Nephrolithiasis and Nephrocalcinosis Panel

DISORDER ALSO KNOWN AS
Kidney Stones; Renal Calculi; Urolithiasis

PANEL GENE LIST (41 GENES)
ADCY10, AGXT, ALPL, AP2S1, APRT, ATP6V0A4, ATP6V1B1, BSND, CA2, CASR, CLCN5, CLCNKA, CLCNKB, CLDN16, CLDN19, CLPB, CYP24A1, FAM20A, GNA11, GPHN, GRHPR, HNF4A, HOGA1, HPRT1, KCNJ1, LRP2, MAGED2, MOCOS, OCRL, SLC12A1, SLC22A12, SLC26A1, SLC2A9, SLC34A1, SLC34A3, SLC3A1, SLC4A1, SLC7A9, SLC9A3R1, VDR, XDH

CLINICAL FEATURES AND GENETICS
Nephrolithiasis (kidney stone formation) affects approximately 1 in 11 people worldwide and in the United States[1,2]. Individuals with kidney stones may be asymptomatic, or may present with pain (renal colic), hematuria, urinary obstruction and/or urinary tract infections. Furthermore, some cases are associated with loss of renal function and an increased risk of hypertension. Kidney stone formation is a multifactorial process involving environmental, dietary and genetic factors leading to metabolic abnormalities in the urine. Recurrence is common, with a 40–50% probability at 5 years after the initial event for idiopathic calcium stones, and a higher probability for stones associated with systemic diseases[3].

Nephrocalcinosis is characterized by the deposition of calcium in the renal parenchyma and tubules. Any disorder that leads to hypercalcemia or hypercalciuria may lead to nephrocalcinosis. If present, clinical symptoms are not typically due to nephrocalcinosis alone, but depend upon the underlying disorder or presence of resulting kidney stones[4].

The majority of the genes on this panel are associated with monogenic diseases, in which nephrolithiasis or nephrocalcinosis is either the primary feature or is one of several features of a syndromic disorder. In addition, a few genes that play a role in the multifactorial etiology of stone formation are included. Polymorphisms in these genes have been associated with a significantly increased risk of nephrolithiasis over the general population risk. Overall, the genetic causes of nephrolithiasis and nephrocalcinosis that are covered by this panel can be classified based on the primary metabolic abnormality in the urine and/or blood (hypercalciuria, hypomagnesemia, cystinuria, hyperoxaluria or disorders of purine metabolism) or the underlying renal transporter defect (Bartter syndrome and distal renal tubular acidosis).

Hypercalciuria: The primary cause of kidney stone formation is supersaturation of urine with stone components. Approximately 88% of kidney stones are calcium-containing, and several genes associated with hypercalciuria have been identified[3]. Pathogenic variants in these genes disrupt calcium homeostasis and cause several disorders including hypophosphatasia (ALPL gene), idiopathic infantile hypercalcemia (CYP24A1 and SLC34A1), familial hypercalcemia (CASR, GNA11 and AP2S1), hypophosphatemic nephrolithiasis/ osteoporosis (SLC34A1 and SLC9A3R1) and hypophosphatemic rickets with hypercalciuria (SLC34A3). Several of these disorders can present in infancy or childhood, sometimes with additional manifestiations such as seizures or bone abnormalities, depending on the specific metabolic abnormality. In addition, polymorphisms in the ADCY10 gene, which is involved in calcium metabolism, are associated with a susceptibility to hypercalciuria and/or nephrolithiasis, although not thought to be directly causative in the absence of other unidentified factors[5]. Hypercalciuria, nephrocalcinosis and nephrolithiasis, along with low molecular-weight proteinuria, are defining features of X-linked recessive Dent disease 1 and Dent disease 2/Lowe syndrome, caused by pathogenic variants in the CLCN5 and OCRL genes, respectively[6]. Of note, the hallmark features of Dent disease have been reported as atypical features of Donnai-Barrow syndrome, an autosomal recessive condition characterized by unusual facial

dysmorphism, deafness, vision problems and brain abnormalities caused by defects in the LRP2 gene. It has been suggested that a subset of patients presenting with Dent disease may actually have a mild form of Donnai-Barrow syndrome[7].

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) results from variants in either the CLDN16 or CLDN19 gene, which lead to renal calcium and magnesium wasting. Most affected individuals present in early or late childhood with recurrent urinary tract infections, nephrolithiasis, polyuria, polydipsia and/or failure to thrive. Approximatley one third of affected individuals develop chronic renal failure during adolescence. Individuals with CLDN19 variants also present with severe ocular abnormalities, including severe myopia, macular colobomata and nystagmus[8]. Inheritance is autosomal recessive, however, heterozygous carriers of variants in either the CLDN16 or CLDN19 gene are noted to be at increased risk of hypercalciuria and nephrolithiasis[9,10] .

Cystinuria, characterized by high concentrations of cystine in urine leading to urinary tract cystine stones, is one of the most common monogenic causes of kidney stones, accounting for about 1-2% of all kidney stones and 6-8% of nephrolithiasis cases in children. Cystinuria is due to pathogenic variants in the SLC7A9 and SLC3A1 genes, which encode proteins required for the reabsorption of cystine in the proximal renal tubule. Most individuals with cystinuria present in childhood with stone formation. Recurrent stones are common and can lead to chronic kidney disease. Inheritance of cystinuria may be autosomal dominant (due to a heterozygous SLC7A9 variant), autosomal recessive (due to biallelic SLC7A9 or SLC3A1 variants) or digenic (involving both SLC7A9 and SLC3A1 genes)[11,12].

Primary hyperoxaluria (PH) is a group of autosomal recessive disorders caused by an inborn error of glycoxylate metabolism resulting in excess production of oxalate. Excess oxalate combines with calcium to form calcium oxalate deposits that precipitate in the kidneys causing nephrocalcinosis or renal stones. Additional clinical manifestations include bladder stones, hematuria, urinary tract infections, end stage renal disease and systemic oxalosis. Age of onset is variable, however, most affected individuals present in early childhood. There are three types of PH, designated as PH1, PH2 and PH3, which are due to variants in the AGXT, GRHPR and HOGA1 genes, respectively[13-15]. Calcium oxalate stones have also been reported in association with autosomal recessive inheritance due to SLC26A1 variants, but not in association with primary hyperoxaluria[16].

Several disorders of purine metabolism result in radiolucent kidney stones that can not be seen on X-ray, and require imaging techniques such as ultrasound or computed tomography. These include hereditary xanthinuria, renal hypouricemia, Lesch-Nyhan syndrome and adenosine phosphoribosyltransferase (APRT) deficiency. Hereditary xanthinuria, a rare cause of nephrolithiasis, is an autosomal recessive disorder caused by variants in the XDH gene (type I) or the MOCOS gene (type II). Hereditary xanthinuria is characterized by low levels of uric acid in blood and urine, and a predisposition to developing xanthine stones due to a high concentration of urinary xanthine [17,18]. A related, but clinically distinct, autosomal recessive disorder known as molybdenum cofactor deficiency also results in elevated urinary xanthine levels. One type of molybdenum cofactor deficiency has been associated with variants in the GPHN gene, which is included on this panel[19]. Renal hypouricemia (RHUC) is an inherited disorder characterized by impaired renal absorption of uric acid leading to high levels in urine, which can lead to uric acid stones and exercise-induced renal failure or remain asymptomatic. Variants in the SLC2A9 gene have been associated with both autosomal dominant and autosomal recessive RHUC, while variants in the SLC22A12 gene are primarily associated with autosomal recessive inheritance[20]. However, single heterozygous variants in SLC22A12 have been reported in individuals with hypouricemia and nephrolithiasis[21]. Uric acid stones are also seen in association with a spectrum of X-linked recessive disorders due to pathogenic variants in the HPRT1 gene. The spectrum ranges from isolated hyperuricemia with increased risk of acute renal failure to Lesch-Nyhan syndrome, which also presents with profound cognitive impairment, behavioral disturbances and motor dysfunction resembling cerebral palsy. Carrier females are typically asymptomatic, but may have increased uric acid excretion with symptoms developing in later years. Additionally, a small number of affected females with

Lesch-Nyhan syndrome due to skewed X-chromosome inactivation have been reported[22]. Lastly, APRT deficiency is an autosomal recessive disorder characterized by excess production and urinary excretion of 2,8-dihydroxyadenine (DHA), which is highly insoluble and leads to kidney stone formation and chronic kidney disease. Although reported to be rare, APRT deficiency may be significantly underrecognized, and progresses to end-stage renal disease in a significant number of affected individuals[23].

Bartter syndrome is a group of disorders characterized by renal salt-wasting due to abnormalities of ion transport. As a result of these abnormalities, affected individuals often exhibit low blood pressure, hypokalemic metabolic alkalosis, hypercalciuria, nephrocalcinosis and nephrolithiasis. Bartter syndrome can present prenatally with polyhydramnios, or in the neonatal or childhood period in less severe forms[24]. Four genes (BSND, CLCKNB, KCNJ1 and SLC12A1) have been identified in association with autosomal recessive Bartter syndrome, and one gene (MAGED2) is associated with a transient antenatal X-linked form of Bartter syndrome, which has a later presentation of increased plasma chloride levels and metabolic alkalosis, among other features[25]. Additionaly, a few patients have been reported to have digenic variants in both the CLCNKA and CLCNKB genes; however, more studies are needed to establish the relationship of the CLCNKA gene with Bartter syndrome[26,27].

Distal renal tubular acidosis (dRTA) is characterized by defects of the distal portion of the nephron tubule and is usually diagnosed in childhood. Features of dRTA include vomiting, dehydration, lethargy, short stature, rickets in children and osteomalacia/osteopenia in adults, weakness, failure to thrive and nephrolithiasis. Hearing loss and hypokalemia have been reported in some cases. Pathogenic variants in the ATP6V1B1, ATP6V0A4 and CA2 genes cause autosomal recessive dRTA, and variants in the SLC4A1 gene cause autosomal dominant, and rarely autosomal recessive, dRTA. Heterozygous carriers of variants in ATP6V0A4 or ATP6V1B1 may have an increased risk of nephrolithiasis and nephrocalcinosis in adulthood[28].

Other causes of nephrocalcinosis/nephrolithiasis: The CLPB, HNF4A and FAM20A genes are included on this panel due to an association with nephrocalcinosis. Variants in the CLPB gene are associated with the autosomal recessive disorder 3-methylglutaconic aciduria type VII, which is characterized by increased levels of 3-methylglutaconic acid, progressive brain atrophy, intellectual disability, congenital neutropenia, cataracts and movement disorder. Nephrocalcinosis and renal cysts have been described in this disorder[29]. Variants in HNF4A are primarily associated with a monogenic form of diabetes, but one specific variant (p.R63W) has been reported in individuals with an atypical Fanconi renotubular syndrome and nephrocalcinosis in addition to neonatal hyperinsulinism and macrosomia[30]. Variants in FAM20A are associated with amelogenesis imperfecta type IG (also known as enamel-renal syndrome), which is characterized by severe enamel hypoplasia and nephrocalcinosis[31]. Finally, heterozygous variants in the VDR gene, which is usually associated with vitamin-D dependent rickets and osteoporosis, have been rarely reported in individuals with idiopathic nephrolithiasis[32].

TEST METHODS

Genomic DNA is extracted from the submitted specimen. For skin punch biopsies, fibroblasts are cultured and used for DNA extraction. The DNA is enriched for the complete coding regions and splice site junctions of the genes on this panel 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 at the exon-level; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. For the CLCNKA, CLPB, LRP2 and MAGED2 genes, sequencing but no copy number testing is performed. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data by NGS. 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.

TECHNICAL TEST SENSITIVITY

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events, but less for 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 identify most deletions and duplications involving coding exons but are less reliable for detecting copy number variants of less than 500 base pairs. Assessment of copy number events also depends on the inherent sequence properties of the targeted regions, including shared homology and exon size. Mosaicism detection is limited and balanced chromosome aberrations cannot be identified.

CLINICAL TEST SENSITIVITY

Nephrolithiasis and nephrocalcinosis are genetically heterogeneous and multifactorial in etiology. 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. Analysis of genes included on this panel has been reported to identify a molecular diagnosis in 15% to 29% of individuals with nephrolithiasis or nephrocalcinosis[32-34]. Diagnostic rate may be higher among individuals with early onset, positive family history, and multiple or recurrent stones[32,34]. This panel is expected to have a clinical sensitivity equal to or greater than the sensitivity estimated in the published studies, as it includes all of the genes analyzed in those studies plus additional relevant genes. Additional information about the general clinical sensitivity of each gene is included in the table below.

Gene	Protein	Inheritance	Disease Associations	Sensitivity
ADCY10	Adenylate cyclase type 10	AD	Susceptibility to absorptive hypercalciuria	Risk alleles found in 45/80 (56%) of absorptive hypercalciuria[5]
AGXT	Alanine-glyoxylate aminotransferase	AR	PH type I	70% of PH[35,36]
ALPL	Alkaline phosphatase, tissue-nonspecific isoenzyme	Semi-dominant	Hypophosphatasia, adult/childhood/infantile; Odontohypophosphatasia	95% for hypophosphatasia[37]
AP2S1	Sigma subunit of adaptor related protein complex 2	AD	FHH type III	14-22% of FHH patients without CASR variants[38,39]
APRT	Adenine phosphoribosyltransferase	AR	APRT deficiency	90-95% of APRT deficiency[23]
ATP6V0A4	ATPase H+ transporting V0 subunit a4	AR	dRTA	34% of dRTA[40]
ATP6V1B1	ATPase H+ transporting V1 subunit B1	AR	dRTA with deafness	28% of dRTA[40]
BSND	Barttin (CLCNK type accessory beta subunit)	AR	Bartter syndrome, type 4a; Sensorineural deafness with mild renal dysfunction	Unknown; 2/5 of Bartter syndrome with hearing loss[41]

CA2	Carbonic anhydrase II	AR	CA II deficiency (osteopetrosis with RTA)	100% of CA II deficiency[42]
CASR	Extracellular calcium-sensing receptor	AD/AR	Disorders of calcium homeostasis	84% of FHH[43], 42% of ADH[44], 14-18% of FIH[45,46]
CLCN5	Chloride channel protein 5	XL	Dent disease 1	60-87% of Dent disease[47,48]
CLCNKA	Chloride voltage-gated channel Ka	AR	Bartter syndrome, type 4b	Rare, possibly digenic with CLCNKB[26,27]
CLCNKB	Chloride voltage-gated channel Kb	AR	Bartter syndrome, types 3 and 4b	Rare[49,50]
CLDN16	Claudin-16	AR	FHHNC	23/25 (92%) families with FHHNC[9]
CLDN19	Claudin-19	AR	FHHNC and severe ocular involvement	26/27 (91%) families with FHHNC with ocular involvement[51]
CLPB	Caseinolytic peptidase B protein homolog	AR	3-methylglutaconic aciduria type VII	Rare; 21 families reported to date[52]
CYP24A1	Vitamin D(3) 24-hydroxylase	AR	IIH-1	25/72 (35%) of hypercalemia[53]
FAM20A	Pseudokinase FAM20A	AR	Amelogenesis imperfecta type IG (enamel-renal syndrome)	16/16 (100%) of families with amelogenesis imperfecta and nephrocalcinosis[31]
GNA11	G protein subunit alpha 11	AD	ADH-2; FHH type II	2/10 (20%) of FHH and 2/8 (25%) of ADH, all negative for CASR variants[54]
GPHN	Gephyrin	AR	Molybdenum cofactor deficiency of complementation group C	Rare[19]
GRHPR	Glyoxylate reductase/ hydroxypyruvate reductase	AR	PH, type II	10% of PH[35,36]
HNF4A	Hepatocyte nuclear factor 4-alpha	AD	Fanconi renotubular syndrome 4, with maturity-onset diabetes of the young	Rare in renal Fanconi syndrome[30]
HOGA1	Mitochondrial 4-hydroxy-2-oxoglutarate aldolase	AR	PH, type III	10% of PH[35,36]
HPRT1	Hypoxanthine-guanine phosphoribosyltransferase	XL	HPRT deficiency, includes Lesch-Nyhan syndrome	90-95% of HPRT deficiency[22]
KCNJ1	Potassium voltage-gated channel subfamily J member 1	AR	Bartter syndrome, type 2	8/14 (57%) families with antenatal Bartter syndrome[55]

LRP2	Low-density lipoprotein receptor-related protein 2	AR	Donnai-Barrow syndrome	Rare in nephrolithiasis/nephrocalcinosis (2 individuals reported to date)[7]
MAGED2	MAGE family member D2	XL	Transient antenatal Bartter syndrome, type 5	9% of antenatal Bartter[25]
MOCOS	Molybdenum cofactor sulfurase	AR	Xanthinuria, type II	Unknown
OCRL	Inositol polyphosphate 5-phosphatase OCRL	XL	Dent disease 2; Lowe syndrome	15% of Dent Disease[6]; 90-100% of Lowe syndrome[56]
SLC12A1	Solute carrier family 12 member 1	AR	Bartter syndrome, type 1	9/13 (69%) families with antenatal Bartter syndrome[57]
SLC22A12	Solute carrier family 22 member 12	AR	RHUC-1	66/71 (93%) of hypouricemia[58]
SLC26A1	Sulfate anion transporter 1	AR	Calcium oxalate nephrolithiasis	2/348 of nephrolithiasis[16]
SLC2A9	Solute carrier family 2, facilitated glucose transporter member 9	AD/AR	RHUC-2	2/23 (8.7%) of hyperuricemia without a SLC22A12 variant [20]
SLC34A1	Sodium-dependent phosphate transport protein 2A	AD/AR	IIH-2; hypophosphatemic nephrolithiasis/ osteoporosis-1	14/126 (11%) of IHH without CYP24A1 variants[59]; 2/20 (10%) of hypophosphatemic nephrolithiasis/osteoporosis[60]; 5/143 (3.5%) of pediatric nephrolithiasis[32]
SLC34A3	Sodium-dependent phosphate transport protein 2C	AR	HHRH	5/5 families with HHRH[61]
SLC3A1	Neutral and basic amino acid transport protein rBAT	AR	Cystinuria	56/164 (34.1%) of cystinuria[12]
SLC4A1	Band 3 anion transport protein	AD/AR	dRTA	10% of dRTA[40]
SLC7A9	b(0,+)-type amino acid transporter 1	AD/AR	Cystinuria	68/164 (41.5%) of cystinuria[12]; 19/268 (7.1%) families with nephrolithiasis or nephrocalcinosis[33]
SLC9A3R1	Sodium/hydrogen exchange regulatory cofactor NHE-RF1	AD	hypophosphatemic nephrolithiasis/ osteoporosis-2	4/92 (4.4%) of patients with hypophosphatemic nephrolithiasis/osteoporosis[62]

VDR	Vitamin D3 receptor	AD/AR	Vitamin-D dependent rickets type 2A, osteoporosis	Rare; 2/143 pediatric cases of nephrolithiasis[32]
XDH	Xanthine dehydrogenase/oxidase	AR	Xanthinuria, type I	Unknown

Abbreviations:
AD – Autosomal dominant
ADH – Autosomal dominant hypocalcemia
AR – Autosomal recessive
dRTA – Distal renal tubular acidosis
FHH – Familial hypocalciuric hypercalcemia
FIH – Familial isolated hyperparathyroidism
FHHNC - Familial hypomagnesemia with hypercalciuria and nephrocalcinosis
HHRH - Hypophosphatemic rickets with hypercalciuria
IIH – Idiopathic infantile hypercalcemia
PH – Primary hypoxaluria
RHUC – Renal hypouricemia
XL – X-linked

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