Exploring the genetic basis of early-onset chronic kidney disease

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Abstract | The primary causes of chronic kidney disease (CKD) in children differ from those of CKD in adults. In the USA the most common diagnostic groups of renal disease that manifest before the age of 25 years are congenital anomalies of the kidneys and urinary tract, steroid-resistant nephrotic syndrome, chronic glomerulonephritis and renal cystic ciliopathies, which together encompass >70% of early-onset CKD diagnoses. Findings from the past decade suggest that early-onset CKD is caused by mutations in any one of over 200 different monogenic genes. Developments in high-throughput sequencing in the past few years has rendered identification of causative mutations in this high number of genes feasible. Use of genetic analyses in patients with early onset-CKD will provide patients and their families with a molecular genetic diagnosis, generate new insights into disease mechanisms, facilitate aetiology-based classifications of patient cohorts for clinical studies, and might have consequences for personalized approaches to the prevention and treatment of CKD. In this Review, we discuss the implications of next-generation sequencing in clinical genetic diagnostics and the discovery of novel genes in early-onset CKD. We also delineate the resulting opportunities for deciphering disease mechanisms and the therapeutic implications of these findings.

Penetrance
The proportion of individuals who express a certain phenotype in relation to the number of individuals that carry the pathogenic variant(s). Incomplete penetrance refers to the observation that some individuals with the mutation do not develop the disease phenotype.

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Chronic kidney disease (CKD) in children is defined by the presence of kidney damage, predominantly by the presence of defined structural or functional abnormalities, or by a glomerular filtration rate that has remained below 60 ml/min/1.73 m^2 for >3 months[1]. Progression of CKD to end-stage renal disease (ESRD) necessitates dialysis or transplantation for survival. Although epidemiologic evidence suggests that the prevalence of CKD is increasing[2], little is known about the reasons for this increase. CKD that manifests in the first 25 years of life is caused to a large degree by congenital anomalies of the kidneys and urinary tract (CAKUT), steroid-resistant nephrotic syndrome (SRNS), chronic glomerulonephritis and renal cystic ciliopathies (TABLE 1). Although many aetiologies of early-onset CKD were not previously viewed as being genetic in origin, studies over the past few years led to the discovery that a monogenic cause of disease can be detected in ~20% of individuals with early-onset CKD, defined as CKD manifesting before 25 years-of-age. Monogenic mutations can cause disease in the absence of any additional damage from biological or environmental causes. The development of disease in all individuals who carry a particular mutation is known as 'full penetrance' of the mutation.

More than 200 monogenic causative genes have now been identified for 70% of the most common aetiologies of CKD in this age group[3–11]. This Review focuses on single-gene causes of early-onset CKD and discusses the implication of next-generation sequencing for the genetic diagnosis of early-onset CKD. We address the discovery of novel genes that cause early-onset CKD if mutated and discuss opportunities for delineating the pathomechanisms by which these mutations cause disease and their potential therapeutic implications.

Epidemiology of CKD in children

The primary causes of early-onset CKD in children differ from those of adult-onset CKD. The 2008 North American Pediatric Renal Trials and Collaborative Studies report, which included data from 7,037 children and young adults with CKD[12], found that the most common diagnostic groups of early-onset CKD were CAKUT, accounting for 49.1% of cases; SRNS, accounting for 10.4% of cases; chronic glomerulonephritis, accounting for 8.1% of cases; and renal cystic ciliopathies, accounting for 5.3% of cases. Together these four diagnostic groups accounted for >70% of the entire paediatric CKD population (TABLE 1). These groups also represent the most common causes of early-onset CKD

Key points

- Approximately 20% of cases of chronic kidney disease (CKD) that manifest before the age of 25 years are caused by single gene mutations in any one of >200 different genes
- Molecular genetic diagnostics can provide patients with a molecular diagnosis for their disease and can generate new insights into disease mechanisms
- Molecular genetic diagnostics might also have consequences for personalized treatment and prevention of CKD
- Indication-driven mutation analysis panels are available to guide the genetic diagnosis of common early-onset kidney diseases, such as congenital anomalies of the kidneys and urinary tract, steroid-resistant nephrotic syndrome, ciliopathies and nephrolithiasis

Next-generation sequencing
A DNA sequencing method that enables simultaneous sequencing of multiple DNA segments in a high-throughput manner. Also known as massively parallel sequencing.

Whole exome sequencing
Targeted capture and sequencing of the exome using next-generation sequencing. This method offers a powerful approach towards the identification of monogenic disease-causing genes.

Variant
A difference in a DNA sequence compared to a 'normal' reference sequence. A variant can be benign (for example, a single nucleotide polymorphism) or disease-causing (for example, a mutation).

Allele
Specific DNA sequence variant in a given gene. Alleles can be designated according to their frequency as common or rare alleles.

Phenotype
The observable characteristics of an individual as a morphological, clinical or biochemical trait. A phenotype can also be the presence or absence of a disease.

Genotype
The set of alleles (variants of genes) that structure an individual's genetic makeup.

Expressivity
Variation of the expression of the phenotype among affected individuals with the same genotype. Variable expressivity refers to different degrees of severity and/or organ involvement in different affected individuals that carry an identical mutation.

in developed countries outside the USA[13]. Their aetiologies have only been revealed in the past decade, with the identification of single-gene (monogenic) mutations providing insights into the pathomechanisms of early-onset CKD. This improved understanding of disease pathogenesis is exemplified, for instance, by the discovery of mutations in *NPHS1* (which encodes nephrin), as a cause of congenital nephrotic syndrome, thereby identifying podocyte dysfunction as central to the pathogenesis of this disease[14–16].

Monogenic diseases (also referred to as Mendelian or single-gene disorders) result from mutations in a single causative gene. Patterns of Mendelian inheritance can be autosomal dominant, autosomal recessive or X-linked. In the past 15 years >200 monogenic causes of early-onset CKD have been identified (TABLE 1). Most of these causative genes have been discovered in the past 5 years owing to an acceleration in gene discovery with the development of modern genetic mapping and whole exome sequencing (WES) technologies. Approximately 36 genes are currently known to be mutated in CAKUT[5,9,10,17], 39 in SRNS[18,19], 10 in chronic glomerulonephritis, and >95 in renal cystic ciliopathies[3,20]. These data demonstrate that a monogenic cause of disease can be identified by mutation analysis in ~20% of patients with early-onset CKD (TABLE 1).

Attributing causality

The degree to which causality is attributed to a certain genetic variant can be classified according to the penetrance of a given disease-causing allele. The degree of genetic penetrance reflects the proportion of individuals with the genetic variant(s) who express the disease phenotype. At one end of the spectrum are autosomal recessive monogenic Mendelian diseases (also known as single-gene disorders), which are characterized by tight genotype–phenotype correlations such that the disease phenotype is almost entirely determined by mutations in a single gene — that is, they show 'full penetrance' (REF. 21; TABLE 2). For example, individuals who carry mutations in both copies of *NPHP1* will develop juvenile nephronophthisis[22], progressing to CKD with renal fibrosis and cysts by the age of 20 years. By contrast, genotype–phenotype correlations can be weaker for autosomal dominant monogenic Mendelian diseases owing to multiple features of these diseases, such as increasing disease penetrance with increasing age; incomplete penetrance, such that some individuals with the mutation do not develop the disease phenotype and the disease can therefore seem to skip a generation in a pedigree; and variable expressivity of the disease such that different organs are affected with differing degrees of severity between individuals (TABLE 2). An example of an autosomal dominant kidney disease with variable expressivity is that caused by *HNF1B* mutations, which can cause CAKUT, CKD and maturity-onset diabetes of the young (MODY) with variable age of onset[23,24]. Variable expressivity mainly describes a complex genotype–phenotype relationship in autosomal dominant diseases; however, a similarly complex situation can exist in recessive diseases that exhibit 'multiple allelism' — the finding that different (homozygous) recessive mutations in the same gene can lead to different clinical outcomes. For instance, certain mutations in *LAMB2* that cause nephrotic syndrome might lack ocular involvement in some individuals[25], or specific combinations of compound heterozygous mutations of *NPHP2* might cause adult-onset rather than childhood-onset nephrotic syndrome[26].

At the other end of the spectrum of causality are more common conditions for which low-penetrance, so-called 'risk alleles', have been described[21]. In these conditions, which often are referred to as polygenic or complex diseases, genetic variants usually exert only small effects on the disease (TABLE 2) and thus only a small fraction of the statistical variance for a disease phenotype can usually be assigned to a risk allele. An exception to this situation occurs with *APOL1* variants, which convey a large phenotypic risk for the development of focal segmental glomerulosclerosis (FSGS) and CKD in African Americans[27–31] (TABLE 2). For instance, an estimated 13–23% of African Americans (compared with 0.3–1.3% of European Americans) have one of the two known *APOL1* risk alleles[32,33]. The risk of developing FSGS is increased 17-fold for African Americans who carry two risk alleles compared with that of individuals who carry no risk alleles or one risk allele[32,33].

Finally, the contribution of genetic modifiers to the disease phenotype is another aspect of genetic causality that should be taken into consideration. This concept, in which specific alleles are responsible for the modification of disease phenotypes, has been described for monogenic forms of cystic kidney disease[34] and glomerulonephritis[35]. Nonetheless, additional supporting evidence is needed for some of these associations in early-onset CKD.

We[10] as well as others[36] have noted that gene variants are often falsely assigned disease causality. Specifically, up to 30% of genetic variants that have been published as likely disease-causing and deposited in genetic databases have not been confirmed as deleterious[37]. Consequently, any attribution of pathogenicity to a given variant should be subject to strict criteria and multiple levels of evidence, such as amino acid sequence conservation, segregation analysis, tissue specific gene expression, functional studies, and animal models, should be considered[36,38]. To decide whether a genetic variant qualifies as potentially disease-causing we follow empiric core

Table 1 | **Causes and genetic diagnosis of early-onset CKD**

Diagnostic group	Indication to run a gene panel	Proportion of cases of early-onset CKD	Number of known causative genes	Percentage of cases caused by known genes (multiplied by fraction of all CKD)	Refs
CAKUT	CAKUT evident by renal imaging	49.1% (obstructive uropathy 20.7%; renal aplasia, hypoplastic or dysplastic kidneys 17.3%; reflux nephropathy 8.4%; prune belly syndrome 2.7%)	36	~17% (8.5%)*	6,9,10, 39,84
SRNS	SRNS	10.4% (FSGS 8.7%; congenital nephrotic syndrome 1.1%; membranous nephropathy 0.5%; Denys–Drash syndrome 0.1%)	39	~30% (3%)	19,44,64
Chronic GN‡	Evidence of proteinuria and haematuria	8.1% (SLE nephritis 1.6%; familial nephritis (Alport syndrome) 1.6%; chronic GN 1.2%; MPGN type I 1.1%; MPGN type II 0.4%; IgAN 0.9%; idiopathic cresentic GN 0.7%; Henoch–Schönlein nephritis 0.6%)	10	~20% (4%)	4
Renal cystic ciliopathies	Increased echogenicity on renal ultrasound or presence of ≥2 renal cysts	5.3% (polycystic kidney disease 4.0%; medullary cystic kidney disease 1.3%)	95	~70% (3.7%)	11,20, 85,86
aHUS	Microangiopathic haemolytic anaemia, thrombocytopaenia, and AKI	2.0%	9	~60% (1.2%)	87–90
Nephrolithiasis or nephrocalcinosis	Known stone disease or nephrocalcinosis	1.6% (cystinosis 1.5%; oxalosis 0.1%)	30	21% (0.4%)	45,91
Other	Other indications of genetic disease	23.5% (renal infarct 2.2%; pyelonephritis or interstitial nephritis 1.4%; Wilms tumour 0.5%; other systemic immunologic diseases 0.4%; granulomatosis with polyangiitis 0.4%; sickle cell nephropathy 0.2%; diabetic glomerulopathy 0.2%; other nonimmunologic causes 18.2%)	Not known	Not known	Not available
Total	—	100%	~219	(~20%)	—

Data are from the 2006 Annual Report of the North American Pediatric Renal Trials and Collaborative Studies[12]. aHUS; atypical haemolytic uraemic syndrome; AKI, acute kidney injury; CAKUT, congenital anomalies of the kidneys and urinary tract; CKD, chronic kidney disease; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; IgAN IgA nephropathy; MPGN, membranoproliferative glomerulonephritis; SLE, systemic lupus erythematosus; SRNS, steroid-resistant nephrotic syndrome. *10% of CAKUT can be caused by deleterious copy number variants[47]. ‡The estimates for chronic nephritis monogenic aetiologies are based only on the relative prevalence of Alport syndrome and MPGN, which together account for 20% of the aetiologies of chronic GN and for which a monogenic cause has been established in almost 100% of cases (in one of the following genes: Alport: *COL4A3*, *COL4A4*, *COL4A5* and *COL4A6*; MPGN: *Factor H*, *Factor I*, *MCP/CD46*, *CFHR 5* and *C3*).

rules that have been described elsewhere[18]. These core rules are not absolute, and provide only general guidance. Furthermore, the number of families with early-onset CKD that have been previously reported to have a mutation in the candidate causative gene should also be considered. For instance, some CAKUT-causing genes have been reported only in single families and therefore any generalization regarding their role must await their description and characterization in additional patients.

Indication-driven gene panel analysis

Mutation analysis in recessive or dominant monogenic kidney diseases can reveal the primary cause of a disease that results from an inherited disease-causing gene. Such analyses can enable disease entities to be categorized on the basis of their genetic aetiologies. As monogenic causes of early-onset CKD (TABLE 1) can be found in a substantial portion of affected individuals[3,10,39–43], we suggest that patients with early-onset CKD who are enrolled in clinical research or drug trials undergo molecular genetic diagnostics to enable cases of 'monogenic disease' to be accounted for in downstream epidemiologic analyses. Failure to do so might confound any conclusions from these studies. Moreover, molecular genetic diagnostics enables prenatal testing and might have prognostic or even therapeutic implications.

We have developed indication-driven diagnostic exon sequencing panels[42] for CAKUT[9,10], SRNS[44], renal cystic ciliopathies[42], glomerulonephritis, and nephrolithiasis or nephrocalcinosis[45]. These five diagnostic groups of CKD alone encompass 72.8% of CKD that manifests before the age of 25 years (TABLE 1). Using a microfluidic technique to perform multiplex PCR-based amplification of 600 exons from ~30 different genes that are known to be mutated

Exon
The protein coding part of a gene. Exons are spliced together following gene transcription to form mRNA, which is translated into protein.

Table 2 | **Degree of genetic causality in mono- and poly-genic kidney diseases**

Feature	Monogenic recessive diseases	Monogenic dominant diseases	Polygenic and/or complex diseases
Penetrance	Full	Full or incomplete	Low
Predictive power of a mutation	Almost 100%	High	Low
Onset	Predominantly during childhood	Childhood or adulthood	Predominantly during adulthood
Disease frequency	Low	Low	High
Number of affected individuals needed for gene discovery	Few	Few	Hundreds to thousands
Gene mapping approaches	Homozygosity mapping* or linkage analysis	Linkage analysis	GWAS
WES or WGS	In consanguinity, single affected families are sufficient	WES in distant relatives to minimize shared variants	NA
Functional analysis in animal models (mice, zebrafish)	Easily feasible (gene knockdown, knockout)	Feasible	Difficult
Examples of genes mutated in kidney diseases	*NPHP1*, *NPHS1*	*PAX2*, *HNF1B*	*APOL1*

GWAS, genome-wide association studies; NA, not applicable; WES, whole exome sequencing; WGS, whole genome sequencing. *Applicable to consanguineous families.

in the respective CKD diagnostic groups, we established a cost-effective mutation analysis screen for large patient cohorts. This method requires that DNA PCR products from each individual are barcoded before next-generation sequencing is performed[6–10,41,42] so that hundreds of PCR products can be sequenced in a single run, thereby drastically reducing costs. Indications to run a diagnostic panel are kept simple (TABLE 1) to ensure that future applications of the panels will achieve similar results. For instance, the indication to run the CAKUT panel is any imaging study showing evidence of CAKUT (such as renal aplasia, renal hypodysplasia, vesicoureteral reflux or ureteropelvic junction obstruction)[10]. For the proteinuria panel the indication is SRNS[8,44]. For the nephrolithiasis (urinary stone disease) panel the indication is any history of nephrolithiasis and/or nephrocalcinosis[45]. For the glomerulonephritis panel the indication is the presence of proteinuria and haematuria. For the renal cystic ciliopathy panel the indication is the presence of two or more renal cysts or increased renal echogenicity on renal sonography[3,42,46]. Of note, over 95 known genes that molecularly explain the vast majority of cases of renal ciliopathies (~70%) have been described.

CAKUT panel

Using gene panels we examined a large international cohort of 650 unrelated families with CAKUT for the presence of mutations in 17 autosomal dominant and six autosomal recessive genes that are known to cause CAKUT[9,10]. Our results showed that >8% of cases of CAKUT are caused by single-gene mutations in one of 23 autosomal dominant or recessive genes. These data together with findings from two independent studies[47,48] in which copy number variations were identified among 10–16% of individuals with CAKUT (most commonly involving the *HNF1B* or the DiGeorge/velocardiofacial locus), suggest that monogenic genes might cause CAKUT in around 17% of cases (TABLES 1,3).

Proteinuria panel

Mutation analysis of 27 known SRNS-causing genes in an international cohort of patients with SRNS manifesting before 25 years-of-age detected a single-gene cause of disease in 29.5% (526 of 1,783) of families (TABLES 1,4). The proportion of families in whom a single-gene cause was identified correlated inversely with age of onset, with a single-gene cause of SRNS detected in 69.4%, 49.7%, 25.3%, 17.8% and 10.8% of patients with disease manifesting in the first 3 months of life, 4–12 months, 1–6 years, 7–12 years and 13–18 years, respectively[44].

The identification of single-gene mutations in SRNS genes could have therapeutic consequences for some individuals. For instance, most individuals with a single-gene cause of nephrotic syndrome will not respond to steroid treatment[49,50]. *WT1* mutations in patients with SRNS can predispose to certain malignancies; consequently, the detection of *WT1* mutations should trigger monitoring and further evaluation of affected individuals for associated tumours that include Wilms tumour and gonadoblastoma. The latter entity has been mainly described in association with a concomitant abnormal chromosomal karyotype and therefore a karyotype analysis should also be obtained for patients with *WT1* mutations[51]. Furthermore, identification of the causative mutation might reveal a therapeutic approach for some rare single-gene causes of SRNS. For example, experimental treatment with coenzyme Q_{10} (CoQ_{10}) might be warranted for patients with mutations in genes that encode enzymes of CoQ_{10} biosynthesis (*COQ2, COQ6, ADCK4,* or *PDSS2*)[52,53]. Partial response to treatment with CoQ_{10} has been described in individuals with SRNS and mutations in *COQ2* (REF. 52), *COQ6* (REF. 53), and *ADKC4* (REF. 54). The efficacy of CoQ_{10} treatment needs to be assessed once greater numbers of patients with mutations in CoQ_{10} biosynthesis components have been identified.

Small Rho-like GTPases (RhoA/Rac1/Cdc42) are part of another pathway that has been implicated in the pathogenesis of nephrotic syndrome through the identification of mutations in the SRNS genes *ARHGDIA, KANK1*, *KANK2*, and *KANK4*, which are regulators of Rho-like GTPase, and through elucidation of the response of the calcineurin target synaptopodin to ciclosporin treatment in patients with SRNS[55–57]. Individuals with mutations in *CUBN* that cause vitamin B_{12} deficiency might be amenable to treatment with vitamin B_{12}, and individuals with *ARHGDIA* could theoretically be responsive to the mineralocorticoid-receptor blocker eplerenone through modulation of Rac I–mineralocorticoid interaction[55]. Finally, two children with recessive mutations in *PLCE1* responded fully to treatment with steroids or ciclosporin[58].

Table 3 | **Monogenic causes of CAKUT**

Gene	Protein	Refs
Autosomal dominant		
BMP4	Bone morphogenetic protein 4	92
CHD1L	Chromodomain helicase DNA binding protein 1-like	93
DSTYK	Dual serine/threonine and tyrosine protein kinase	39
EYA1	Eyes absent homolog 1	94
GATA3	GATA binding protein 3	95,96
HNF1B	HNF1 homeobox B	97
MUC1	Mucin 1	98
PAX2	Paired box 2	99
RET	Proto-oncogene tyrosine-protein kinase receptor Ret	100
ROBO2	Roundabout, axon guidance receptor, homolog 2 (*Drosophila*)	101
SALL1	Sal-like protein 1 (also known as spalt-like transcription factor 1	102
SIX1	SIX homeobox 1, 2 and 5	103
SIX2	SIX homeobox 2	92
SIX5	SIX homeobox 5	104
SOX17	Transcription factor SOX-17	105
SRGAP1	SLIT-ROBO Rho GTPase activating protein 1	106
TBX18	T-box transcription factor TBX18	17
TNXB	Tenascin XB	107
UMOD	Uromodulin	108
UPK3A	Uroplakin 3A	109
WNT4	Protein Wnt-4	110–112
Autosomal recessive		
ACE	Angiotensin I-converting enzyme	113
AGT	Angiotensinogen	113
AGTR1	Angiotensin II receptor, type 1	113
CHRM3	Muscarinic acetylcholine receptor M3	114
FGF20	Fibroblast growth factor 20	115
FRAS1	Extracellular matrix protein FRAS1	116
FREM1	FRAS1 related extracellular matrix proteins 1	9
FREM2	FRAS1 related extracellular matrix proteins 2	9
GRIP1	Glutamate receptor interacting protein 1	9
HPSE2	Inactive heparanase 2	117
ITGA8	Integrin α8	118
LRIG2	Leucine-rich repeats and immunoglobulin-like domains 2	119
REN	Renin	113
TRAP1	Heat shock protein 75 (also known as TNF receptor-associated protein 1)	6
X-linked		
KAL1	Anosmin 1	120

In the future it might be advisable to initiate mutation analysis of all known nephrosis genes in any patient with an episode of proteinuria persistent for >3 days (urine protein greater than 4 mg/m^2 per h). In a first episode with gross proteinuria steroid treatment might be commenced at the same time as mutation analysis is initiated. If results from the mutation analysis are returned within a few weeks, they might then guide the decision as to whether steroid treatment should be continued or terminated, depending on whether sufficient data exist to suggest that the presence of a certain mutation warrants discontinuation of treatment. Using this approach unnecessary steroid toxicity could be avoided.

Nephritis panel

In individuals with a diagnostic constellation compatible with chronic glomerulonephritis (that is, small grade proteinuria with microscopic haematuria), exon sequencing of 10 monogenic nephritis genes yields a monogenic cause of nephritis in ~20% of individuals[59] (TABLES 1,5).

Cystic kidney disease panel

In 50–70% of individuals who exhibit the presence of two or more cysts and/or a finding of increased echogenicity by ultrasonography, a monogenic cause of disease can be detected by exon sequencing of 95 genes[3,41,42,46] (TABLES 1,6). *PKD1* and *PKD2*, which are mutated in autosomal dominant kidney disease (ADPKD) are not part of this panel for several reasons. First, analysis of mutations in *PKD1* and *PKD2* requires a very specialized approach as it involves genotyping of long-range PCR fragments[60]; second, the manifestation of disease in patients with ADPKD often occurs after 25 years-of-age; and third, mutation analysis is rarely requested within the polycystic kidney disease community as molecular diagnosis is valuable in only a few specific situations and mostly not in paediatric patients.

Nephrolithiasis panel

We have demonstrated that 21% of cases of nephrolithiasis and/or nephrocalcinosis with onset before the age of 18 years and 12% of cases with onset after the age of 18 years can be explained by mutations in one of 14 genes[45] (TABLES 1,7). The cystinuria gene *SLC7A9* is the most frequently mutated in these individuals, with mutations identified in 15% of our study cohort[45]. Molecular diagnosis of urinary stone disease has important implications for affected individuals as well as for unaffected family members. Genetic screening of asymptomatic relatives might identify individuals who carry the disease-causing mutation; this information will guide clinicians to monitor these individuals for the development of disease and to institute preventive treatment when appropriate. In addition, standard treatment for urinary stone disease, such as increasing fluid intake, limiting sodium intake, use of thiazide diuretics and potassium citrate[61], might not directly address the pathophysiology of particular molecular diagnoses. For example, clinicians should monitor for tetany and seizures, which have been reported in patients with *CLDN16* mutations[62].

In summary, we expect that the use of diagnostic exon sequencing panels will expand the number of genes examined for each of these CKD groups in the future. In addition, other exon sequencing panels will be introduced into clinical practice to detect monogenic causes of CKD in additional diagnostic groups of early-onset CKD,

Table 4 | **Monogenic genes causes of SRNS**

Gene	Protein	Refs
Autosomal recessive		
*ADCK4**	AarF domain containing kinase 4	54
*ARHGDIA**	Rho GDP dissociation inhibitor 1	55
*CD2AP**	CD2-associated protein	75,121
*CFH**	Complement factor H	122
*COQ2**	Coenzyme Q2 4-hydroxybenzoate polyprenyltransferase	52,80
*COQ6**	Coenzyme Q6 monooxygenase	53
CRB2	Crumbs homolog 2	7
*CUBN**	Cubilin	123
*DGKE**	Diacylglycerol kinase epsilon	124
EMP2	Epithelial membrane protein 2	79
FAT1	Protocadherin Fat 1	F.H. unpublished
*ITGA3**	Integrin α3	125
*ITGB4**	Integrin β4	126
KANK1	KN motif and ankyrin repeat domain containing proteins 1	56
KANK2	KN motif and ankyrin repeat domain containing proteins 2	56
KANK4	KN motif and ankyrin repeat domain containing proteins 4	56
*LAMB2**	Laminin β2	78
MTTL1	Mitochondrially encoded tRNA leucine 1	127
*MYO1E**	MYO1E variant protein	128
*NPHS1**	Nephrin	14
*NPHS2**	Podocin	74
NUP93	Nuclear pore complex protein Nup93	F.H. unpublished
NUP107	Nuclear pore complex protein Nup107	129
NUP205	Nuclear pore complex protein Nup205	F. H. unpublished
*PDSS2**	Decaprenyl-diphosphate synthase subunit 2	130
*PLCE1**	Phospholipase C epsilon 1	58
*PTPRO**	Receptor-type tyrosine-protein phosphatase O	131
*SCARB2**	Lysosome membrane protein 2	132
*SMARCAL1**	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a like 1	133
WDR73	WD repeat domain 73	134–136
XPO5	Exportin 5	F. H. unpublished
Autosomal dominant		
*ACTN4**	Actinin α4	76
ANLN	Anillin, actin binding protein	137
*ARHGAP24**	Rho GTPase activating protein 24	138
*INF2**	Inverted formin-2	77
*LMX1B**	LIM homeobox transcription factor 1β	139
MYH9	Myosin heavy chain 9	140
*TRPC6**	Short transient receptor potential channel 6	141,142
*WT1**	Wilms tumor 1	143

*Sequenced by our group[44].

for example, in patients with monogenic forms of hypertension. The ongoing discovery of novel genes that cause CKD when mutated, together with the continuing trend of cost reduction in exome sequencing technologies, suggests that in the near future, indication-driven molecular genetic diagnostics will be performed using WES, which sequences the exons of all 20,000 genes in the human genome in parallel at low cost[3,63]. However, in this context it will be important to maintain an indication-driven *a priori* approach, in which only genes known to cause the respective disorder are evaluated for mutations on the basis of clearly defined clinical indication criteria as described above (TABLE 1).

Generalizability of mutation detection rates

Generalizations regarding the rates of mutations detected across the different aetiologies of early-onset CKD and among different populations should take several important factors into consideration. First are the effects of consanguinity and patient age on mutation rates across different disease cohorts. In our analyses of families with early-onset SRNS and urinary stone disease, the proportion of individuals in whom a molecular genetic diagnosis was made correlated inversely with age of disease onset and directly with degree of consanguinity[44,45]. Although our findings suggest that different mutation rates might apply to cohorts with differing ages of disease onset or degrees of consanguinity, we think that our reported rates of mutation in SRNS will translate to other cohorts, as similar mutation rates have been confirmed by two independent European groups[19,64]. Likewise, we have shown that causative mutations can be identified in approximately 18–21% of patients with childhood-onset urinary stone disease (F. Hildebrandt, unpublished work)[45]. Of course, the success rates of mutation identification will most likely increase as a greater number of monogenic renal genes and mutations are identified.

Second, as more data from extensive whole exome studies on human genetic variation accrue, questions regarding incomplete penetrance of certain alleles can be addressed and studied. A degree of incomplete penetrance and variable expressivity is increasingly apparent, especially for monogenic dominant causes of CAKUT but also for other recessive aetiologies. For instance, in early-onset SRNS for which recessive disease-causing mutations are fairly frequent and often convey full penetrance, a few exceptions in which mutated genes seem to convey partial penetrance have also been described[65].

Third, the potential for false positive attribution of mutated genes as being monogenic disease-causing as a result of inappropriate filtering criteria or increased sequencing of patients who might have a low probability of having monogenic disease can also hamper the true frequency of mutation detection rates. Minimizing the false assignment of genetic variants as disease-causing will be one of the most important tasks in the renal research area over the next 10 years. Confirmation of the disease-causing role of identified genes is required through use of cell-based functional assays, animal models, and large databases that describe genetic variants in large multinational populations. Fourth, for dominantly

Table 5 | **Monogenic causes of chronic glomerulonephritis**

Gene	Protein	Disease	Refs
Autosomal recessive			
CFH	Complement factor H	MPGN	88
Autosomal dominant			
CFI	Complement factor I	MPGN	144
CFHR5	Complement factor H-related protein 5	MPGN	90,145–147
FN1	Fibronectin 1	GFND	148
Autosomal dominant or recessive			
COL4A3	Collagen type IV α3	Alport	149,150
COL4A4	Collagen type IV α4	Alport	149,150
CD46	Membrane cofactor protein (MCP)	MPGN	151
C3	Complment component 3	MPGN	89
X-linked			
COL4A5	Collagen type IV α5	Alport	152
COL4A6	Collagen type IV α6	Alport with LM	153

Alport: Alport syndrome; GFND: glomerulopathy with giant fibronectin deposits; LM: leiomyomatosis; MPGN, membranoproliferative glomerulonephritis; TMA, thrombotic microangiopathy.

inherited conditions, the presence of familial cases will often also positively influence the rate at which mutations are detected[66].

Finally, one additional concern of mutation analysis is the potential adverse effects of screening for monogenic disease-causing mutations in unaffected family members. The finding of a mutated candidate gene could be particularly detrimental to an individual if the disease allele is incompletely penetrant or shows variable expressivity, leading to prognostication of an unfavourable health condition that might never manifest. In this context it is important to observe the recommendation by the American College of Medical Genetics and Genomics[67], which discourages mutation analysis in individuals who have not manifested with symptoms of disease. Nonetheless, certain circumstances exist in which clinical judgment should be applied in which a disease can be 'silent' or 'subtle', whereby apparently 'unaffected' persons are in fact asymptomatic (for example, in patients with asymptomatic nephrocalcinosis or asymptomatic renal hypodysplasia).

Novel gene discoveries using WES

The exome comprises the entirety of all exon-encoding sequences in a genome. Although the exome represents only 1% of the human genome, it contains all of the protein-encoding sequences. Sequencing of the exome through WES therefore offers a powerful approach towards the identification of novel monogenic causes of disease. A detailed description of WES can be found elsewhere[68,69], but briefly, the technique involves the sequencing of short fragments of genomic DNA that have been hybridized to oligonucleotides representing exons of the human genome. The millions of sequencing reads that are generated are aligned for comparison with a 'normal' reference sequence of the human genome and a WES data output file is generated, which contains all genetic variants from the reference sequence that are found in the DNA of the tested individual. If a genetic sequence variant leads to a phenotypic change, for instance causes disease, that sequence variant is called a 'mutation'. Other sequence variants are called 'variances of unknown significance'.

The identification of mutations in novel disease-causing genes using WES can reveal previously unrecognized causes of disease. For instance, WES analyses first revealed a role for mutations in genes that are involved in CoQ_{10} biosynthesis — *COQ2*, *COQ6*, *ADCK4* and *PDSS2* — in the pathogenesis of SRNS[52–54]. However, the utility of WES for novel gene discovery is hampered by the fact that a large number of genetic variants are identified by comparing the exome sequences of an individual to a 'normal' reference sequence. On average, WES of an individual identifies 2,000–4,000 non-synonymous variants with minor allele frequency <1%. This limitation can be overcome by restricting sequence variant filtering to smaller regions of interest that are generated for instance by homozygosity mapping or linkage analysis[70], or by analysing only shared variants across several affected individuals within the same family. These approaches enable DNA variants to be excluded from further consideration and allow an *a priori* restriction for the pool of potentially causal mutations. Finally, WES can result in the identification of incidental findings, which are not related to the indication for performing WES but might still be of medical importance to the patient. A policy statement with recommendations regarding the utility and reporting of incidental findings have been published by the American College of Medical Genetics[71]. Use of WES might also detect disease-causing genes that were not suspected on the basis of the patient's clinical presentation. For instance, by combining homozygosity mapping with WES in 10 sibling pairs with renal cystic ciliopathies, we detected the causative gene in seven of the 10 families studied[3]. In five families we identified mutations of known renal cystic ciliopathies genes; however, in two families we found mutations in other known CKD-causing genes, specifically *SLC4A1* (a causative gene for distal renal tubular acidosis) and *AGXT* (the causative gene for hyperoxaluria type 1). Neither diagnosis had been made clinically and represented phenocopies for renal cystic ciliopathies[3]. Other examples of phenocopies that have been identified through WES have been described for other non-renal conditions[72,73].

Identification of pathogenic pathways

The identification of disease-causing mutations using WES can provide new insights into disease pathogenesis, as exemplified by WES analysis of patients with nephrotic syndrome. This condition is defined by proteinuria, with hypoalbuminaemia, oedema and hyperlipidaemia, and is categorized by the patient's clinical response to steroid therapy as either steroid-sensitive or steroid-resistant. SRNS is the second most frequent cause of CKD in children and young adults (TABLE 1). The mechanisms of SRNS are poorly understood and no curative treatment

Exome
The protein coding sequences of the entire genome (comprising ~1% of the human genome).

Variant filtering
The process of excluding variants as disease-causing. For instance, very common variants and variants that do not alter the protein sequence are excluded.

Homozygosity mapping
A technique in which the homozygous regions across the genome are identified. This strategy is effective for the discovery of autosomal recessive monogenic disease genes in consanguineous families.

Phenocopies
A variation in a phenotype of given trait that can mimick a different trait.

Table 6 | **Monogenic causes of nephronophthisis-related ciliopathies**

Gene (alternative name)	Protein	Refs
NPHP1 (JBTS4)	Nephrocystin-1	154,155
INVS (NPHP2)	Inversin	156
NPHP3	Nephrocystin-3	157
NPHP4	Nephroretinin	158,159
IQCB1 (NPHP5)	IQ calmodulin-binding motif-containing protein 1	160
CEP290 (NPHP6)	Centrosomal protein 290 kDa	161
GLIS2 (NPHP7)	Zinc finger protein GLIS2	162
RPGRIP1L (NPHP8)	Protein fantom	163
NEK8 (NPHP9)	Serine/threonine-protein kinase Nek8	164
SDCCAG8 (NPHP10)	Serologically defined colon cancer antigen 8	63
TMEM67 (NPHP11)	Meckelin	165
TTC21B (NPHP12)	Tetratricopeptide repeat domain 21B	166
WDR19 (NPHP13)	WD repeat-containing protein 19	167
ZNF423 (NPHP14)	Zinc finger protein 423	168
CEP164 (NPHP15)	Centrosomal protein 164 kDa	168
ANKS6 (NPHP16)	Ankyrin repeat and sterile α motif domain containing protein 6	169

The table lists the 16 most-frequent monogenic causes of nephronophthisis-related ciliopathies. Monogenic (recessive) mutations in the following genes are less frequent causes of nephronophthisis-related ciliopathies (Meckel syndrome, Senior–Loken syndrome, Joubert syndrome and Bardet–Biedl syndrome): *XPNPEP3*, *ATXN10*, *FAN1*, *SLC41A1*, *CEP83*, *SLC12A3*, *CLCNKB*, *AGXT*, *GRHPR*, *HOGA1*, *PKHD1*, *INPP5E*, *TMEM216*, *AHI1*, *ARL13B*, *CC2D2A*, *OFD1*, *KIF7*, *TCTN1*, *TMEM237*, *CEP41*, *TSGA14*, *TMEM138*, *C5orf42*, *TMEM231*, *CSPP1*, *PDE6D*, *TBC1D32*, *SCLT1*, *MKS1*, *TCTN2*, *B9D1*, *B9D2*, *KIF14*, *BBS1*, *BBS2*, *ARL6*, *BBS4*, *BBS5*, *MKKS*, *BBS7*, *TTC8*, *PTHB1*, *C21orf58*, *TRIM32*, *C4orf24*, *WDPCP*, *LZTFL1*, *ALMS1*, *IFT122*, *WDR35*, *IFT140*, *C14ORF179*, *DYNC2H1*, *WDR34*, *WDR60*, *IFT80*, *IFT172*, *TRAF3IP1*, *NEK1*, *POC1A*, *EVC*, and *EVC2*.

is available. The most frequent renal histological feature of SRNS is FSGS, which carries a 33% risk of recurrence in kidney transplant recipients, thereby leading to ESRD[49]. Insights into the primary aetiology and pathomechanisms of SRNS through the identification of genes that, if mutated, cause recessive or dominant monogenic forms of SRNS, have provided fundamental insights into the disease mechanisms[14–16,74]. The discovery of novel SRNS genes has led to the understanding that the renal glomerular podocyte represents the cell type at which these disease mechanisms converge[18]. Over 39 genes are now known to cause SRNS if mutated (TABLE 4). Those genes encode proteins that can currently be grouped into the following four major categories: proteins that are associated with the glomerular slit membrane, such as nephrin (encoded by *NPHS1*)[14], podocin (*NPHS2*)[74], and CD2-associated protein (*CD2AP*)[75]; proteins that are involved in actin binding and regulation and hence affect the podocyte cytoskeleton, such as those encoded by *ACTN4* (REF. 76), *INF2* (REF. 77), and *ARHGDIA*[55]; proteins associated with focal adhesions that tether the sole of the podocyte to the underlying glomerular basement membrane, such as those encoded by *LAMB2* (REF. 78) and *EMP2* (REF. 79); and proteins involved in the biosynthesis of CoQ_{10}, such as those encoded by *COQ2* (REF. 80), *COQ6* (REF. 53) and *ADCK4* (REF. 54) (FIG. 1).

Consequences for therapy

A diagnosis of CKD in a patient aged <25 years should trigger the clinician to consider referring the patient for genetic analysis. Molecular analysis of early CKD-causing genes using panels of known genes is increasingly available. Following identification of a CKD-causing mutation, the patient should be referred to a clinical laboratory with Clinical Laboratory Improvement Amendments certification as well as for genetic counselling. Optimally, care for patients with monogenic CKD should be provided by a multidisciplinary team comprising nephrologists, urologists, and clinical geneticists.

Identification of the causative mutation might have therapeutic consequences for patients with SRNS that harbour mutations in genes involved in CoQ_{10} biosynthesis, as these patients can receive CoQ_{10} supplementation[53,54]. CoQ_{10} deficiency might lead to nephrotic syndrome through the excess production and accumulation of reactive oxygen species[81]. The finding that CoQ_{10} treatment is beneficial for patients with SRNS resulting from mutations in CoQ_{10} biosynthetic genes has opened a window of opportunity for these patients, especially since CoQ_{10} is an innocuous food supplement that has a high safety profile. Initial case reports[82,83] showed that CoQ_{10} supplementation in patients with CoQ_{10} deficiency secondary to mutations in its biosynthesis genes improved neurologic symptoms but failed to show any benefit on renal function, as advanced chronic renal failure had developed before the initiation of CoQ_{10} supplementation. A subsequent case report[52], however, suggested that early initiation of the treatment, immediately after the onset of renal symptoms, was beneficial in reducing proteinuria in a patient with nephrotic syndrome caused by recessive mutations in *COQ2*. This form of monogenic SRNS, for which further study is needed, provides one of

Table 7 | **Monogenic causes of urinary stone disease**

Gene	Protein	Disease entity	Mode of inheritance	Refs
ADCY10/SAC	Adenylate cyclase 10 (soluble)	Hypercalciuria, calcium oxalate nephrolithiasis	AD	170
AGXT	Alanine-glyoxylate aminotransferase	Primary hyperoxaluria, type 1	AR	171
APRT	Adenine phosphoribosyltransferase	Adenine phosphoribosyltransferase deficiency, urolithiasis (DHA stones), renal failure	AR	172
ATP6V0A4	ATPase, H^+ transporting, lysosomal V0 subunit a4	dRTA	AR	173
ATP6V1B1	ATPase, H^+ transporting, lysosomal 56/58kDa, V1 subunit B1	dRTA with deafness	AR	174
CA2	Carbonic anhydrase II	Osteopetrosis and dRTA or pRTA	AR	175
CASR	Calcium-sensing receptor	Hypocalcaemia with Bartter syndrome and/or hypocalcaemia	AD	176
CLCN5	H^+/Cl^- exchange transporter	Dent disease or nephrolithiasis, type 1	XR	177
CLCNKB	Chloride channel, voltage-sensitive Kb	Bartter syndrome, type 3	AR	178
CLDN16	Claudin 16	FHHNC	AR	179
CLDN19	Claudin 19	FHHNC with ocular abnormalities	AR	180
CYP24A1	Cytochrome P450, family 24, subfamily A, polypeptide 1	1,25-(OH) D-24 hydroxylase deficiency, infantile hypercalcaemia	AR	181
FAM20A	Pseudokinase FAM20A	Enamel-Renal syndrome, amelogenesis imperfecta and nephrocalcinosis	AR	182
GRHPR	Glyoxylate reductase/ hydroxypyruvate reductase	Primary hyperoxaluria, type 2	AR	183
HNF4A	Hepatocyte nuclear factor 4α	MODY, Fanconi syndrome and nephrocalcinosis	AD	184
HOGA1	4-hydroxy-2-oxoglutarate aldolase 1	Primary hyperoxaluria, type 3	AR	185
HPRT1	Hypoxanthine phosphoribosyltransferase 1	Kelley–Seegmiller syndrome, partial HPRT deficiency, HPRT-related gout	XR	186
KCNJ1	ATP-sensitive inward rectifier potassium channel 1	Bartter syndrome, type 2	AR	187
OCRL	Inositol polyphosphate 5-phosphatase OCRL-1	Lowe syndrome/Dent disease 2	XR	188
SLC12A1	Solute carrier family 12, member 1	Bartter syndrome, type 1	AR	189
SLC22A12	Solute carrier family 22 (organic anion/urate transporter), member 12	Renal hypouricaemia, type 1	AD/AR	190
SLC2A9	Solute carrier family 2 (facilitated glucose transporter), member 9	Renal hypouricaemia, type 2	AD/AR	191
SLC34A1	Solute carrier family 34 (sodium phosphate), member 1	Hypophosphataemic nephrolithiasis/ osteoporosis-1, (NPHLOP1) or Fanconi renotubular syndrome 2	AD/AR	192
SLC34A3	Solute carrier family 34 (sodium phosphate), member 3	Hypophosphataemic rickets with hypercalciuria	AR	193
SLC3A1	Solute carrier family 3 (cystine, dibasic and neutral amino acid transporters, activator of cystine, dibasic and neutral amino acid transport), member 1	Cystinuria, type A	AR	194
SLC4A1	Solute carrier family 4, anion exchanger, member 1 (erythrocyte membrane protein band 3, Diego blood group)	Primary distal renal tubular acidosis,	AD/AR	195
SLC7A9	solute carrier family 7 (glycoprotein associated amino acid transporter light chain, bo, + system), member 9	Cystinuria, type B	AD/AR	196
SLC9A3R1	Solute carrier family 9, subfamily A (NHE3, cation proton antiporter 3), member 3 regulator 1	Hypophosphataemic nephrolithiasis/ osteoporosis-2, (NPHLOP2)	AD	197
VDR	Vitamin D (1,25- dihydroxyvitamin D3) receptor	Idiopathic hypercalciuria	AD	198
XDH	Xanthine dehydrogenase	Xanthinuria, type 1	AR	199

AD, autosomal dominant; AR, autosomal recessive; dRTA, distal renal tubular acidosis; FHHNC, familial hypomagnesaemia with hypercalciuria and nephrocalcinosis; MODY, maturity onset diabetes of the young; pRTA, proximal renal tubular acidosis; XR, X-linked recessive.

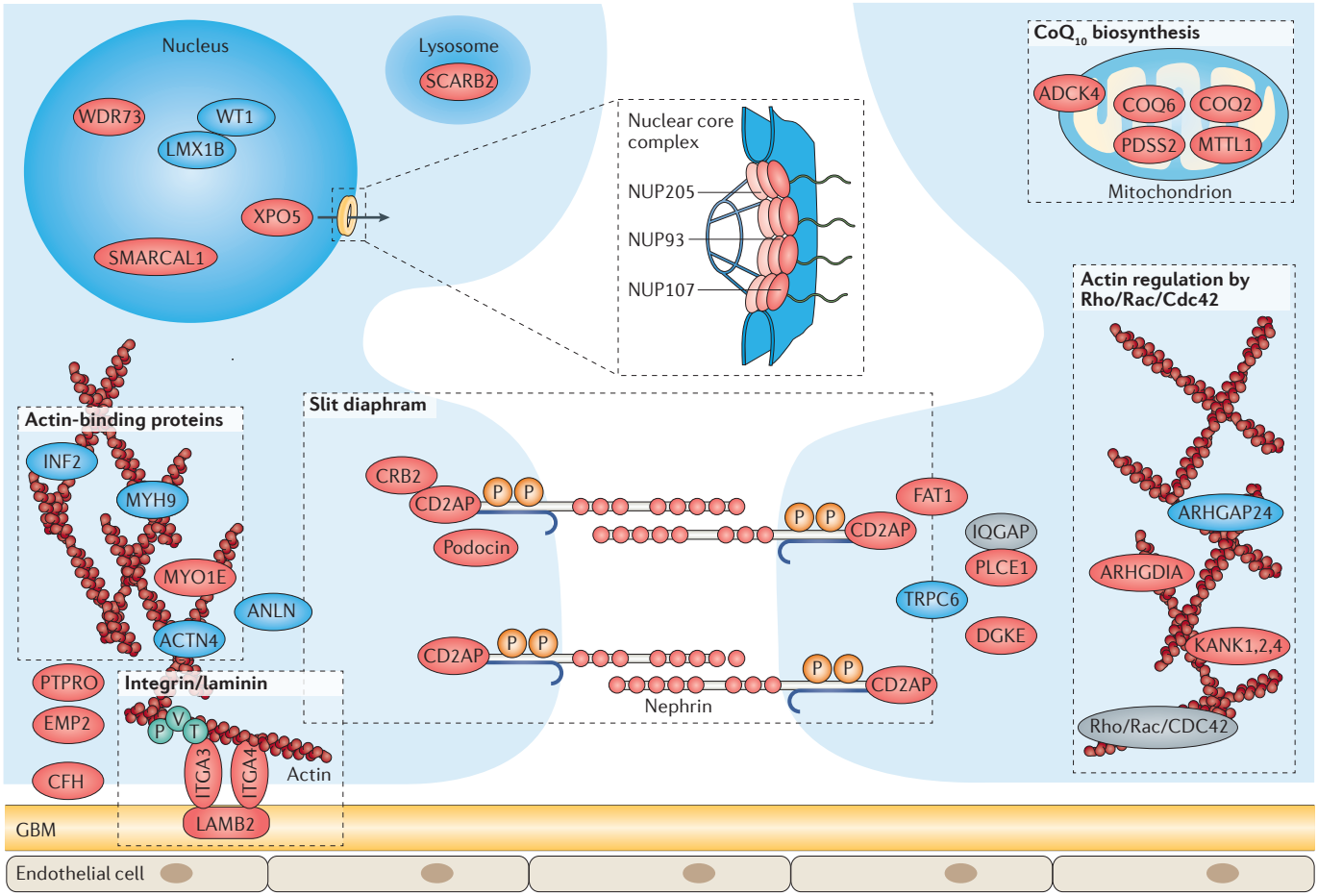

Figure 1 | **Pathogenic pathways of steroid resistant nephrotic syndrome (SRNS).** The identification of single-gene (monogenic) causes of SRNS has identified the podocyte as a central player in the pathogenesis of this disease with the identification of proteins and functional pathways that are essential for glomerular function. Proteins that form protein–protein interaction complexes are grouped according to their structural activities or signalling pathways. Proteins that if altered cause recessive monogenic forms of SRNS are coloured red, and proteins that if altered cause dominant forms of SRNS are coloured blue.

the first examples as to how the identification of a monogenic cause of SRNS might open new therapeutic avenues to treat this disease for which no efficient treatment currently exists.

The identification of monogenic causes of disease will improve the future categorization of diseases for the investigation of outcomes in clinical trials. In the immediate term, however, the identification of a disease-causing mutation already has several clinical implications, including the ability to provide the patient and their family with a definitive description of the cause of their disease; the potential to place the clinical phenotype into context by gene-specific stratification and through the delivery of personalized medicine; the ability to provide precise genetic counselling for family planning; to diagnose previously unrecognized affected family members; to avoid unnecessary diagnostic procedures, tests and treatments; to detect and treat asymptomatic (or subtle) extrarenal manifestations early; to provide guidance for the monitoring of potential future complications; and to guide advanced medical management on a gene-specific basis (BOX 1).

In our opinion, mutation analysis by WES and indication-driven analysis of relevant gene panels can currently be recommended for all individuals who manifest with one of the following before 25 years-of-age: CKD, SRNS, increased echogenicity or two or more cysts on renal ultrasonography, urinary stone disease, CAKUT, or chronic glomerulonephritis. The likelihood of identifying a causative monogenic mutation is estimated to be ~20% in this setting and this rate will rise in the future as more disease genes and causative mutations are identified. Our understanding of the clinical consequences of monogenic mutations will rapidly accumulate as genotype–phenotype correlations are discovered and investigated over the coming years.

Conclusions and future directions

Two-thirds of early-onset CKD is caused by CAKUT, SRNS, renal cystic ciliopathies or chronic glomerulonephritis. Over the past 10 years, >200 genes that if mutated can cause monogenic forms of these disorders have been identified. High throughput exon sequencing using exon panels or WES now enables identification of

Box 1 | **Clinical implications of genetic testing in patients with early-onset chronic kidney disease**

Provides a definitive diagnosis

Places the clinical phenotype into context and potentially facilitates delivery of personalized medicine

- For example, heterozygous contiguous gene deletions in the 17q12 region (which includes *HNF1B*) can cause congenital anomalies of the kidneys and urinary tract (CAKUT) with neurologic phenotypes such as autism spectrum disorder or schizophrenia
- Future possible implications include allele-specific treatments as are available for other genetic diseases such as cystic fibrosis*

Might enable precise genetic counselling for family planning

- For example, by predicting disease recurrence and facilitating pre-implantation genetic diagnosis

Might enable diagnosis of affected family members.

- Index patients with CAKUT caused by *PAX2* or *GATA3* mutations, for example, might have a parent, child or sibling with undiagnosed CAKUT, which is only detected by recognizing the genetic nature of the disease; this finding should trigger renal ultrasonographic screening for CAKUT in other family members
- Genetic screening may enable the identification of asymptomatic individuals harbouring heterozygous *COL4A4* or *COL4A5* mutations, who should be monitored yearly for proteinuria and hypertension

Enable unnecessary diagnostic procedures, tests and treatments to be avoided

- For example, renal biopsy is not needed in patients with congenital or infantile nephrotic syndrome secondary to *NPHS1* or *NPHS2* mutations or in patients with a characteristic nephronophthisis phenotype and *NPHP1* mutations
- For example, aggressive pretransplantation 'anti-recurrence' treatment should be avoided in kidney transplant recipients with focal segmental glomerulosclerosis secondary to *NPHS2* mutations, which has a low risk of recurrence
- For example, patients with CAKUT secondary to *HNF1B* mutations might have elevated liver function tests; acknowledging this finding as part of the HNF1B-spectrum can prevent unnecessary invasive investigation of liver abnormalities

Early detection and treatment of asymptomatic (or subtle) extrarenal manifestations

- For example, heterozygous mutations in *HNF1B* can cause 'isolated CAKUT' or 'syndromic CAKUT' associated with one or more of the following extrarenal manifestations: maturity onset diabetes of the young (MODY) type 5, hyperuricaemia and hypomagnesaemia; early identification of those conditions can lead to early monitoring and treatment
- Similarly, deafness has been associated with CAKUT-causing mutations in *EYA1*, *SALL1* or *PAX2*
- Patients with CAKUT secondary to *GATA3* mutations might have hypoparathyroidism, which can be asymptomatic in early disease stages but should be recognized and treated

Providing guidance for monitoring of potential future complications

- For example, patients with nephrotic syndrome caused by *WT1* mutations are at increased risk of Wilms tumour
- Patients with *WT1* mutations in the donor splice site of intron-9, resulting in the splice form +KTS are at risk of gonadoblastoma
- Patients with nephronophthisis secondary to *NPHP5* mutations are at risk of progressive blindness secondary to retinitis pigmentosa (Senior–Løken syndrome)

Guide advanced medical management on a gene-specific basis.

- For example, recessive mutations in *CTNS* establish a diagnosis of cystinosis and should trigger treatment with cystine-depleting agents
- CoQ_{10} supplements should be considered for patients with nephrotic syndrome who harbour mutations in genes of the CoQ_{10} biosynthesis pathway
- The finding of *MYH9* mutations in patients with nephrotic syndrome should guide thrombocytopaenia management

* Lumacaftor and ivacaftor are effective in patients who have a homozygous Phe508del mutation in *CFTR*[200].

the causative mutation in a high proportion (~20%) of individuals with early-onset CKD. Molecular genetic diagnostics can be planned in a well-defined, clinical indication-driven manner for patients with SRNS, cystic kidney diseases, CAKUT, glomerulonephritis, or nephrolithiasis or nephrocalcinosis. Indication-driven gene panel analysis with the use of next-generation sequencing is an emerging tool, which will continue to be used in clinical research and practice[72,73]. The identification of novel disease-causing genes will enable molecular genetic diagnosis, aetiologic classification of disease for therapeutic trials and development of animal models of disease, as well as small molecule screening for therapeutic purposes. Furthermore, the progress in high-throughput sequencing will ensure that additional CKD-causing genes will be detected in the near future. Findings from such studies could lead to more relevant aetiologic categorization of disease entities than can be provided by ultrasound imaging or histopathology alone. Lastly, detection of monogenic causes of CKD already has implications for genetic counselling as well as for clinical management of patients with CKD.

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Competing interests statement

F.H. receives royalties for a mutation analysis panel that is licensed to Claritas Genomics. A.V. declares no competing interests.