THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Next Generation Sequencing Panel for Renal Cystic Disorders

Clinical Features: Renal cystic diseases are a genetically heterogeneous group of conditions characterized by isolated renal disease or renal cysts in conjunction with extrarenal features (1). Age of onset of renal cystic disease ranges from neonatal to adult onset. Common features of renal cystic diseases include renal insufficiency and progression to end stage renal disease (ESRD). Identification of the genetic etiology of renal cystic disease can aid in appropriate clinical management of the affected patient.

Our Renal Cystic Disorders Panel includes sequence and deletion/duplicaton analysis of all 79 genes listed below.

Renal Cystic Disorders Sequencing Panel					
AHI1	BMPER	HNF1B	NEK8	TCTN3	WDPCP
ANKS6	C5orf42	IFT27	NOTCH2	TFAP2A	WDR19
ARL13B	CC2D2A	IFT140	NPHP1	TMEM107	XPNPEP3
ARL6	CDC73	IFT172	NPHP3	TMEM138	ZNF423
B9D1	CEP104	INPP5E	NPHP4	TMEM216	
B9D2	CEP120	INVS	OFD1	TMEM231	
BBIP1	CEP164	IQCB1	PDE6D	TMEM237	
BBS1	CEP290	JAG1	PKD2	TMEM67	
BBS10	CEP41	KIAA0556	PKHD1	TRIM32	
BBS12	CEP83	KIAA0586	REN	TSC1	
BBS2	CRB2	KIF14	RPGRIP1L	TSC2	
BBS4	CSPP1	KIF7	SALL1	TTC21B	
BBS5	DCDC2	LZTFL1	SDCCAG8	TTC8	
BBS7	GLIS2	MKKS	TCTN1	UMOD	
BBS9	GLIS3	MKS1	TCTN2	VHL	

Disorder	Genes	Inheritance	Clinical features/molecular genetics
Bardet Biedl syndrome	*ARL6* *BBS1* *BBS10* *BBS12* *BBS2* *BBS4* *BBS5* *BBS7* *BBS9* *CEP290* *MKKS* *MKS1* *SDCCAG8* *TRIM32* *TTC8* *WDPCP*	AR	Bardet-Biedl syndrome (BBS) is an autosomal recessive multi-systemic ciliopathy characterized by retinal dystrophy, obesity, postaxial polydactyly, leaning difficulties, renal involvement and genitourinary abnormalities (2). Visual prognosis is poor, and the mean age of legal blindness is 15.5 years. Birth weight is typically normal but significant weight gain begins within the first year. Renal disease is a major cause of morbidity and mortality. There is considerable interfamilial and intrafamilial variability in the clinical presentation (3). Generally speaking BBS is considered to be an autosomal recessive condition. There are several reported cases of a triallelic mode of inheritance where three mutations in BBS genes are required before the phenotype becomes apparent, or alternatively where a third disease locus acts as a disease modifier (2). Triallelic inheritance is considered to be uncommon (4).

Joubert syndrome	*AHI1* *ARL13B* *C5orf42* *CC2D2A* *CEP41* *CEP104* *CEP290* *CSPP1* *IFT172* *INPP5E* *KIAA0556* *KIAA0586* *KIF7* *KIF14* *OFD1* *NPHP1* *PDE6D* *RPGRIP1L* *TCTN1* *TCTN3* *TMEM67* *TMEM107* *TMEM138* *TMEM216* *TMEM231* *TMEM237* *TTC21B*	AR	Joubert syndrome (JBTS) is characterized by hypotonia, oculomotor apraxia, nystagmus, and intellectual disability. In these patients, brain MRI reveals the pathognomonic "molar tooth sign" (MTS) with absent or hypoplastic cerebellar vermis, deepened interpenduncular fossa, and elongated superior cerebellar peduncles. The term Joubert syndrome and related disorders (JSRD) is used to describe individuals who, in addition to having the core neurological features, also have additional findings including retinal dystrophy, ocular colobomas, kidney disease, liver fibrosis, occipital encephalocele, oral hamartomas, endocrine abnormalities and polydactyly (5).
Meckel-Gruber syndrome	*B9D1* *B9D2* *CC2D2A* *CEP290* *CSPP1* *KIF14* *MKS1* *NPHP3* *RPGRIP1L* *TCTN2* *TCTN3* *TMEM107* *TMEM216* *TMEM231* *TMEM67*	AR	Meckel Gruber syndrome (MKS) is the most common syndromic form of neural tube defect and the classic triad of clinical features is characterized by occipital encephalocele, cystic kidneys and fibrotic changes to the liver. The clinical phenotype has since been broadened to include features such as postaxial polydactyly, skeletal dysplasia, microphthalmia, genital anomalies, cleft lip and palate, and heart defects (6). Mutations are identified in approximately 75% of cases of Meckel Gruber syndrome.
Autosomal dominant tubulointerstitial kidney disease	*REN* *UMOD*	AD	Autosomal dominant tubulointerstitial kidney disease (ADTKD, previously known as medullary cystic disease) is characterized by slowly progressive interstitial kidney disease leading to end stage renal disease (ESRD) and need for kidney transplantation (7). The age of ESRD varies widely among affected individuals, even within the same family. Medullary cysts may or may not be present. ADTKD can be caused by mutations in one of three genes, *MUC1, UMOD,* and *REN* (7-9). However, **please note that this panel does not evaluate the *MUC1* gene,** as *MUC1*-related ADTKD is caused by an insertion within a variable-number tandem repeat that is not detectable by next-generation sequencing (10).
Nephronophthisis	*ANKS6* *CEP164* *CEP290* *CEP83* *DCDC2* *GLIS2* *INVS* *IQCB1* *NEK8* *NPHP1* *NPHP3* *NPHP4* *RPGRIP1L* *SDCCAG8* *TMEM67* *TTC21B* *WDR19* *XPNPEP3*	AR	Nephronophthisis (NPHP), the most frequent genetic cause of renal failure in children, is an autosomal recessive cystic kidney disease in childhood or adolescence. The onset is typically marked by polydipsia and polyuria as a result of a defect in urine concentration. Additional findings include small-to-normal-sized hyperechogenic kidneys with reduced corticomedullary differentiation on abdominal ultrasonography and histopathological alterations characterized by thickened or disrupted tubular basement membranes, tubular atrophy and dilation, interstitial fibrosis and occasional renal cysts (11). NPHP can also present with additional extrarenal manifestations, including retinitis pigmentosa (Senior-Loken syndrome, Bardet-Biedl syndrome, Alstrom syndrome), liver fibrosis, cerebellar vermis hypoplasia (Joubert syndrome), and multiple developmental and neurologic abnormalites (Meckel Gruber syndrome) (12).
Polycystic kidney disease, autosomal dominant	*PKD2*	AD	Autosomal dominant polycystic kidney disease (ADPKD) is a late-onset, multisystemic disease characterized by renal cysts as well as cysts in other organs, including the liver, pancreas, and seminal vesicles (1). Other extrarenal features include mitral valve prolapse, abdominal wall hernia, and vascular abnormalities including intracranial aneurysm and aortic root dilatation (13). Approximately half of individuals with ADPKD progress to end stage renal

			disease by 60 years of age. ADPKD is caused by a mutation in either *PKD2* or *PKD1*. **Please note that this panel does not evaluate the *PKD1* gene due to the presence of multiple *PKD1* pseudogenes.**
Polycystic kidney disease, autosomal recessive	*PKHD1*	AR	Autosomal recessive polycystic kidney disease (ARPKD) is a congenital disorder characterized by enlarged, echogenic kidneys with multiple small cystic spaces involving the renal cortex and medulla (1). Renal cystic disease is typically noted in the neonatal period. Over half of children with ARPKD progress to end stage renal disease (ESRD) within the first decade of life (14). Other features of ARPKD include hypertension, hepatobiliary disease, and pulmonary hypoplasia secondary to oligohydramnios (14). ARPKD is caused by mutations in the *PKHD1* gene.
Senior-Loken syndrome	*NPHP1* *NPHP4* *IQCB1* *CEP290* *SDCCAG8*	AR	The main features of Senior-Loken syndrome are nephronophthisis and retinopathy. Congenital retinal dystrophy consistent with Leber congenital amaurosis is the most common retinal finding in patients with Senior-Loken syndrome. However, some patients exhibit retinitis pigmentosa with later onset of retinal symptoms (15). Satran *et al.,* 1999, reported that the majority of patients with a clinical diagnosis of Senior-Loken syndrome also have cerebellar vermis hypoplasia and intellectual disabilities (15).
Tuberous sclerosis	*TSC1* *TSC2*	AD	Tuberous sclerosis complex (TSC) is a multisystemic disorder with features including skin abnormalities, CNS tumors, seizures, and intellectual disabilities. Renal findings include renal angiomyolipomas and renal cysts. Individuals with TSC exhibit significant variability, even within the same family. Clinical diagnostic criteria have been developed to aid in the diagnosis of TSC (16). Mutations in *TSC2* are identified in approximately 66% of cases of TSC and mutations in *TSC1* are identified in approximately 24% of cases. The remaining 10% of cases do not have an identifiable underlying molecular cause (17).
Von Hippel-Lindau syndrome	*VHL*	AD	Von Hippel-Lindau (VHL) syndrome is a hereditary cancer syndrome characterized by multiple tumor types, including hemangioblastomas of the central nervous system, pheochromocytoma, and paraganglioma. Renal findings include renal cysts and clear cell renal cell carcinoma (18). VHL is caused by heterozygous mutations in the *VHL* gene. Approximately 80% of individuals with VHL have an affected parent (18).
Renal cysts and diabetes syndrome	*HNF1B*	AD	Heterozygous pathogenic variants in *HNF1B* are associated with renal cysts and diabetes syndrome. Individuals affected with this condition have variable renal disease and diabetes, which may occur before the age of 25, making it consistent with a diagnosis of maturity-onset diabetes of the young (MODY). Affected individuals may also have genitourinary abnormalities (OMIM#137920).
Townes-Brocks syndrome	*SALL1*	AD	Townes-Brocks syndrome (TBS) is an autosomal dominant condition characterized by imperforate anus, dysplastic ears and thumb malformations. Renal impairment is reported in 42% of individuals with TBS with or without structural impairment. Most pathogenic variants resulting in TBS occur in the N-terminal third of the *SALL1* coding region (19)
Neonatal diabetes mellitus with congenital	*GLIS3*	AR	Biallelic mutations in *GLIS3* are a rare cause of neonatal diabetes and hypoparathyroidism. In a 2015 study, 7 of 12 patients with *GLIS3*-related neonatal

hypothyroidism			diabetes and hypothyroidism also presented with renal cystic dysplasia ranging from an isolated cyst to extensive cystic renal dysplasia (20).
Ventriculomegaly with cystic kidney disease	*CRB2*	AR	Slavotinek *et al*. reported five fetuses and an infant from three families with ventriculomegaly and cystic kidney disease. Families presented in the prenatal setting with high AFP levels or abnormal ultrasound findings prior to the end of the second trimester. All but one pregnancy were terminated; the affected infant died at seven months and had ventriculomegaly, gray matter heterotopia, seizures, nephrotic syndrome and a ventricular septal defect (21).
Hajdu-Cheney syndrome	*NOTCH2*	AD	Hajdu-Cheney syndrome, caused by heterozygous mutations in *NOTCH2*, is characterized by short stature, bowing of the bones, vertebral and craniofacial abnormalities, and cardiac defects. Progressive focal bone destruction is a characteristic feature of this condition. Renal cysts are commonly reported in patients with Hajdu-Cheney syndrome, as well as in patients with *NOTCH2*-related Alagille syndrome (22)
Hyperparathyroidism-jaw tumor syndrome	*CDC73*	AD	Hyperparathyroidism-jaw tumor (HPT-JT) syndrome is caused by heterozygous mutations in the *CDC73* gene, and is characterized by the occurrence of primary hyperparathyroidism, ossifying fibroma of the maxilla and/or mandible, as well as renal and uterine tumors. In two studies including 3 families with HPT-JT syndrome, multiple affected individuals also presented with cystic kidney disease (23, 24)
Branchiooculofacial syndrome (BOFS)	*TFAP2A*	AD	Branchiooculofacial syndrome (BOFS) is a craniofacial disorder characterized by branchial cleft sinus defects, ocular anomalies, dysmorphic facial features, and ear abnormalities. This condition is caused by heterozygous mutations in the *TFAP2A* gene. In a study by Milunsky *et al*, 12/34 individuals affected with BOFS (35%) were found to have renal anomalies including dysplasia, agenesis, multicystic kidneys and vesicoureteral reflux (25).
Alagille syndrome-1	*JAG1*	AD	Alagille syndrome is caused by heterozygous mutations in *JAG1*. This condition is characterized by cholestatic liver disease, cardiac disease, skeletal and ocular abnormalities and a characteristic facial phenotype. Renal abnormalities are reported in 39% of patients with Alagille syndrome, and can include multicystic kidney disease (26).
Diaphanospondylodys-ostosis	*BMPER*	AR	Diaphanospondylodysostosis is a rare perinatal lethal skeletal disorder caused by biallelic mutations in the *BMPER* gene. Skeletal features for patients with this condition include small chest, abnormal vertebral segmentation and posterior rib gaps containing incompletely differentiated mesenchymal tissue. Craniofacial abnormalities are also present in patients with diaphanospondylodysostosis. The most commonly noted extraskeletal finding is nephroblastomatosis with cystic kidneys (27).
Short-rib thoracic dysplasia (SRTD) with or without polydactyly	*WDR35* *NEK1* *IFT140* *IFT172* *CEP120*	AR	The short rib polydactyly syndromes are a heterogeneous group of lethal chondrodysplasias caused by ciliary dysfunction during embryogenesis. Characteristic features include: constricted thoracic cage, short ribs, shortened tubular bones, a 'trident' appearance of the acetabular roof, and variable presence of polydactyly. Multisystem, variable nonskeletal involvement is also present in patients with SRTD, and cystic kidneys have been reported in affected individuals (28)

Test methods:
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

Renal Cystic Disorders Panel (79 genes)

Sample specifications:	3 to10 cc of blood in a purple top (EDTA) tube
Cost:	$2000
CPT codes:	81406
	81407
Turn-around time:	8 weeks

Note: We cannot bill insurance for the above test.

Results:
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

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