VHL is highly penetrant and virtually all individuals who harbor a variant in the VHL gene develop symptoms by 70 years of age.[24] However, the clinical manifestations and disease severity are highly variable, even among family members with the same variant.
Other genes previously reported to be associated with kidney cyst presentation and included in this panel are ALG9, BICC1, COL4A1, CRB2, GLIS3, HNF1B, IFT172, JAG1, NOTCH2, PAX2, PMM2, RMND1 and WDR35.

INHERITANCE PATTERN/GENETICS:
Autosomal Dominant, Autosomal Recessive, X-Linked

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. Of note, the CEP290 intronic c.2991+1655 A>G (IVS26+1655) pathogenic variant is captured by our methodology.
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] In addition to NGS-CNV methodology, gene-specific long-range PCR analysis followed by nested amplification of each exon will be used for sequencing of exons 1-33. This sequencing methodology is designed to largely avoid false-positive/negative PKD1 sequencing results and to reveal the presence of gene conversion events involving the PKD1 gene and the pseudogenes, which have been published in association with ADPKD.

Multiplex Ligaton-Dependent Probe Amplification (MLPA) is performed to identify most intragenic deletions or duplications involving at least one (PKD2) or two or more (PKD1) exons. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. For the NOTCH2 gene, sequencing and deletion/duplication testing is not performed for exons 1-4. Additional gene specific exclusions for exon-level deletion/duplication testing for this panel are: AHI1, ALG8, CEP120, CSPP1, MKKS, RMND1, WDR35 – no copy number testing; TMEM231 – only whole gene deletions or duplications may be reported, and gene conversion is not detected. Reportable clinically significant variants are confirmed by an appropriate method, and reported according to the International System for Human Cytogenetic Nomenclature (ISCN) guidelines. 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.

DNA sequencing will detect nucleotide substitutions and small insertions and deletions, while NGS-CNV analysis, array CGH, or MLPA will detect exon-level deletions and duplications. The technical sensitivity of sequencing is estimated to be greater than 99% sensitive at detecting single nucleotide events, and lesser for deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. NGS-CNV analysis and array CGH methodologies 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. Some genes, such as PKD1, have inherent sequence properties (including repeats, homology, or pseudogene regions, gene rearrangements, high GC content and rare polymorphisms) that may result in suboptimal data, potentially impairing accuracy of the results.

TEST SENSITIVITY:

CKLD is a genetically heterogeneous group of diseases. 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. Additional information about the general clinical sensitivity of each gene is included in the table below.

Gene	Protein	Inheritance	Disease Associations	Sensitivity
AHI1	Abelson helper integration site 1; Jouberin	AR	JS 3	7-10% of JS 27-31
ALG8	Alpha-1,3-glucosyltransferase	AD / AR	AD PLD 3, with or without kidney cysts / AR CDG 1h	~3% of isolated PLD[14,32]
ALG9	Alpha-1,2-mannosyltransferase ALG9	AR	CDG 1L / GIKANIS	Rare[33-34]
ANKS6	Ankyrin repeat and sterile alpha motif domains-containing protein 6	AR	NPHP 16	~2% of NPHP[35-36]

BICC1	BicC family RNA binding protein 1	AD	CAKUT / Cystic renal dysplasia	Rare[37-38]
CC2D2A	Coiled-coil and C2 domain containing 2A	AR	MKS 6 / JS 9 / COACH syndrome	~4-9% of MKS[39-40] ~8-11% of JS[30-31,41-43] Rare in COACH syndrome
CEP120	Centrosomal protein 120KD	AR	JS 31 / SRTD 13	~1% of JS and Rare in SRTD[44-45]
CEP290	Centrosomal protein 290KD	AR	SLS 6 / JS 5 / LCA 10 / MKS 4	Rare in SLS and MKS[40,46-47] ~7-10% of JS[27,30-31,48-51]
CEP83	Centrosomal protein 83KD	AR	NPHP 18	<1% of NPHP[52]
COL4A1	Collagen type IV alpha 1 chain	AD	HANAC	Rare[53-54]
CRB2	Crumbs cell polarity complex component 2	AR	Ventriculomegaly with Cystic Kidney Disease	Rare[55]
CSPP1	Centrosome and spindle pole associated protein 1	AR	JS 21	2-4% of JS[30-31,48,56]
GANAB	Glucosidase II Alpha Subunit	AD	PKD 3, with or without PLD	~2% of isolated PLD[6,32] <1% of ADPKD6
GLIS2	GLIS family zinc finger 2	AR	NPHP 7	Rare[18]
GLIS3	GLIS family zinc finger 3	AR	NDH	Rare[57-58]
HNF1B	HNF1 Homeobox B	AD	Renal cysts and diabetes syndrome (RCAD/MODY5)	40-70% of RCAD (MODY5)[26,59]
IFT172	Intraflagellar transport 172	AR	SRTD 10	Rare[13]
INVS	Inversin	AR	NPHP 2	1-2% of NPHP [18.60-61]
IQCB1	IQ motif containing B1	AR	SLS 5	35/67 individuals with SLS[46]
JAG1	Jagged canonical Notch ligand 1	AD	ALGS	~94% of ALGS[62-63]
LRP5	Low density lipoprotein receptor-related protein 5	AD / AR	FEVR / LRP5-associated bone disorders / PLD 4 with or without kidney cysts	10-25% of FEVR[64-66] ~2% of isolated PLD[67]
MKKS	Bardet-Biedl syndrome 6 protein	AR	MKKS / BBS6	~5% of BBS[68]
MKS1	MKS transition zone complex subunit 1	AR	BBS 13 / MKS 1 / JS 28	~4% of BBS[69] ~2-6% of JS[30-31,70] 3-14% of MKS[40,71-72]
NEK8	NIMA related kinase 8	AR	RHPD 2 / NPHP 9	Rare[73]
NOTCH2	Notch receptor 2	AD	ALGS / HCS	~1-2% of ALGS[74-75] ~83-100% of HCS[76-79]
NPHP1	Nephrocystin 1	AR	JS 4 / SLS 1 / NPHP 1	1-2% of JS[80-81] 20-25% of NPHP[18,82]

NPHP3	Nephrocystin 3	AR	MKS 7 / NPHP 3 / RHPD 1	~1-2% of NPHP [18,61,83] Rare in MKS and RPHD[84-86]
OFD1	OFD1, centriole and centriolar satellite protein	XL	JS 10 / OFD 1	80-85% of OFD187 Rare in JS [27,30,88-89]
PAX2	Paired box 2	AD	FSG 7 / Papillorenal syndrome	50% of papillorenal syndrome[90-93]
PKD1	Polycystin 1	AD	PKD 1	~80% of ADPKD[5,94]
PKD2	Polycystin 2	AD	PKD 2	~15% of ADPKD[5,94]
PKHD1	Fibrocystin	AR	PKD 4, with or without hepatic disease	~75% of ARPKD95-96
PMM2	Phosphomannomutase 2	AR	CDG 1a	~90-100% of CDG 1a[97-99]
PRKCSH	Hepatocystin	AD	PLD 1	~15-33% of isolated PLD[100-102]
RMND1	Required for meiotic nuclear division 1 homolog	AR	Combined oxidative phosphorylation deficiency 11	Rare103-105
RPGRIP1L	RPGRIP1 like	AR	COACH syndrome / JS 7 / MKS 5	~1-4% of JS[30, 106-108] Rare in COACH and MKS[40,42]
SEC61A1	Sec61 translocon alpha 1 subunit	AD	ADTKD	Rare109
SEC63	Translocation protein SEC63 homolog	AD	PLD 2	6-15% of isolated PLD[67,102, 110]
TMEM138	Transmembrane protein 138	AR	JS 16	Rare111
TMEM216	Transmembrane protein 216	AR	JS 2 / MKS 2	~3% of JS30 Rare in MKS112
TMEM231	Transmembrane protein 231	AR	JS 20 / MKS 11	Rare[27,113-115]
TMEM237	Transmembrane protein 237	AR	JS 14	Rare[40,72,116-117]
TMEM67	Transmembrane protein 67	AR	COACH syndrome / JS 6 / MKS 3 / NPHP 11	~74-80% of COACH[42,118] ~10-28% of MKS[40,71] ~5-10% of JS[27,30] ~2-3% of NPHP [18,60-61]
TSC1	Hamartin	AD	Tuberous sclerosis 1	15-17% of TSC119-121
TSC2	Tuberin	AD	Tuberous sclerosis 2	Rare in ADPKD21 50-65% of TSC119-121
TTC21B	Tetratricopeptide repeat domain-containing protein 21b	AR	NPHP 12 / SRTD 4	Rare in NPHP and SRTD[18,122-123]
UMOD	Uromodulin	AD	ADTKD	>95% of ADTKD-UMOD[124]
VHL	von Hippel-Lindau tumor suppressor	AD	VHL	~90-100% of VHL125
WDR35	WD repeat domain 35	AR	SRTD 7	Rare126

Abbreviations: AR – Autosomal Recesive ; AD – Autosomal Dominant ; XL – X-Linked

ADTKD – Autosomal Dominant Tubulointerstitial Kidney Disease ; ALGS – Alagille syndrome ; BBS – Bardet-Biedl syndrome ; CAKUT – Congenital anomalies of the kidney and urinary tract ; CDG – Congenital Disorders of Glycosylation ; FSG – Focal Segmental Glomerulosclerosis ; GIKANIS - Gillessen-Kaesbach-Nishimura syndrome ; HANAC - Hereditary angiopathy with nephropathy, aneurysms, and muscle cramps ; HCS - Hadju-Cheney syndrome ; JS – Joubert syndrome ; MKKS – McKusick-Kaufman syndrome ; MKS – Meckel syndrome ; NDH – Neonatal Diabetes Mellitus with Congenital Hypothyroidism ; NPHP – Nephronopthisis; OFD - Orofaciodigital syndrome ; PKD – Polycystic Kidney Disease ; PLD – Polycystic Liver Disease ; RHPD - Renal-hepatic-pancreatic dysplasia ; SLS – Senior-Loken syndrome ; SRTD – Short-Rib Thoracic Dysplasia with or without polydactyly ; VHL – von Hippel Lindau syndrome

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