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Genetic kidney diseases

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Abstract

Knowledge of the primary cause of a disease is essential for understanding its mechanisms and for adequate classification, prognosis, and treatment. Recently, the etiologies of many kidney diseases have been revealed as single-gene defects. This is exemplified by steroid-resistant nephrotic syndrome, which is caused by *podocin* mutations in ~25% of childhood and ~15% of adult cases. Knowledge of a disease-causing mutation in a single-gene disorder represents one of the most robust diagnostic examples of "personalized medicine", because the mutation conveys an almost 100% risk of developing the disease by a certain age. Whereas single-gene diseases are rare disorders, polygenic "risk alleles" are found in common adult-onset diseases. This review will discuss prominent renal single-gene kidney disorders and polygenic risk alleles of common disorders. We delineate how emerging techniques of total exome capture and large-scale sequencing will facilitate molecular genetic diagnosis, prognosis and specific therapy and lead to a better understanding of disease mechanisms, thus enabling development of new targeted drugs.

Genetic causality and predictive power of mutation analysis

In single-gene disorders, which are also known as "monogenic diseases", a mutation of a single gene (out of the total of ~25,000 genes) is sufficient to cause the disease. Conversely, in polygenic disorders mutations of multiple different genes are necessary to result in a disease. The degree of genetic causality varies with the mode of inheritance (Table 1). At one end of the spectrum there is tight genotype-phenotype correlation in monogenic recessive diseases, where the disease phenotype is almost exclusively determined by the single-gene causative mutation in way of "full penetrance" with a very high predictive power of mutation analysis (Table 1). Recessive diseases usually manifest prenatally, in childhood or in adolescence. Dominant diseases manifest typically in adults (e.g., in autosomal dominant polycystic kidney disease) (Table 1). Their tightness of genotype-phenotype correlation is somewhat reduced when compared to recessive diseases, because they may exhibit incomplete penetrance (i.e., skipping of the disease phenotype in a generation) and variable expressivity (i.e., varying degrees of organ involvement), as for instance in glomerulocystic kidney disease (GCKD).

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Search strategy and selection criteria

This review is based on an ongoing review of the literature over the last 10 years pertaining to genetic kidney diseases. We searched PubMed for review articles on the terms [kidney AND "molecular genetics"]. In addition, we searched OMIM (http://www.ncbi.nlm.nih.gov/sites/entrez) for "renal tubular + #". Recent review articles on the topic were taken into consideration.

Conflict of interest statement

The author declares no conflict of interest.

At the other end of the spectrum of causality are polygenic diseases, in which genotype-phenotype correlation is very weak (Table 1), and usually only a relative risk can be assigned to a genetic change, as for instance in an association between makers of the *MYH9* locus and focal segmental glomerulosclerosis (see below). Polygenic diseases usually manifest in adulthood and are much more frequent than monogenic diseases. As they show less heritability they leave more room for environmental influences. Risk alleles in polygenic diseases are usually derived from genome-wide association studies (Table 1)(1).

Mutation analysis in single-gene kidney diseases

Due to the strong genotype-phenotype correlation of almost 100% that is seen in recessive single-gene renal disorders (Table 1), mutation analysis in these diseases reveals the primary cause of the disease, permits prenatal diagnostics, and has a very high diagnostic and prognostic value. Identification of a mutation in a known recessive disease gene may be viewed as probably the most robust diagnostic example of “personalized medicine”, because the recessive mutation conveys an almost 100% risk that the patient will develop the respective disease by the end of adolescence, as for example in autosomal recessive polycystic kidney disease (ARPKD). When performing molecular genetic diagnostics, genes are examined for disease-causing DNA sequence changes. Mutation analysis is usually performed by PCR of exons followed by direct exon sequencing, as it is estimated that about 85% of all disease-causing mutations in single-gene disorders are positioned within a coding exon.

Mutation analysis in single-gene renal disorders requires informed consent and submission of a blood sample from the affected individual for DNA extraction. Multiple web sites identify non-commercial research laboratories that offer mutation analysis, often in conjunction with interpretation of results (www.genetests.org, www.renalgenes.org). Given the potential ethical, legal, emotional and economic consequences that may result from molecular genetic diagnostics, the request should ideally be initiated from a genetic counseling session, in which the patient (and/or parents in childhood cases) receives counseling by a certified genetic counselor.

Tables 2–6 provide an overview on single-gene renal diseases, for which molecular genetic diagnosis is available. Usually, molecular genetic diagnosis is sought to clarify the etiology of a rare disease that is otherwise difficult to diagnose. To aid in the selection of target genes for molecular genetic diagnosis kidney diseases are grouped by leading diagnostic feature (Tables 2–6).

In glomerular diseases mutations determine age of onset and treatment response

The leading diagnostic feature of renal glomerular diseases is proteinuria. Steroid-resistant nephrotic syndrome (SRNS), which typically manifests histologically as focal segmental glomerulosclerosis (FSGS), remains one of the most intractable kidney diseases. In children it carries a 30% risk of recurrence in a kidney transplant. Multiple single-gene causes of SRNS have been identified (Table 2)(2). Recessive mutations in *NPHS1* (nephrin) cause congenital nephrotic syndrome with onset by 90 days of life(3). Mutations of *NPHS2* (podocin)(4) cause 10–28% of all non-familial childhood SRNS cases (Table 2)(5). With very few exceptions, all monogenic forms of SRNS lead to chronic kidney disease (CKD)(6) and are resistant to steroid treatment.

There is a strong correlation between causative gene mutations and the age of onset of FSGS or CKD in at least two ways: (1) Mutations in different genes SRNS with onset at different

ages. For instance, mutations in *NPHS1* (nephrin), *NPHS2* (podocin), *LAMB2* (laminin-β2), and *PLCE1* (phospholipase C epsilon 1) cause childhood onset SRNS, whereas the rare mutations in dominant genes, including *actinin-α4* (*ACTN4*), *TRPC6* lead to adult onset disease(7, 8) with few exceptions(9) (Table 2). The earlier the onset of SRNS, the more likely it is of monogenic origin (Table 1). This is exemplified by the fact that 85% of all SRNS that manifests in the first 3 months of life and 66% of all SRNS manifesting in the first year of life are caused by mutations in one of only four genes, *NPHS1*, *NPHS2*, *LAMB2*, or *WT1*(10). (2) For recessive *podocin* mutations, the combination of the two parental alleles determines age of onset of SRNS and end-stage renal failure (ESRF)(11). Specifically, the presence of at least one truncating mutation of the mutation "R138Q" leads to early onset of SRNS at a median age of 1.7 years rather than 4.7 years(11). Recently, it was shown that compound heterozygosity for the R229Q variant of podocin and one "*bona fide*" podocin mutation causes adult onset in up to 15% of SRNS cases(12). In childhood nephrotic syndrome an important correlation between genotype and treatment response has been revealed, in that patients with two recessive mutations of the *podocin* gene do not respond to standard steroid treatment but have a strongly reduced likelihood of FSGS recurrence in a renal transplant (35% *vs*. 8%)(13, 14).

Renal cystic "ciliopathies" exemplify mechanisms of genotype-phenotype correlation

Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent lethal dominant disease in the United States and Europe, afflicting about 1 in 1,000 individuals(15). CKD develops by age 60 – 70 years. The two genes mutated in ADPKD, *PKD1* and *PKD2*, encode polycystin 1 and polycystin 2, which play a role in the maintenance of renal tubular cell differentiation (Table 3)(16). Although ADPKD1 and ADPKD2 mutations segregate in families in an autosomal dominant way, the cellular defect leading to renal cysts is most likely recessive on the basis of "second hit" mutations that occur throughout life in certain renal tubule cells thereby inducing cysts growth(17). Whereas molecular genetic diagnostics have been technically very difficult until recently, up to 90% of cases with ADPKD can now be diagnosed, which is very helpful for clinical decision making, especially regarding living related donor transplantation.(18)

Autosomal recessive polycystic kidney disease (ARPKD) is characterized by bilateral renal cystic enlargement that may start *in utero*. CKD develops directly postnatally, or in childhood or adolescence, depending on the severity of the two recessive mutations in the causative *PKHD1* gene (Table 3). Intrahepatic bile duct dysplasia causes chronic liver fibrosis with abnormal bile duct structure (Caroli's disease). The presence of truncating mutations in *PKHD1* is associated with perinatal onset of ARPKD.

Nephronophthisis (NPHP) is the most frequent genetic cause for CKD in the first three decades of life(19–21). CKD develops by at a median age of 13 years. In contrast to PKD, cysts are mostly restricted to the corticomedullary border of the kidneys, and kidney size is normal or reduced. Mutations in nine different recessive genes (*NPHP1-NPHP9*) have been identified as causing NPHP (Table 3)(22–31). It can be associated with retinal degeneration (Senior-Loken syndrome, SLSN), liver fibrosis, or cerebellar vermis aplasia (Joubert syndrome, JBTS). Bardet-Biedl syndrome(32) is an autosomal recessive multi-system disorders that is characterized by the cardinal features of retinitis pigmentosa, polydactyly, mental retardation, hypogenitalism and obesity(33–42).

A unifying pathogenic concept for cystic kidney diseases was recently developed from the discovery that all gene products that if mutated cause cystic kidney disease (e.g., ARPDK, ARPKD, NPHP, BBS) are expressed at the "primary cilia/centrosome complex"(43).

Centrosomes, who convert into the spindle poles during mitosis, play an important role in cell cycle regulation and assembly of sensory cilia. This has lead to a pathogenic concept that summarizes the cystic kidney diseases ADPKD, ARPKD, NPHP, Meckel-Gruber syndrome, BBS and others as "renal cystic ciliopathies"(44¯46). The current mechanistic concept of renal cyst development holds that during renal morphogenesis, when renal tubules normally elongate, malorientation of the mitotic spindle causes dilation rather than elongation and thereby cystic widening of tubules(16, 47).

In NPHP the nature of the two recessive mutations determines severity and extent of organ involvement, leading to seemingly different disorders. Within this varied genotype-phenotype correlation loss-of-function mutations cause severe, early-onset, dysplastic, multiorgan disease (Meckel-Gruber syndrome), whereas reduced function mutations cause mild, late-onset, degenerative disease with limited organ involvement (NPHP with retinal degeneration). More specifically, the extent and severity of organ involvement, are determined by the following three genetic mechanisms:

1. Specific genes. Different genes cause different severity of phenotypes.
2. Multiple allelism. Whereas 2 truncating mutations of *NPHP3*, *NPHP6* or *NPHP8* cause Meckel-Gruber syndrome (Table 3), the presence of at least 1 missense mutation may lead to a "rescue" towards the milder phenotype of Joubert syndrome with involvement of kidney, eye and cerebellum.
3. Modifier genes. In homozygous *NPHP1* deletions the presence of an additional heterozygous mutation in *NPHP6* or *NPHP8* may cause additional eye or cerebellar involvement(48, 49). "Oligogenic" modifier effects have initially been demonstrated in BBS(50). However, the importance of modifier alleles within the concept of "oligogenicity" will have to be solidly founded on the basis of animal models before conclusions on its clinical impact can be drawn. Taken together, in renal cystic ciliopathies gene identification has allowed profound insights into its pathogenesis, which has recently spurned therapeutic trials in ADPKD.(17)

Finally, multiple benign and malignant tumors of the kidney can be caused by single-gene defects including mutations in *TSC1*, *TSC2*, *VHL*, *WT1* and the *MET* protooncogen (Table 3) (51), and molecular genetic diagnostics play an important role for prevention in kindred in whom mutations in these genes segregate.

Many renal tubular disorders allow unequivocal genetic diagnostics

Renal tubular function governs reabsortion of water and solutes from the golmerular filtrate. An increasing number of tubulopathies are being recognized as caused by single-gene mutations (Table 4). For some diseases, such as Bartter syndrome, similar disease phenotypes may be caused by mutations in different genes(52¯57). The single-gene basis of renal tubulopathies allows for unequivocal molecular genetic diagnosis.

In renal tubulopathies the primary genetic defect causes loss of function of a specific renal transport protein or signaling molecule. As certain transport systems are expressed in specific tubule segments, clinical and diagnostic features allow focussing genetic diagnosis on genes expressed in those tubule segments. Consequently, functional disturbances of certain tubule segments lead to the folllowing defects of tubular reabsorption (Table 4): Proximal tubular defects cause glucouria, phosphaturia, aminoaciduria and/or proximal renal tubular acidosis (RTA). This combination of features is known as „renal Fanconi syndrome". Dysfunction of sodium reabsorption in the thick ascending limb of Henle's loop causes Bartter syndrome, renal salt loss and secondary hypokalemic metabolic alkalosis. Defects of the distal convoluted tubule cause Gitelman syndrome(58) and other forms of

hypomagnesemia(59–61). Tubulopathies of the collecting duct impair reabsorption of water, sodium, potassium and protons, resulting in polyuria, salt loss, hyperkalemia, and acidosis, respectively. Mutations in the aquaporin-2 water channel AQP2(62) cause recessive nephrogenic diabetes insipidus (NDI), and mutations in the vasopressin-2-receptor cause X-linked NDI (Table 4)(63, 64). In *secondary tubulopathies* the genetic defect does not directly affect a tubular transport or transport signaling protein, but rather unspecifically leads to damage of renal tubule cells and thereby to renal tubular dysfunction (Table 4). Gene identification has rendered the often enigmatic disease group of tubulopathies accessible to unequivocal diagnostics.

Nephrolithiasis

Multiple single-gene causes of nephrolithiasis have been identified (Table 5)(65). Many of them represent rare abnormalities of specific renal tubular transport channels and transporters. Whether “mild” mutations in these genes may represent alleles conveying an increased risk for nephrolithiasis is currently unclear. This question may find an answer once exome capture and large-scale sequencing data have become available from large numbers of patients with nephrolithiasis (see below).

Congenital abnormalities of the kidney and urinary tract (CAKUT)

Congenital abnormalities of the kidney and urinary tract (CAKUT) account for approximately 50% of children with end-stage kidney disease. CAKUT occur in about 3 to 6 per 1,000 live births and constitute 20–30% of all anomalies identified in the neonatal period(66, 67). Single-gene mutations in many different genes (Table 6) may cause a wide phenotypic spectrum of CAKUT(68). Disease phenotypes include renal agenesis(69, 70), renal hypodysplasia(71), multicystic/dysplastic kidney(72), hydronephrosis, ureteropelvic junction obstruction, megaureter, ureter duplex or fissus, prevesical stenosis, and vesicoureteral reflux(73–77) (Table 6). CAKUT may present as an isolated feature or as part of clinical syndromes(78–80) in association with extrarenal manifestations as for example in branchio-oto-renal syndrome(81–83) or Kallman syndrome(84).

The pathomechanistic basis of CAKUT lies in the disturbance of normal nephrogenesis(85) (86, 87). Mutations in genes that govern nephrogenesis may cause CAKUT. Not surprisingly, many of the CAKUT-causing genes encode transcription factors(88–90), which partially may explain the variable expressivity. The near future will probably reveal that most forms of CAKUT are due to a multitude of rare single-gene defects, which will allow important advances for preventive diagnostics.

Gene identification informs diagnostics, therapy, and pathogenesis

A very important feature of monogenic diseases is the fact that the mutation in itself represents the primary cause (etiology) of the disease. This provides the following opportunities for diagnostics, therapy, and insights into pathogenesis: i) Unequivocal molecular genetic diagnostics can be performed to avoid invasive procedures, e.g. the diagnosis of nephronophthisis can be made without the necessity for renal biopsy. ii) Prenatal diagnosis is possible, e.g. for diagnostics of the perinatal lethal Meckel-Gruber syndrome. iii) Specific prognostic outcomes can be delineated for specific mutations, e.g. in mutations of *PKD1* or *PKD2*, which cause earlier or later onset of autosomal dominant polycystic kidney disease, respectively. iv) Subgroups of diseases may be classified for differential therapy, e.g. in mutations in *NPHS2*, which convey resistance to steroid treatment in nephrotic syndrome. v) Disease mechanisms (pathogenesis) can be studied in related monogenic animal models, e.g. in cystic kidney diseases, in which mouse models

offered the first insights into disease mechanisms of renal cystic ciliopathies. vi) New drugs can be developed, for example by studying knockout animal models.

Risk alleles in common and polygenic renal disorders

In single-gene disorders the penetrance, i.e. the predictive value of mutations for the disease to manifest is close to 100% (Table 1), with the exception of age-dependent penetrance and, in dominant diseases with the exceptions of incomplete penetrance (skipping of a generation) and variable expressivity (different extent and severity of organ involvement). In contrast, in polygenic diseases multiple mutated alleles in different genes have to act in concert to cause disease (Table 1).

Recently, the clear-cut lines between single-gene (Mendelian) diseases and polygenic diseases have become somewhat blurred: In the examples of Bardet-Biedl syndrome(91) and nephronophthisis(49) modifier gene effects have been demonstrated. For example, most patients with complete absence of *NPHP1* function due to homozygous deletions of the *NPHP1* gene (Table 3) develop isolated nephronophthisis only. However, the presence of a heterozygous mutation in *NPHP6* causes in these patients the additional disease phenotypes of retinal degeneration or ataxia(92). In this context the heterozygous mutation in *NPHP6* is considered to exert a “modifier gene” effect on *NPHP1*, because a heterozygous mutation alone in the recessive gene *NPHP6* does not elicit a disease phenotype.

Disease-causing genes of single-gene disorders are rare, exert strong causality on the disease phenotype with (almost) full penetrance, manifest early in life, leave little room for environmental influences, and are usually detected by linkage mapping (Table 1). In contrast, polygenic disorders are more common, exert weak causality on the disease phenotype, manifest later in life, leave more room for environmental influences, and are usually detected by “genome-wide association studies (GWAS) (Table 1). In comparison between gene identification of single-gene disorders by linkage mapping and of polygenic disorders by GWAS, the latter offer the advantage that common (rather than rare) disease genes may be identified, but they also carry the disadvantage that GWAS often only explains a few percent of the variance of the phenotype, and that it is often difficult to assign an associated marker allele mechanistically to loss of function of a specific gene(1).

An example of successful identification of disease risk alleles in kidney diseases is the identification of specific haplotypes in the *MYH9* locus that were found to be associated with an increased risk for focal segmental glomerulosclerosis (FSGS) and CKD in African American patients(93, 94). About 60% of the African American population in the US (compared to 4% of European Americans) carry this risk allele, and the risk of developing FSGS is increased 5-fold. Whether this incomplete penetrance of the risk allele is due to other polygenic influences or mostly goverened by environmental factors will have to be established. In addition, variants of the *ELMO1* (*engulfment and cell motility 1*) gene have been associated with type 2 diabetes-associated nephropathy(95).

For the global phenotype of chronic kidney disease (CKD) a risk association was demonstrated for the *UMOD* gene, which causes autosomal dominant medullary cystic kidney disease type 2 (Table 3), when Koettgen et al. identified a polymorphic SNP (*rs12917707*) near the *UMOD* locus as strongly associated with CKD(96). Furthermore, risk allele associations have been described for hypertension (OMIM #145500), atypical hemolytic uremic syndrome (#235400) and for the *ATGR2* locus in ureteropelvic junction obstruction (#145500).

Future directions

For the approximately 5,400 known Mendelian disorders in humans the causative genes have been identified in only about 2,600, whereas in approximately 2,800 the disease-causing gene is still elusive. Very recently, two novel techniques were developed that may significantly facilitate rapid discovery of causative genes for single-gene disorders. One of these techniques is “total human exome capture”, which describes the ability to “capture” by hybridization the entire “exome” of all ~180,000 protein-encoding human exons(97). Exome capture is followed up with another technique, “large-scale sequencing” (also known as “next-generation sequencing”). As there are estimates that about 85% of all disease-causing mutations in Mendelian disorders are positioned within coding exons, exome capture with consecutive large-scale sequencing will strongly accelerate disease gene discovery in the near future. This approach will further facilitate molecular genetic diagnosis, enhance our understanding of disease mechanisms, thus enabling development of new targeted drugs. It will also provide guides for mutation-specific prognosis and therapy. However, modern techniques of exome capture and large-scale sequencing will produce a high number of sequence variants, which renders identification of the true disease-causing mutation difficult. Therefore, it will become increasingly important that molecular genetic diagnostics are driven by leading clinical features (Tables 2–6) that generate candidate genes to be evaluated preferentially for disease-causing mutations.

In summary, novel molecular genetic techniques will rapidly provide deep novel insights into kidney diseases, especially regarding their diagnosis, nosologic classification, mechanistic understanding, recapitulation in animal models, and development of new therapeutics. The power of molecular genetic diagnosis will require solid implementation of genetic counseling and equitable access to these new opportunities for patients with kidney diseases.

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Table 1

Degrees of genetic causality and power of molecular genetic diagnostics in recessive, dominant and polygenic diseases.

	Monogenic		Polygenic
	Recessive	**Dominant**	
Genetic causality	Strong	Intermediate	Weak
Penetrance	Full	Sometimes incomplete	Weak
Predictive power of mutation analysis	Almost 100%	Strong[a]	Weak
Age of onset	Fetus, child, adolescent	Adult	Adolescent, adult
Molecular genetic approaches	Direct exon sequencing of known disease genes	Direct exon sequencing of known disease genes	Only assignment of relative risk possible
Frequency	<1:40,000 (rare)	<1:1,000 (rare)	<1:5 (frequent)
Data usually derived from	Gene mapping and gene identification	Gene mapping and gene identification	Genome wide association studies (GWAS)
Confirmation by animal model	Very feasible	Feasible	Difficult

[a] Except for incomplete penetrance and variable expressivity

Table 2

Single-gene glomerular diseases. (The leading diagnostic feature is proteinuria).

GLOMERULAR DISEASES	OMIM No.	MOI	Characteristic signs and features	*Gene symbol(s)*, gene product(s)
Congenital SRNS (Finnish type)	#256300	AR	congenital nephrotic syndrome, CKD	*NPHS1*, nephrin
SRNS type 2	#600995	AR	SRNS, FSGS, CKD	*NPHS2*, podocin
SRNS type 3	#610725	AR	SRNS (SSNS), DMS, FSGS, CKD	*PLCE1*, phospholipase C
SRNS type 4	#600995	AR, (AD)	SRNS, FSGS	*CD2AP*, CD2AP
Pierson syndrome	#609049	AR	SRNS and microcoria	*LAMB2*, *laminin-β2*
SRNS, adult-onset	#600995	AD	Adult-onset SRNS, FSGS, CKD	*NPHS2*, α-actinin-4 (*ACTN4*)
SRNS, adult-onset	#603965	AD	Adult-onset SRNS, FSGS, CKD	*TRPC6*, transient receptor potential cation channel C6
Denys-Drash syndrome, Frasier syndrome	#194080	AD	Wilms' tumour, pseudohermaphroditism, nephrotic syndrome	*WT1*, WT suppressor gene
Nail-Patella syndrome	#161200	AD	Nail dysplasia, absent patella, SRNS	*LMX1B*, LIM homeodomain protein
Schimke immuno-osseous dystrophy	#242900	AR	Bone abnormalities, immunodeficiency, SRNS	*SMARCAL1*, HepA-related protein (HARP)
Mitochondrial disorders with SRNS	#607426	AR	SRNS +/− neurologic impairment/SND	*COQ2*, *PDSS2*, *MTTL1*
Lysosomal disorders with SRNS	#254900	AR	Action myoclonus, SRNS, CKD	*SCARB2*, lysosomal integral membrane protein (LIMP2)
Glomerulopathy with fibronection deposits	#601894	AD	Proteinuria, dRTA	*FN1*, fibronectin-1
Alport syndrom	#301050	XD	Nephritis, SND, CKD	*COL4A5*, α5(IV)-collagen
Alport syndrom with leiomyomatosis	#308940	XD	Alport syndrom with leiomyomatosis, CKD	*COL4A6*, α6(IV)-collagen
Alport syndrom	#203780	AR	Alport syndrome or benign familial hematuria	*COL4A3*, α3(IV)-collagen
Alport syndrom	*120131	AR	Nephritis, SND, CKD	*COL4A4*, α4(IV)-collagen

AD=autosomal dominant, AR=autosomal recessive, CKD=chronic kidney disease, DMS=diffuse mesangial sclerosis, FSGS=focal segmental glomerulosclerosis, MOI=mode of inheritance, SND =sensorineural deafness, SSNS=steroid sensitive nephrotic syndrome, SRNS=steroid resistant nephrotic syndrome, XD=X-linked dominant

Table 3

Renal cystic, interstitial and tumorous kidney diseases. (The leading diagnostic features are renal ultrasound findings of cysts, increased echogenicity, or tumor, respectively).

CYSTIC, INTERSTITIAL AND TUMOROUS KIDNEY DISEASES	OMIM No.	MOI	Characteristic signs and features	*Gene symbol(s)*, gene product(s)
ADPKD, type 1	#601313	AD	Polycystic kidneys, liver cysts, brain aneurysms, CKD	*PKD1*, polycystin 1
ADPKD, type 2	#173910	AD	Polycystic kidneys, CKD	*PKD2*, polycystin 2
ARPKD	#263200	AR	Polycystic kidneys, liver fibrosis, CKD	*PKHD1*, fibrocystin/polyductin
Nephronophthisis types 1–9	#256100	AR	Polyuria, polydipsia, anemia, CKD	*NPHP1-NPHP9*, nephrocystin 1–9
Medullary cystic kidney disease	#174000	AD	Adult onset CKD, hyperuricemia, FJHN	*UMOD*, Tamm-Horsfall protein
Meckel-Gruber syndrome (MKS)	#249000 #607361	AR	Polycystic kidneys, multiple organ dysplasia, perinatal lethal	*MKS1; MKS3*, meckelin (also allelic with NPHP genes)
Bardet-Biedl syndrome types 1–12	#209900	AR	Retinitis pigmentosa, polydactyly, MR, hypogenitalism and obesity	*BBS1-BBS12*, BBS proteins
Tuberous sclerosis types 1 and 2	#191100 #191092	AD	Renal angiomyolipomas, skin changes, seizures	*TSC1*, hamartin *TSC2*, tuberin
von-Hippel-Lindau disease	#193300	AD	Lindau tumor, retinal angiomatosis, pheochromocytoma, renal tumor	*VHL*, Tumor suppressor gene g7
Wilms-tumor-aniridia syndrome	#194072	AD	Wilms tumour, aniridia, growth retardation	*WT1*, WT suppressor gene
Papillary renal cell carcinoma	#164860	AD	Papillary renal cell carcinoma	*MET* gene, protooncogen

ADPKD=autosomal dominant polycystic kidney disease, AD=autosomal dominant, AR=autosomal recessive, CNV=central nervous system, FJHN=familial juvenile hyperuricemic nephropathy, MR=mental retardation, XR=X-linked recessive

Table 4

Renal tubular and metabolic diseases. The leading diagnostic features are polyuria or renal tubular loss of electrolytes, sugar, amino acids or other metabolic findings.

RENAL TUBULAR DISEASES AND METABOLIC DISEASES	OMIM No.	MOI	Characteristic signs and features	*Gene symbol(s)*, gene product(s)	Tubule segment expressing this transporter/ channel
Renal glucosuria	*182380 #233100	AR, AR	Renal glycosuria type A; Renal glycosuria type B, Glu/ Gal malabsorption	*SLC5A2*, SGLT2; *SLC5A1*, Na/Glu cotransporter SGLT1	PT
Aminoacidurias			(see Table 5)		PT
Proximal renal tubular acidosis (RTA)	#259730 #604278	AR	Proximal RTA with extrarenal abnormalities	*CA2*, carbonic anhydrase 2; *SLCA4A*, NaHCO2 cotransporter	PT
Hypophosphatemic ricketts	#307800 #241530	XD AR	Vit. D resistant rickets; Vit. D resistant rickets with hyocalciuria	*PHEX*, endopeptidase; *SLC34A3*, NaP-cotran., (also *FGF23*, *DMP1*)	PT
Bartter syndrome types 1–4	#601678 #241200 #607364 #602522	AR	Hypokalemic alkalosis, hypercalcuria, polyuria, growth retardation	*SLC12A1*, NKCC2; *CLCNKB*, Clc-Kb; *KCNJ1*, ROMK; BSND; barttin	mTAL
Gitelman syndrome	#263800	AR	Hypocalciuria, hypomagnesemia, hypotension	*SLC12A3*; thiazide sensitive NaCl- cotrans.	DCT
Hypomagnesemia	#248250	AR	Hypomagnesemia, NC, CKD, seizures	*CLDN16*; claudin 16	DCT
Hypomagnesemia	#154020	AD	Hypomagnesemia, seizures	*ATP1G1*; FXYD2	DCT
Liddle syndrome	#177200	AD	Pseudoaldosteronism, hypertension	*SCNN1B,G*; Na channel gain of function	CD
Gordon syndrome (PHA type 2)	#145260	AD	Pseudohypoaldosteronism type 2, $\uparrow K^+$, $\uparrow Cl^-$, acidosis, hypertension	*WNK4; WNK1*, wnk kinases	CD
Pseudohypoaldosteronism type 1	#264350 ”renal”	AD	Pseudohypoaldosteronism type 1, $\downarrow Na^+$, $\uparrow K^+$	*SCNN1A,B,G*; Na channel loss of function	CD
Pseudohypoaldosteronism type 1	#264350 ”multiple”	AR	Pseudohypoaldosteronism type 1, $\downarrow Na^+$, $\uparrow K^+$	*MLR1;* mineralo-corticoid receptor	CD
SeSAME syndrome	#612780	AR	Seizures, SND, ataxia, MR, electrolyte wasting	*KCNJ1*, K channel	CD
Distal renal tubular acidosis (dRTA)	#267300 #602722	AR, AR	dRTA, NC, SND, growth failure, osteomalacia	*ATP6B1; ATP6N1B*, vacuolar ATPase units	CD
Distal renal tubular acidosis type I, AD	#179800	AD	dRTA with hemolytic anemia	*SLC4A1*; erythrocyte band 3 (AE1)	CD
Diabetes insipidus, nephrogenic	#304800 #222000	XD AR	Polyuria, polydipsia	*AVPR2*, AVP2 receptor *AQP2*, aquaporin-2	CD
Cystinosis	#219800	AR	Renal Fanconi syndrome, photophobia, $\downarrow T_4$	*CTNS*, lysosomal membrane protein	Secondary
Lowe syndrome	#309000	XR	Cataract, vit. D-resistent ricketts, MR, RTA, CKD	*OLRL1*, PIB5PA	Secondary

RENAL TUBULAR DISEASES AND METABOLIC DISEASES	OMIM No.	MOI	Characteristic signs and features	*Gene symbol(s)*, gene product(s)	Tubule segment expressing this transporter/ channel
Hemolytic uremic syndrome, atypical	#235400	AR	Thrombocytopenia, hemolytic anemia, acute renal failure	*CFH*, complement FH; *CFHR1; CFHR3, MCP; ADAMTS13* (aut. dom.)	Secondary
Fabry disease	#301500	XR	Angiokeratoma, FSGS, adult-onset CKD	*GLA* α-galactosidase A	Secondary

AD=autosomal dominant, AR=autosomal recessive, CD=collecting duct, CKD=chronic kidney disease, DCT=distal convoluted tubule, MR=mental retardation, NC=nephrocalcinosis, mTAL=medullary thick ascending limb, PT=proximal tubule, secondary=secondary tubulopathy due to cell damage, SND=sensorineural deafness, XD=X-linked dominant, XR=X-linked recessive

Table 5

Nephrolithiasis. The leading diagnostic features are renal calculi or nephrocalcinosis.

NEPHROLITHIASIS	OMIM No.	MOI	Characteristic signs and features	*Gene symbol*, gene product
Cystinuria, type 1	#220100	AR	Cystin calculi	*CSNU1*, SLC3A1 amino acid transporter
Cystinuria, non-type 1	#604144	AR	Cystin calculi	*SLC7A9*, amino acid transporter
Dent disease	#300009	XR	NL, NC, renal Fanconi syndrome	*CLCN5*, renal Cl-Channel
Primary hyperoxaluria type 1	#259900	AR	NL, CKD	*AGXT*, Ala-glyoxylate aminotransferase
Primary hyperoxaluria type 2	#260000	AR	NL	*GRHPR*, glyoxylate reductase
Lysinuric protein intolerance	#222700	AD	NL, phosphate wasting, osteopenia	*SLC9A3R1*, NHERF1
Adenine-phosphoribosyl-transferase deficiency	#102600	AR	NL	*APR5*, adenine phosphoribosyl transferase
Xanthinuria	#278300	AR	NL, xanthine calculi	*XHD*, xanthin dehydrogenase
Distal renal tubular acidosis	#179800	AD	NL, ricketts	*SLC4A1*, RTA

AD=autosomal dominant, AR=autosomal recessive, NC=nephrocalcinosis, NL=nephrolithiasis, RTA=renal tubular acidosis, XR=X-linked recessive

Table 6

Congenital abnormalities of the kidney and urinary tract (CAKUT).

CONGENTIAL ABNOR-MALITIES OF THE KIDNEY AND URINARY TRACT (CAKUT)	OMIM	MOI	Renal features	Extrarenal features	*Gene*
CAKUT	*601090	AD	CAKUT	iridiodysgenesis	*FOXC1*, forkhead transcription factor C1
Renal agenesis (RA)	#191830	AD	Renal agenesis/adysplasia, VUR	Allelic with *MEN2A;* Facial defects	*RET*, ret protooncogen; *UPK3A*, uroplakin 3A
Renal hypodysplasia (RHD)	*112262 *604994	AD	RHD	Microphthalmia, cleft lip	*BMP4*, bone morpho-genetic protein 4; *SIX2*, sine oculis 2
Multicystic renal dysplasia (MRD)	*602868 *600390	AD AD	MRD	-	*CDC5L*, cell division cycle; *USF2*
Vesicoureteral reflux (VUR 2)	*602431 *603746	AD AD	VUR	Subtle facial and limb defects	*ROBO2*, roundabout 2; *SLIT2*
Branchio-oto-renal syndrome (BOR)	*601653 *159980 *601205 *600963	AD	CAKUT, RHD, VUR	Deafness, ear malformation, branchial cysts	*EYA1*, eyes absent 1; *MYOG*, myogenin; *SIX1*, sine oculis 1; *SIX5*, sine oculis 5
Fraser syndrome	*607830 *608945	AR AR	Renal agenesis, RHD	Cryptophthalmos-syndactyly	*FRAS1*, ECM protein; *FREM2*, Fras1-related ECM protein
HDR syndrome	#146255	AD	CAKUT	Hypoparathyroidism, deafness, renal defects (HDR)	*GATA3*, GATA binding protein 3
Kallman syndrome	+308700	AD	Renal agenesis	Anosmia, hypogenitalism	*KAL1*, anosmin
Renal coloboma syndrome	*167409	AD	CAKUT (VUR, RHD)	Retinal coloboma	*PAX2*, paired box gene 2
Renal cysts and diabetes syndrome (RCAD), GCKD	#13792 #609886	AD, AD	RHD, cysts	MODY5 diabetes, genital anomalies, GCKD	*TCF2/HNF1B*, transcription factor 2
Split-hand/split-foot malformation (SHFM)	*603273	AD	Urethral malformation	SHFM	*Bmp7; Dlx5; Dlx6; p63*
Townes-Brocks syndrome	#107480	AD	Renal agenesis, RHD	Limb, ear, anal abnormalities	*SALL1*

AD=autosomal dominant; AD=autosomal recessive; BOR=branchio-oto-renal syndrome; GCKD=glomerulocystic kidney disease; MRD=multicystic renal dysplasia; RCAD=renal cysts and diabetes syndrome, RCS=renal-coloboma syndrome; RHD=renal hypodysplasia; SHFM=Split-hand/split-foot malformation; TBS=Townes-Brocks syndrome; UPJO=ureteropelvic junction obstruction.