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Exome Sequencing Frequently Reveals the Cause 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 adult onset CKD. In the United States the most common diagnostic groups of CKD that manifests before 25 years of age are: i) congenital anomalies of the kidneys and urinary tract (CAKUT) (49.1%), ii) steroid-resistant nephrotic syndrome (SRNS) (10.4%), iii) chronic glomerulonephritis (8.1%), and iv) renal cystic ciliopathies (5.3 %), encompassing >70% of CKD together. Recent findings suggest that early-onset CKD is caused by mutations in any one of over 200 different monogenic genes. High-throughput sequencing has very recently rendered identification of causative mutations in this high number of genes feasible. Molecular genetic diagnostics in early onset-CKD (before the age of 25 years) will, i) provide patients and families with a molecular genetic diagnosis, ii) generate new insights into diseases mechanisms, iii) allow etiology-based classification of patient cohorts for clinical studies and, iv) may have consequences for personalized treatment and prevention of CKD. In this review, we will discuss the implications of next-generation sequencing for clinical genetic diagnostics and discovery of novel genes in early-onset CKD. We also delineate the resulting opportunities for deciphering disease mechanisms and therapeutic implications.

Keywords

genetic kidney disease; monogenic disease; clinical genetic testing; chronic kidney disease (CKD); end-stage kidney disease (ESKD)

Introduction

Chronic kidney disease (CKD) in children is defined by the presence of kidney damage or by a glomerular filtration rate that has remained below 60 ml/min/1.73 m^2 for more than 3 months[1]. Progression of CKD to end-stage renal disease (ESRD) requires dialysis or transplantation for survival. Although the prevalence of CKD has been increasing for as yet

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unidentified reasons[2], little is known about any of the disease mechanisms. CKD that manifests in the first 25 years of life is caused to a large degree by CAKUT, SRNS, chronic glomerulonephr-iotis and renal cystic ciliopathies (Table 1). Whereas previously many of the diagnostic groups of early-onset CKD were not viewed as being of genetic origin, recently the discovery was made that in early-onset CKD (defined as CKD manifesting before 25 years of age) a monogenic cause of disease can be detected in the surprisingly high fraction of ~20% of individuals with early-onset CKD (Table 2). Monogenic mutations are sufficient as a singular cause of disease without requiring any additional biological or environmental causes of functional damage. This mechanism of genetic disease causation is known as “full penetrance” of the mutation (see glossary).

More than 200 monogenic causative genes have now been identified for the 70% most common etiologies of CKD in this age group[3–12]. We focus here on single-gene causes of early-onset CKD and discuss the implication of next-generation sequencing for the genetic diagnosis of early-onset CKD. We then address the discovery of novel genes that if mutated cause early-onset CKD and discuss resulting opportunities for delineating the pathomechanisms and therapeutic implications.

Epidemiology of chronic kidney disease in children

The primary causes of early-onset CKD in children differ from adult-onset CKD (Table 1). The 2008 report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS), which included data from 7,037 children and young adults with CKD,[13] found the most common diagnostic groups to be (1) congenital anomalies of the kidneys and urinary tract (CAKUT) (49.1%), (2) steroid-resistant nephrotic syndrome (SRNS) (10.4%), (3) chronic glomerulonephritis (8.1%), and (4) renal cystic ciliopathies (5.3%), together encompassing over 70% of the entire pediatric CKD population (Table 1). Those diagnostic groups also represent the most common causes of early-onset CKD in developed countries outside the United States[14]. The etiologies of the above diagnostic groups of CKD were unknown before the past decade, when identification of many single-gene (monogenic) causes of CKD revealed their primary causes (etiologies) and providing a powerful approach to delineate the related pathomechanisms. This improved understanding of disease is exemplified, for instance, by the discovery of *NPHS1 (nephrin)* mutations as a cause of congenital nephrotic, thereby identifying dysfunction of the glomerular podocyte as central to the pathogenesis of steroid resistant nephrotic syndrome (SRNS)[15–17].

Monogenic diseases (also referred to as Mendelian or single-gene disorders) result from mutations in a single causative gene. Patterns of Mendelian inheritance include: autosomal dominant, autosomal recessive, and X-linked. Over the past 15 years over 200 monogenic causes of early onset CKD have been identified (Table 2). Most of them were discovered in the last 5 years due to acceleration of gene discovery by modern technologies of genetic mapping and whole exome sequencing. Currently there are approximately 36 genes known to be mutated in CAKUT[10,11,1819], 39 genes in SRNS[8,20] (Hildebrandt et al. 2015, NDT, in press), 10 genes in chronic glomerulonephritis, and over 95 genes in renal cystic ciliopathies[4,21]. These data demonstrate that in ~ 20% of patients with early-onset CKD a monogenic cause of disease can be identified by mutation analysis (Table 2).

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Genetic disease 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. Genetic "penetrance" reflects the proportion of individuals that express a certain disease phenotype in relation to the number of individuals that carry the genetic variant(s). "Full penetrance" means that 100% of individuals that carry a genetic variant also express the disease phenotype[22]. At one end of the range of genetic causality are recessive monogenic Mendelian diseases (also known as single-gene disorders), which have a tight genotype-phenotype correlation, so that the disease phenotype is almost entirely determined by disease-causing mutations in a single gene (full penetrance) (Table 3). This is the case for instance in *NPHP1* mutations that cause juvenile nephronophthisis in any patient who carries mutations on both copies of the *NPHP1* gene[23]. Those mutations inescapably cause CKD with renal fibrosis and cysts by the age of 20 years. Autosomal dominant monogenic Mendelian diseases, in contrast to recessive diseases, have reduced tightness of genotype-phenotype correlation, due to multiple characteristics of dominant diseases including (Table 3): i) age-related penetrance (with increasing age, a higher fraction of individuals that carry the causative mutation express the disease); ii) incomplete penetrance, i.e. some individuals with the mutation do not develop the diseases phenotype at all. The disease thereby appears to be skipping generations in a pedigree; iii) variable expressivity (i.e. different degrees of severity and/or organ involvement occur in different affected individuals that carry identical mutated alleles). An example of an autosomal dominant kidney disease with variable expressivity is given by *HNF1B* mutations that cause CAKUT, CKD and maturity-onset diabetes of the young (MODY) with variable age of onset and variable presence of MODY diabetes[24,25]. Variable expressivity mainly describes a complex genotype-phenotype relationship in dominant diseases. A similarly complex situation exists in recessive diseases that may exhibit 'multiple allelism'. This phenomenon refers to the finding that different (homozygous) recessive mutations in the same gene may lead to different clinical outcomes. For instance, certain mutation in *LAMB2* that cause nephrotic syndrome may lack ocular involvement[26], or specific combinations of compound heterozygous mutations of *NPHP2* may cause adult onset rather than childhood onset nephrotic syndrome[27].

At the other end of the spectrum of causality are more common conditions for which low-penetrance, so-called "risk alleles", have been described[22]. In those conditions, which often are referred to as polygenic or complex diseases genetic variants usually exert small effects on the disease (Table 3). Therefore, usually only a small fraction of the statistical variance for a disease phenotype can be assigned to a risk allele. An exception from this situation occurs in the *APOL1* gene, in which specific genetic variants, apparently in a recessive way, convey a large phenotypic risk for the development of CKD in the African American population[28,29] (Table 3). An example of successful identification of disease risk alleles in kidney diseases is that of specific genotypes in the *APOL1* locus that were associated with an increased risk of focal segmental glomerulosclerosis and chronic kidney disease in African-American patients.[2830–32] For instance, about 13–23% of African-Americans (compared with 0.3–1.3% of European Americans) have one out of the known two *APOL1* risk alleles[33,34]. For African Americans carrying 2 risk alleles in trans, the risk of developing

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focal segmental glomerulosclerosis is increased 17-fold compared to control individuals carrying 0–1 risk allele[33,34].

Finally, another aspect of genetic causality that should take into consideration is the contribution of genetic modifiers. This concept in which specific alleles are responsible for modification of disease phenotypes, have been described for monogenic forms of cystic kidney disease[35] and glomerulonephritis[36]. Nonetheless, additional supporting evidence is needed for some of these associations in early onset CKD.

We[11] as well as others[37] have noted that there are many false assignments of potential disease causality at the variant level. Specifically, it has been noted that up to 30% of genetic variants published as likely disease causing and deposited in genetic databases were not confirmed as deleterious[38]. Consequently, any attribution of pathogenicity to a given variant should be subject to strict criteria and taking into consideration multiple levels of evidence such as amino acid sequence conservation, segregation analysis, tissue specific gene expression, functional studies, and animal models[37,39]. For the decision if a genetic variant qualifies as potentially disease causing we follow empiric core rules that are outlined in Box 1 for recessive monogenic diseases and in Box 2 for dominant genes. These core rules are not absolute, and provide only general guidance. Furthermore, the number of families with early CKD that have been previously reported to have a mutation in the candidate causative gene should also be considered. For instance, some of the CAKUT-causing genes were reported in only single families and therefore any generalizations regarding their role, however, must await the description and characterization of mutations in additional patients.

Indication-driven gene panel analysis using next generation sequencing

Mutation analysis in recessive or dominant monogenic kidney diseases may reveal the primary cause (etiology) of a disease resulting from an inherited disease-causing gene. Such analyses can enable disease entities to be categorized on the basis of their genetic etiologies. A monogenic cause of the early onset CKD diagnoses listed in Table 1 may be found in a substantial portion of affected individuals who are enrolled in clinical research or drug trials[4,11,40–47]. Because of this, we suggest that these subjects all undergo molecular genetic diagnostics to account for subjects with “monogenic disease” in downstream epidemiologic analyses. Failure to do so may confound any conclusions. Moreover, molecular genetic diagnostics enables prenatal testing and may have prognostic and sometimes therapeutic implications.

We have developed indication-driven diagnostic exon sequencing panels[45,48] for CAKUT[10,11], steroid resistant nephrotic syndrome[8], renal cystic ciliopathies[45], glomerulonephritis, and nephrolithiasis/nephrocalcinosis (Table 2)[3]. These 5 diagnostic groups of CKD alone encompass 72.8% of CKD that manifest before 25 years of life (Table 1). Using a microfluidic technique (Fluidigm™) for multiplex PCR-based amplification of 600 exons of about 30 different gene known to be mutated in the respective CKD diagnostic groups, we established a cost-effective mutation analysis screen of large patient cohorts. This method includes barcoding of individual DNAs PCR product followed by next generation sequencing[3,7–11,44,45]. PCR products are barcoded per individual so that

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hundreds of PCR products can be sequenced in a single next-generation sequencing run thereby strongly reducing cost. Indications to run a diagnostic panel were kept simple (Table 2) to allow that in future applications of the panels similar results can be expected: for the CAKUT panel the indication to run the panel was any imaging study showing evidence of CAKUT (renal aplasia, renal hypodysplasia, vesicoureteral reflux or uretero-pelvic junction obstruction)[11]. For the proteinuria panel the indication was SRNS[9,49]. For the nephrolithiasis (urinary stone disease) panel indication was any history of nephrolithiasis/ nephrocalcinosis[47]. For the glomerulonephritis panel the indication to run the panel was the presence of proteinuria and hematuria. For the renal cystic ciliopathy panel the indication was the presence of 2 renal cysts or increased renal echogenicity on renal sonography[4,45,50] (Braun, in press 2015). Of note, the latter has over 95 known disease causing genes molecularly explaining the vast majority of cases (~70%).

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 6 autosomal recessive known CAKUT-causing genes[10,11]. Our results showed that over 8% of cases with CAKUT are caused by single-gene mutations in one of the 17 genes. These results as well as results from two independent studies[51,52] in which copy number variations (CNVs) were identified among 10–16% of individuals with CAKUT (most commonly involving the *HNF1B* or the DiGeorge/velocardiofacial locus), suggest that CAKUT genes may already yield a monogenic cause in around 17% of affected individuals (Tables 2, 4).

Proteinuria panel

Mutation analysis of 27 known SRNS-causing genes in an international cohort of patients with SRNS manifesting before 25 years of age[8] detected a single-gene cause in 29.5% (526/1,783) of families (Tables 2, 5). The fraction of families, in whom a single-gene cause was identified correlated inversely with age of onset. The fraction of families with detection of a single-gene cause of SRNS was 69.4%, 49.7%, 25.3%, 17.8% and 10.8% for the age groups of manifestation in the first 3 months of life, 4–12 months, 1–6 years old, 7–12 years and between 13–18 years respectively[8].

The identification of single-gene mutations in SRNS genes may have therapeutic consequences in some cases. For instance, most individuals with a single-gene cause of SRNS will not respond to steroid treatment.[53,54] *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 tumors that include wilms tumor and gonadoblastoma. The latter has been mainly described with concomitant abnormal chromosomal karyotype and therefore a karyotype analysis should also be obtained.[55] Furthermore, identification of the causative mutation may reveal that a potential therapy is available for some rare single-gene causes of SRNS. For example, if a mutation in a gene encoding enzymes of the coenzyme Q_{10} biosynthesis is detected (*COQ2, COQ6, ADCK4*, or *PDSS2*), experimental treatment with coenzyme Q_{10} may be warranted,[56,57] because a partial response to treatment with coenzyme Q_{10} has been described in individuals with SRNS and mutations in *COQ2*,[56] *COQ6*,[57] and *ADKC4*[58]. The

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efficacy of CoQ10 treatment has to be assessed once higher numbers of patients with mutations in genes of CoQ10 biosynthesis have become known.

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 ARHGDI, KANK2,3, and 4 and through elucidation of the response of synaptopodin to cyclosporine A treatment in patients with SRNS[59–61]. Also, individuals with mutations of *CUBN* may be amenable to treatment with vitamin B_{12}, and individuals with *ARHGDIA* may theoretically be responsive to the eplerenone treatment.[59] Finally, a patient with recessive mutations in *PLCE1* responded fully to treatment with steroids or cyclosporine A.[62]

In the future it may be advisable to initiate mutation analysis of all known nephrosis genes in any patient with an episode of proteinuria persistent for more than 3 days (urine protein greater than 4mg/m2/hour). In a first episode with gross proteinuria steroid treatment may have been commenced at the same time of initiating mutation analysis. If results from mutation analysis are returned within a few weeks, they may then guide the decision whether to complete a full course of steroid treatment or to terminate treatment, depending on whether there is enough data available for a certain mutation that would warrant discontinuation of treatment. In this way unnecessary steroid toxicity may be avoided in the near future.

Nephritis panel

In individuals with a diagnostic constellation compatible with chronic glomerulonephritis (small grade proteinuria with microscopic hematuria) exon sequencing of 10 monogenic nephritis genes may already yield a monogenic cause of nephritis in about 20% of individuals[63] (Tables 2, 6).

Cystic kidney disease panel

In 50–70% of all individuals who exhibit upon renal ultrasound the presence of 2 or more cysts and/or a finding of increased echogenicity, a monogeic cause of disease can be detected by exon sequencing of one of 95 genes (Tables 2, 7).[4,44,45] (Braun et al. in press). The PKD1 and PKD2 genes, which are mutated in ADPKD are not part of this panel, because their mutation analysis requires a very specialized approach[64], because onset of disease in ADPKD is primarily far beyond 25 of age, and because mutation analysis is rarely requested within the PKD community as molecular diagnosis is valuable in only few specific situations mostly not for the pediatric population.

Nephrolithiasis panel

Similarly, we demonstrated that 21% of cases with onset of nephrolithiasis/nephrocalcinosis before 18 years of age and 12% of cases with onset after 18 years can be explained by mutations in one of 14 genes known to cause nephrolithiasis/nephrocalcinosis[3] (+Braun et al, 2015 in press) (Tables 2, 8). For this phenotype, the cystinuria gene *SLC7A9* was the most frequently mutated (Table 8), being found in 15% of the cohort. Making a molecular genetic diagnosis in urinary stone disease had important implications for affected individuals

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as well as unaffected family members. Genetic screening of asymptomatic relatives may identify individuals who carry the same disease causing mutation. This information will guide clinicians to monitor these individuals for development of disease and to institute preventative treatment when possible. In addition, consensus guidelines recommend standard treatment for urinary stone disease such as increased fluid intake, limited sodium intake, treatment with thiazide diuretics, and potassium citrate therapy[65] that may not directly address the pathophysiology of a particular molecular diagnosis. For example, clinicians should monitor for tetany and seizures, which have been reported in patients with *CLDN16* mutations. We recently published such related therapeutic implications that resulted from making a molecular genetic diagnosis in urinary stone disease (Braun et al. 2015).

In summary, it is expected that the use of diagnostic exon sequencing panels will expand the number of genes examined in the future for each of these groups of monogenic causes of CKD. In addition, other exon sequencing panels will be introduced into the clinical practice in order to detect monogenic causes of CKD in additional diagnostic groups of early onset CKD such as monogenic forms of hypertension. The ongoing discovery of novel genes that if mutated cause CKD, together with the continuing trend of cost reduction in exome sequencing implies that indication-driven molecular genetic diagnostics in the near future will be performed using whole exome sequencing (WES) data, which sequences all exons of all 20,000 genes in the human genome in parallel at low cost[4,66]. 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 mentioned above (Table 2).

Generalizability of mutation detection rates

The generalizability of the current mutation detection rates across the different early CKD etiologies and among different populations should take into consideration several important factors. First, the relative fractions in whom a molecular genetic diagnosis was made were inversely correlated with age and directly correlated to degree of consanguinity as described in the original publications for SRNS[8] (Figure 1) and for urinary stone disease[3]. Still, it is very likely that these rates of mutation identification in SRNS (Figure 1) will hold up in other cohorts as they have been confirmed by 2 European groups[20,67]. Likewise, in urinary stone disease we have recently performed 2 different studies that showed a rate of detecting causative mutations in the range of 18–21% in childhood onset urinary stone disease. The rates of successful mutation identification will most likely increase as more monogenic renal genes and mutations become known.

Second, as more data from extensive whole exome studies are rapidly accruing on human genetic variation, question regarding incomplete penetrance of certain alleles can be address and studied. There is increasingly apparent degree of incomplete penetrance and variable expressivity especially for monogenic dominant causes of CAKUT, but also for other recessive etiologies. For instance, in early–onset disease where recessive mutation are more frequent and usually convey full penetrance, few exceptions have also been described[68].

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Third, the potential for false positive attribution of monogenic disease resulting from inappropriate filtering criteria or increased sequencing of patients who may have a lower probability of having monogenic disease can also hamper the true frequency of mutation detection rates. Minimization of the problem of false positive assignment of genetic variants as disease causing will be one of the most important task in the renal research area for the next 10 years to come. These data will be generated using cell-based functional assays, animal models, and large data bases on genetic variants in large populations around the world. Fourth, for dominantly inherited conditions, the presence of familial cases will often also positively influence the mutation detection rate[69].

Finally, one of the potential adverse outcomes of mutation analysis in monogenic disease genes may result from mutational screening of unaffected family members. This may be particularly detrimental to an individual if there is incomplete penetrance or variable expressivity for a disease allele, leading prognostication of an unfavorable health condition that may never manifest. In this context it is important to observe the recommendation by the American College of Medical Genetics and Genomics[70] that discourages mutation analysis in individuals that have not manifested with symptoms of disease. Nonetheless, there are certain circumstances where clinical judgment should be applied in which a disease can be “silent” or “subtle” and apparently “unaffected” persons are affected but are asymptomatic (e.g. asymptomatic nephrocalcinosis or asymptomatic renal hypodysplasia).

Novel gene discoveries using whole exome sequencing (WES)

The “exome” describes the entirety of all exons-encoding sequences in the human genome. Although the exon represents only one percent of the human genome, it represents the protein-encoding sequences. WES offers also a powerful approach towards identification of novel monogenic causes of disease. Detailed description of the WES technique can be found elsewhere[71,72]. Briefly, genomic DNA is mechanically broken into random short fragments, which then are hybridized (bound by sequence matching) to oligonucleotides that represent all human exons. The unbound fragments are washed off (99% of the genome), and the exon-bound DNA fragments are eluted specifically and then loaded onto a next generation sequencer for whole exome sequencing. The millions of sequencing reads that are thus generated are aligned for comparison with a “normal reference sequence” of the human genome. Finally, WES data output file is generated containing all genetic variants from reference sequence found in the tested individual’s DNA. If a genetic sequence variant leads to a phenotypic change of an organism, for instance causes disease, that sequence variant is called a “mutation”. Other sequence variants are called “variance of unknown significance”.

The detection of mutations in novel disease-causing genes using WES can reveal new medical conditions that were not previously recognized. For instance, it was that mutations in genes regulating coenzyme Q_{10} biosynthesis may cause steroid resistant nephrotic syndrome (CQO2, COQ6, ADCK4, PDSS2)[56–58]. However, the utility of WES for novel gene discovery is hampered by the fact that a large number of genetic variants results when comparing the exome sequences of the studied individual to the normal genome reference sequence. On average in WES data of an individual there are between 2,000 to 4,000 non-synonymous variants. This limitation can be overcome by restricting sequence variant

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calling to smaller regions of interest that are generated for instance by homozygosity mapping or linkage analysis[73], or by analyzing only shared variants across several affected individuals within the same family. These approaches enable one to exclude DNA variants from further consideration and allow an *a priori* restriction for the pool of potentially causal mutations. Finally, WES can result in identification of incidental findings - that are results not related to the indication for performing WES but may still be of medical importance to the patient. A policy statement with recommendations regarding the utility and reporting of incidental findings were published by the American College of Medical Genetics (ACMG).[74] Considering to strictly consenting the patient for the purpose of only identifying the molecular cause of the kidney disease in question should minimize this problem.

Using WES, disease-causing genes may be detected that were not suspected from 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 7 out of the 10 families studied. In 5 families we identified mutations of known renal cystic ciliopathies genes, however, in 2 additional 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[4]. Similar results regarding phenocopies have been described for other non-renal conditions[75,76].

Exome sequencing reveals pathogenic pathways: The example of nephrotic syndrome

Nephrotic syndrome (NS) is a chronic kidney disease defined by proteinuria, that causes hypoalbuminemia, edema and hyperlipidemia. The condition is categorized by the patient's clinical response to steroid therapy as "steroid-sensitive" (SSNS) *vs.* "steroid-resistant" (SRNS). SRNS is the second most frequent cause of CKD in children and young adults (Table 1). The disease mechanisms are poorly understood and no curative treatment is available. The most frequent renal histological feature of SRNS is focal-segmental glomerulosclerosis (FSGS), which carries a 33% risk of recurrence in a kidney transplant, thereby leading again to end-stage kidney disease[53]. For SRNS, the primary etiology and pathomechanisms have been obscure until recently. However, identification of genes that, if mutated, cause recessive or dominant monogenic forms of SRNS has dramatically changed this picture by providing the first fundamental insight into disease mechanisms of SRNS[15–17,77]. The discovery of novel SRNS genes has led to the understanding that the renal glomerular podocyte represents the cell type at which disease mechanisms of SRNS converge (Figure 2)[16,78]. At this juncture there are over 39 genes known to cause SRNS if mutated (Table 5). Those genes encode proteins that can currently be grouped into the following four major categories (Figure 2): (1) Proteins that are associated with the glomerular slit membrane, e.g. Nephrin (NPHS1)[15], Podocin (NPHS2)[79], and CD2-associated protein (CD2AP)[80]; (2) proteins that are involved in actin binding and regulation and hence affect the cytoskeleton of the podocyte, e.g. ACTN4[81], INF2[82], and ARHGDIA[59]; (3) proteins associated with focal adhessions that tether the sole of the podocyte to the underlying glomerular basement membrane, e.g. LAMB2[83] and EMP2[84], and (4) proteins involved in the biosynthesis of coenzyme Q_{10} (CoQ_{10}), e.g. CoQ2[85], CoQ6[86] and ADCK4[87] (Figure 2).

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Consequences for therapy

Early CKD diagnosis should trigger clinicians to consider genetic analysis for their patients. Molecular analysis of early CKD-causing genes using experimental known genes panels are becoming increasingly avilable. Following identification of early CKD-causing mutations, the patient should be referred to a CLIA (Clinical Laboratory Improvement Amendments) certified clinical laboratory, as well as for genetic counselling. Optimally, the care for patients with monogenic CKD should be provided by a multidisciplinary team of nephrologist, urologists, and clinical geneticists.

Identification of the causative mutation of an individual with SRNS, for example, may have expiramnetal therapeutic consequences in some forms of SRNS, because patients harboring mutations in genes of the CoQ_{10} biosynthesis pathway can be treated with CoQ_{10} supplementation[8687]. The discovery that CoQ_{10} treatment is beneficial for patients with SRNS due to mutations in the CoQ_{10} biosynthetic genes opened a window of opportunity for treatment with CoQ_{10} especially since $CoQ_{10,}$ is an innocuous food supplement with a high safety profile. It has been suggested that reactive oxygen species production and accumulation may play a role in the pathophysiology of many mitochondrial diseases and associated renal damage leading to nephrotic syndrome[88]. Treatment with CoQ_{10} supplementation for CoQ_{10} deficiency was first described for CoQ_{10} deficiency caused by *CoQ2* recessive mutations[56]. Initially several case reports were published[89,90] which showed improvement in the neurologic symptoms but failed to show any benefit on renal function, since advanced chronic renal failure had already developed. Subsequently, a case report study by Salviati et al[56] suggested that early initiation of the treatment, immediately after the onset of renal symptoms, was beneficial in resolution of the proteinuria in a patient with nephrotic syndrome secondary to *COQ2* mutations. This form of monogenic SRNS, for which further study is needed, provides one of the first examples how identification of monogenic causes of SRNS may revealed the possibility to treat this disease, for which currently no efficient treatment exists.

Identifying a monogenic caouse for disease provides a better disease categorization for clinical trials that study outcome of diseases. Nontheless, in addition to research and future implications, identifying a monogenic cause for patients with early CKD has already several imidiate clinical implications which include: 1) providing the patient and family with the definitive cause of their disease; 2) placing the clinical phenotype into context by gene specific stratification and delivery of personalized medicine; 3) allowing precise genetic counseling for family planning; 4) detection of previously unrecognized affected family members; 5) avoiding unnecessary diagnostic procedures, tests and treatments; 6) early detection and treatment initiation of asymptomatic (or subtle) extra renal manifestations; 7) providing guidance for monitoring of potential future complications and 8) guiding advanced medical management on a gene specific basis. Box 3 outlines specific examples of monogenic early CKD causes for each one of those implications.

In summary, 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 age 25 years: CKD, steroid-resistant nephrotic syndrome, renal ultrasound

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showing increased echogenicity or 2 or more cysts, urinary stone disease, CAKUT, or chronic glomerulonephritis. The likelihood of identifying a causative monogenic mutation is estimated to be ~20% in this setting currently. It will rise in the future as more disease genes and causative mutations become known. Clinical consequences from these findings are currently emerging (Braun et al. cJASN, in revision). The literature on clinical consequences from identification of monogenic mutations will rapidly accumulate as genotype-phenotype correlations and relationships between genotype and clinical consequences will accrue over the next years.

Conclusions and future directions

Two thirds of early-onset CKD is due to CAKUT, SRNS, renal cystic ciliopathies or chronic glomerulonephritis. Recently, over 200 genes, that if mutated cause monogenic forms of these disorders have been identified.

High throughput exon sequencing using exon panels or WES now allows identification of the causative mutation in a high proportion (~20%) of individuals with early onset CKD (Table 2). Molecular genetic diagnostics can be planned in a well defined clinical indication-driven way for SRNS, cystic kidney diseases (presence of >/=2 cysts or increased echogenicity, presence of CAKUT, glomerulonephritis, or nephrolithiasis/nephrocalcinosis (history of at least one stone or nephrocalcinosis).

Indication-driven gene panel analysis with the use of next generation sequencing is an emerging tool, which will continue to be introduced into clinical research and practice[75,76]. Despite several challenges it is expected to be further implemented for clinical use in the near future. Novel gene identification will allow establishing an molecular genetic diagnosis, etiologic 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. This may lead to more relevant etiologic 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 consulting as well as for clinical management of patients with CKD (Box 3).

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GLOSSARY OF GENETIC TERMS

Allele

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

Exon

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

Exome

The protein coding sequences of the entire genome (about 1% of the human genome)

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 identical mutation

Genotype

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

Homozygosity

The presence of identical alleles in the two copies of a gene or locus. The presence of different alleles is referred to as heterozygosity

Homozygosity mapping

A technique in which the homozygous region across the genome are identified. This is an effective strategy for the discovery of autosomal recessive monogenic diseases genes in consanguineous families

Next generation sequencing

This is a DNA sequencing method, also known as massively parallel sequencing, which allows to simultaneously sequence multiple DNA segments in a high-throughput manner

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

Penetrance

The proportion of individuals that express a certain phenotype in relation to the number of individuals that carry the pathogenic variant(s). It can be age dependent. Incomplete penetrance refers to the observation that some individuals with the mutation do not develop the diseases phenotype at all

Sanger sequencing (first generation sequencing)

DNA sequencing method (invented by Frederick Sanger) that involves termination of polymerized DNA strands at the position of specific labeled nucleotides

Variant filtering

Variant filtering refers to the process of excluding variants between the individual examined and a "normal reference individual" from further consideration as disease causing. For

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instance, very common variants and variants which do not alter the protein sequence are excluded

Variant

A difference in a DNA sequence as compared to normal reference sequence. A variant may be benign, i.e. single nucleotide polymorphism (SNP) or disease causing (i.e. mutation)

Whole exome sequencing

Targeted capture and sequencing of the exome (exons of all genes) using next generation sequencing. This method offers a powerful approach towards identification monogenic disease causing genes

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Key points

- ~20% of CKD that manifest before 25 years of age are caused by single gene mutations in more than 200 different genes
- Molecular genetic diagnostics can provide patients with molecular diagnosis, and can generate new insights into diseases mechanisms
- Molecular genetic diagnostics may also have consequences for personalized treatment and prevention of CKD.
- Indication driven mutation analysis panels are available for early-onset CKD e.g. CAKUT, SRNS, ciliopathies and nephrolithiasis (www.renalgenes.org).

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Box 1

Assignment of autosomal recessive mutations as being disease causing

- **Include allele as disease causing if:**
  - Truncating mutation (Stop, abrogation of start or stop, obligatory splice, frameshift) in an expressed gene (well annotated mRNA, sequence conservation, protein expression) or:
  - Missense mutation if:
    - Continuously conserved at least up to *danio rerio* (zebrafish) and:
    - Loss of function in human allele is supported by functional data.
- **Exclude allele as disease causing if:**
  - Heterozygous allele frequency >1% (in EVS server: 13,000 control chromosomes) or single homozygous reported.
  - Non-segregation (e.g. “compound heterozygous” in cis; affected family member is without the variant; unaffected parent is with homozygous variant)

Base line assumptions: 1) Full penetrance (age related). 2) Defined clinical phenotype. 3) “Mutation” implies that an allele changes the phenotype. 4) Known genes with similar phenotype have been excluded.

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Box 2

Assignment of autosomal dominant mutations as being disease causing

- **Include allele as disease causing if:**
  - Truncating mutation (Stop, abrogation of start or stop, obligatory splice, frame-shift) in an expressed gene (well annotated mRNA, sequence conservation, protein expression) and:
    - Continuously conserved to at least up to *danio rerio* (zebrafish) or:
  - Missense mutation if:
    - Continuously conserved to *danio rerio*. And:
    - Human allele is supported by functional data. And:
    - Full segregation exists And:
    - Known genes with similar phenotype have been excluded.
- **Exclude allele as disease causing if:**
  - Heterozygous allele frequency >0.1%
  - Non-segregation – i.e. affected family member is without the allele.
  - Warning regarding non-segregation: if an unaffected family member is with the allele consider incomplete penetrance and variable expressivity.

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Box 3

Clinical implications of genetic testing of early onset chronic kidney diseases

- **Providing the patient and family with the definitive cause of their disease**
- **Placing the clinical phenotype into context by gene specific stratification and delivery of personalized medicine. This may have both immediate as well as future clinical implications**. *e.g.* (1) it is increasingly recognized that heterozygous contiguous gene deletions in the 17q12 region (which includes the gene *HNF1B*) can result in congenital anomalies of the kidney and urinary tract (CAKUT) with a neurologic phenotype such as autism spectrum disorder or schizophrenia; (2) Future possible implications include allele specific drug treatments as it has been established for other genetic diseases like cystic fibrosis*
- **Allows precise genetic counseling for family planning**. *e.g.* (1) prediction of disease recurrence; (2) providing the option for preimplantation genetic diagnosis.
- **Detection of previously unrecognized affected family members**. *e.g.* (1) patients with dominantly inherited CAKUT can be asymptomatic in early disease stages. For instance, index patients with CAKUT secondary to *PAX2* or *GATA3* mutations may have affected parent/child or sibling with overlooked CAKUT which can only be detected by recognizing the genetic nature of the disease which can apparently present as "sporadic" case. This should trigger renal ultrasonographic screening for CAKUT in other family members; (2) identification of asymptomatic individuals harboring heterozygous *COL4A4* or *COL4A5* mutations, who should be monitored yearly for proteinuria and hypertension. Both of which may be the first sign of evolving chronic kidney disease.
- **Avoiding unnecessary diagnostic procedures, tests and treatments**. *e.g.* (1) avoiding renal biopsy. For instance, in patients with congenital or infantile nephrotic syndrome who has established genetic diagnosis secondary to *NPHS1* or *NPHS2* mutations or for patients with characteristic nephronophthisis phenotype and *NPHP1* mutations; (2) avoiding aggressive anti- recurrence treatment for FSGS in kidney transplant patients with FSGS secondary to *NPHS2* mutations. The latter has been shown to have low recurrence risk; (3) patients with CAKUT secondary to *HNF1B* mutations may have elevated liver function tests. Acknowledging this as part of the HNF1B-mutation related phenotype can prevent unnecessary invasive investigation (such as liver biopsy for "idiopathic elevated LFTs").
- **Early detection and treatment initiation of asymptomatic (or subtle) extra renal manifestations**. *e.g.* (1) heterozygous mutations in HNF1B may cause "isolated CAKUT" or "syndromic CAKUT" that is associated with one or more of the following extra renal manifestations: maturity onset diabetes of the young (MODY type 5), hyperuricemia and hypomagnesaemia. Early identification of those conditions can lead to early monitoring and treatment; (2) similarly, deafness has been associated with three other CAKUT-causing mutations in *EYA1*, *SALL1* or *PAX2*; (3) patients with CAKUT secondary to *GATA3* mutations may have hypoparathyroidism which can be asymptomatic in early disease stages however should be recognized and treated.
- **Providing guidance for monitoring of potential future complications**. *e.g.* (1) patients with nephrotic syndrome secondary to *WT1* are at increased risk for WT1-related Wilms tumor; (2) patients with *WT1* mutations in the donor splice site of intron-9, resulting in the splice form +KTS are at risk for gonadoblastoma; (3) patients with nephronophthisis secondary to *NPHP5* mutations are at risk for progressive blindness secondary to retinitis pigmentosa (i.e. Senior-Løken syndrome)
- **Guiding advanced medical management on a gene specific basis**. *e.g.* (1) recessive mutations in *CTNS* establish the diagnosis of cystinosis and should trigger treatment with cystine-depleting agents; (2) considering CoQ10 supplements for patients with nephrotic syndrome harboring mutations in genes of the CoQ10 biosynthesis pathway such as *CoQ2*, *CoQ4* and *ADCK4*; (3) guiding thrombocytopenia management for patients with nephrotic syndrome secondary to *MYH9* mutations.

* Lumacaftor and ivacaftor therapy have been specifically shown to have clinical efficacy in patients who are homozygous for the Phe508del CFTR mutation[211].

"One author declares competing financial interests: F.H. receives royalties on a mutation analysis panel licensed to Claritas (Cambridge)."

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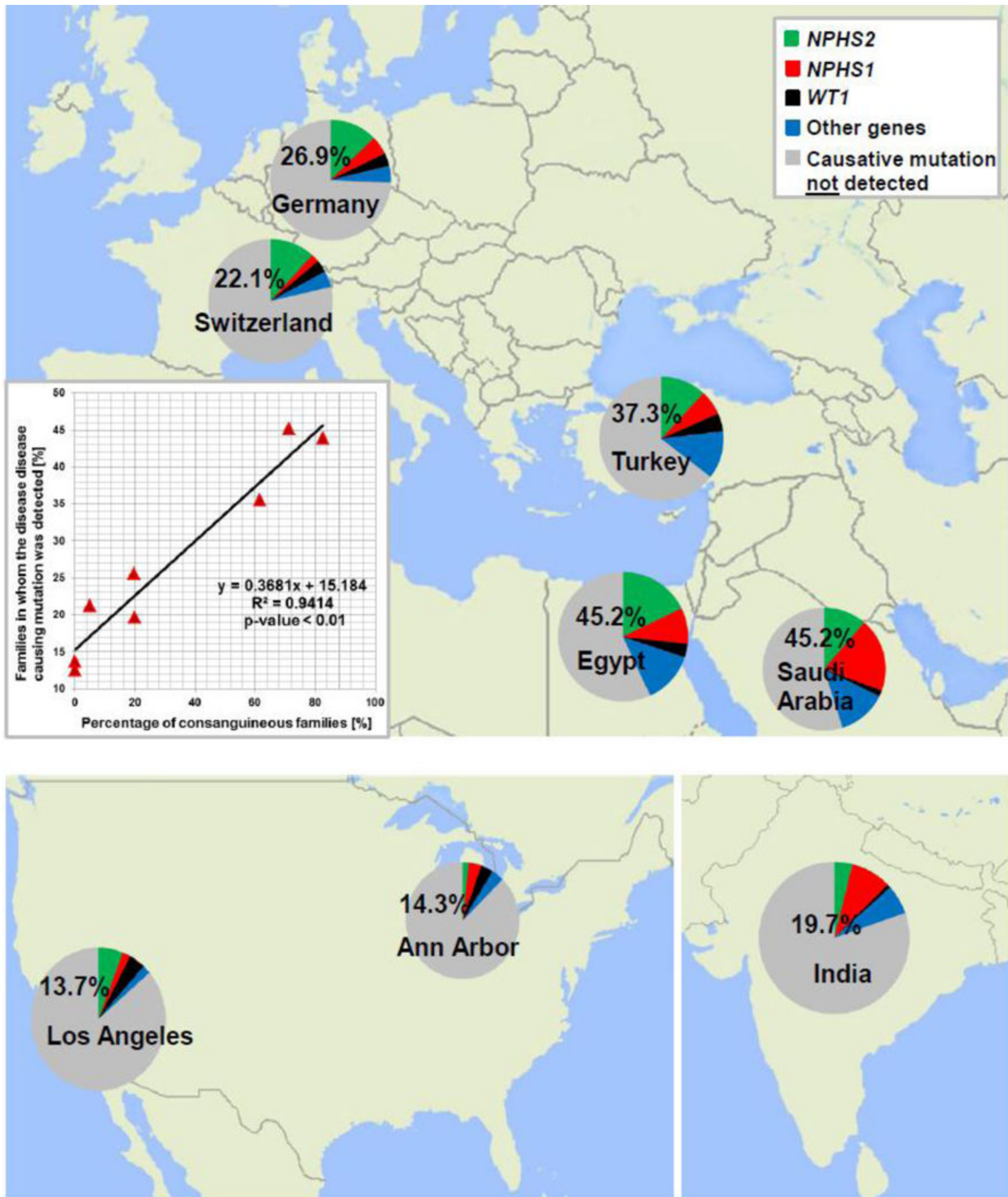

Figure 1.

Percentage of genetic findings in SRNS families. We previously obtained samples from 1,783 SRNS families worldwide and detected the disease-causing mutation in 526 families (29.5%). For 8 centers we detected the disease causing mutations in the following fractions: (families, in whom we detected the causative mutation/total families examined from this center): Saudi-Arabia (45.2%, 28/62), Egypt (45.2%, 66/146), Turkey (37.3%, 62/169), Germany (26.9%, 123/457), Switzerland (22.1 %, 21/94), India (19.7%, 25/127,), Ann Arbor (14.3%, 8/56), and Los Angeles (13.7%, 7/51). Inset: The detection rate of the

disease-causing mutations strongly correlates with the rate of consanguinity between the different centers (R2=0.9414)

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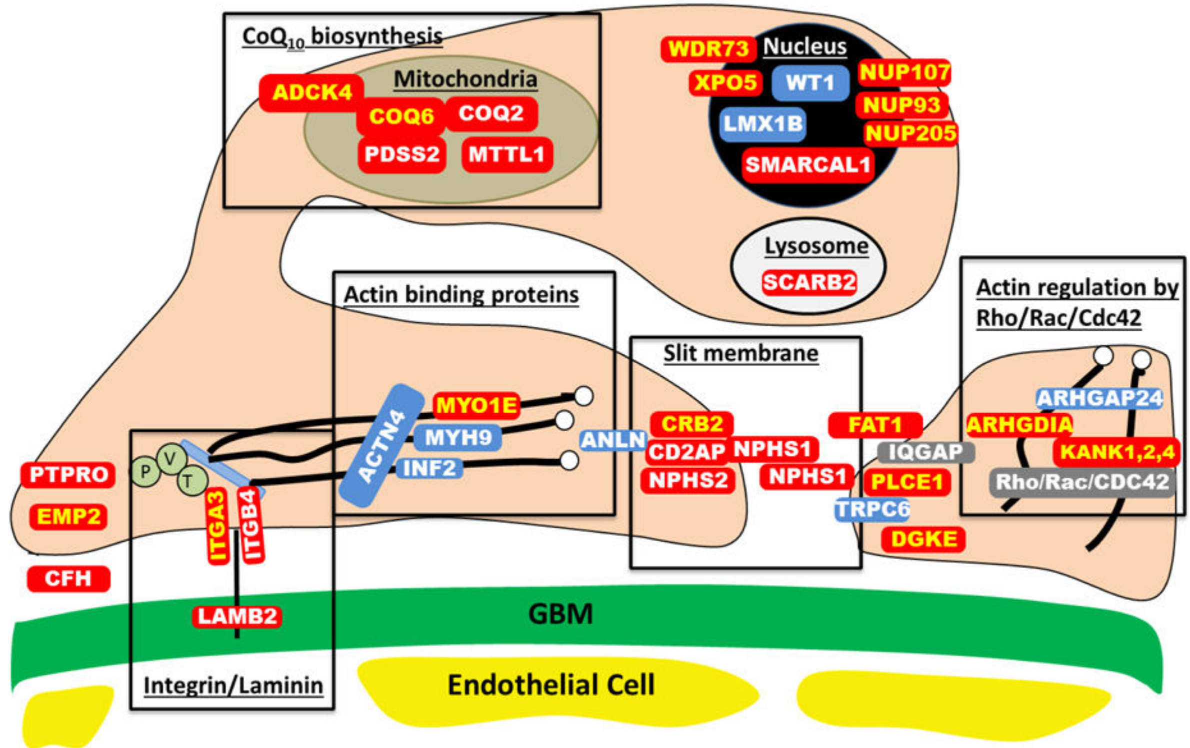

Figure 2. Proteins involved in single-gene causes and pathogenic pathways of steroid resistant nephrotic syndrome

Identification of single-gene (monogenic) causes of steroid resistant nephrotic syndrome has revealed the renal glomerular epithelial cell, the podocyte, as the center of action in the pathogenesis of SRNS, because all of the related genes are highly expressed in podocytes. In this way identification of genes that, if mutated, cause SRNS revealed certain proteins and functional pathways as essential for glomerular function, because a mutation in any single one of them is sufficient to cause SRNS.

This figure depicts a simplified cross section through two neighboring podocyte foot processes, that attach to the glomerular basement membrane (GBM) *via* laminin-integrin receptors. Proteins that if mutated cause recessive monogenic forms of SRNS in red, and proteins that if mutated cause dominant forms of SRNS in blue. These SRNS-related proteins were found to be part of protein-protein interaction complexes that participate in defined structural components or signaling pathways of podocyte function (black frames). These proteins include: laminin/integrin receptors (focal adhessions), actin binding proteins, glomerular slit membrane-associated components, actin regulating small GTPases of the Rho/Rac/Cdc42 family, lyposomal proteins, nuclear transcription factors, and proteins involved in coenzyme Q_{10} biosynthesis. IQGAP, IQ motif containing GTPase activating protein 1; P, Paxillin; V, Vinculin and T, Talin.

Proteins that are encoded by recessive SRNS genes are marked in red:

ADCK4, AarF domain containing kinase 4; ARHGDIA, Rho GDP dissociation inhibitor (GDI) alpha; CD2AP, CD2-associated protein; CFH, Complement factor H; COQ2, coenzyme Q2 4-hydroxybenzoate polyprenyltransferase; COQ6, coenzyme Q6 monooxygenase 6; CRB2, Crumbs family member 2; DGKE, Diacylglycerol kinase,

epsilon; EMP2, epithelial membrane protein 2; FAT1, FAT tumor suppressor homolog 1; GBM, glomerular basement membrane. ITGA3, integrin, alpha 3; ITGB4, integrin, beta 4; KANK, KN otif And Ankyrin Repeat Domains 1/2/4; LAMB2, laminin, β2; MTTL1, mitochondrial tRNA leucine 1; MYO1E, homo sapiens myosin 1e; NPHS1, nephrin; NPHS2, podocin; NUP93, Nucleoporin 93 kDa; NUP107, Nucleoporin 107 kDa; NUP205, Nucleoporin 205 kDA; PDSS2, prenyl (decaprenyl) diphosphate synthase, subunit 2; PLCE1, phospholipase C, epsilon 1; PTPRO, protein tyrosine phosphatase, receptor type, O; SCARB2, scavenger receptor class B, member 2; SMARCAL1, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a-like 1.

WDR73, WD repeat domain 73; XPO5, Exportin 5.

Proteins that encoded by dominant SRNS genes are marked in blue:

ACTN4, actinin, alpha 4; ANLN, anillin; ARHGAP24, Rho GTPase activating protein 24; INF2, inverted formin, FH2 and WH2 domain containing; LMX1B, LIM homeobox transcription factor 1-beta; MYH9, Myosin, heavy chain 9; TRPC6, transient receptor potential cation channel, subfamily C, member 6; WT1, Wilms tumor 1.

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Table 1

Causes of chronic kidney disease (CKD) manifesting before age 25 years, and its relative frequency[a].

DIAGNOSTIC GROUPS	Total
CAKUT	**49.1%**
Obstructive uropathy (20.7%), a/hypo/dysplastic kidney (17.3%), reflux nephropathy (8.4%), prune belly syndrome (2.7%)	
SRNS	**10.4%**
FSGS (8.7%), congenital nephrotic syndrome (1.1%), membranous nephropathy (0.5%), Denys-Drash syndrome (0.1%)	
Chronic glomerulonephritis	**8.1%**
SLE nephritis (1.6%), familial nephritis (Alport syndrome) (1.6%), chronic glomerulonephritis (1.2%), MPGN-Type I (1.1%), MPGN-Type II (0.4%), IgA nephritis (0.9%), idiopathic cresentic GN (0.7%), Henoch-Schonlein nephritis (0.6%)	
Renal cystic ciliopathies	**5.3%**
Polycystic kidney disease (4.0%), medullary cystic kidney disease (1.3%)	
Hemolytic uremic syndrome	**2.0%**
Nephrolithiasis/nephrocalcinosis	**1.6%**
Cystinosis (1.5%), oxalosis (0.1%)	
Other	**20.9%**
Renal infarct (2.2%), pyelo/interstitial nephritis (1.4%), Wilms tumor (0.5%), Other systemic immunologic diseases (0.4%), Wegener's granulomatosis (0.4%), sickle cell nephropathy (0.2%), diabetic glomerulopathy (0.2%), other (15.6%)	
Unknown	**2.6%**
Total	**100% (N=7,037)**

[a]From NAPRTCS - NAPRTCS, North American Pediatric Renal Trials and Collaborative Studies[13]. CKD, chronic kidney disease; CAKUT, congenital anomalies of the kidneys and urinary tract; FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; MPGN, membranoproliferative glomerulonephritis; SRNS steroid-resistant nephrotic syndrome.

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Table 2

Indication-driven diagnostic panels of about 200 genes identify a causative mutation in ~20% of cases with CKD that manifests before <25 years of life (www.renalgenes.org).

Diagnostic group	Clinical indication to run a gene panel	Proportion of CKD manifesting before 21 years of life[a]	Number of currently known causative genes	Fraction of causative mutations identified for the diagnostic group (multiplied by fraction of all CKD)	References
CAKUT	CAKUT evident by renal imaging	50%	36	[c]~17% (8.5%)	7,11,18,40,41,91
Steroid-resistant nephrotic syndrome	Steroid-resistant nephrotic syndrome	10.3%	39	~30% (3%)	49,67,92
Chronic glomerulonephritis[b]	Evidence of proteinuria and hematuria	8.1%	10	~20% (4%)	5
Renal cystic ciliopathies	Increased echogenicity on renal US or presence of 2 renal cysts	5.3%	95	~70% (3.7%)	12,21,93,94
aHUS	Microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury.	~2%	9	~60% (1.2%)	95–98
Nephrolithiasis/nephrocalcinosis	Known stone disease or nephrocalcinosis	1.6%	30	21% (0.4%)	47,99
Other		23.6	?	?	
Total (N=7,037)[a]		**100%**	**~219**	**(~20%)**	

[a]NAPRTCS 2008[100].

[b]The estimates for chronic nephritis monogenic etiologies are based only on the relative prevalence of Alport's syndrome and MPGN (membranoproliferative glomerulonephritis) which together account for 20% of the etiologies of chronic glomerulonephritis and for which monogenic cause has been establish 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*)

[c]10% of CAKUT may be caused by deleterious copy number variants.[101]

CKD, chronic kidney disease; CAKUT, Congenital anomalies of the kidneys and urinary tract; aHUS, atypical hemolytic uremic syndrome.

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Table 3

Degrees of genetic causality in monogenic and polygenic kidney diseases.

	Monogenic recessive diseases	Monogenic dominant diseases	Polygenic/complex Diseases, Risk alleles
Penetrance	Full	Full or incomplete	Low
Predictive power of a mutation	Almost 100%	High	Low
Onset	Predominantly during childhood	Childhood and adulthood	Predominantly during adulthood
Disease frequency	Low	Low	High
Number of affected subjects needed for gene discovery	Few	Few	Hundreds to ten thousands
Gene mapping approaches include	Homozygosity mapping* or linkage analysis	Linkage analysis	Genome-wide association studies (GWAS)
Whole exome/genome sequencing (WES)	In consanguinity, single affecteds are sufficient	WES in distant relatives to minimize shared variants	N/A
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*

*Applicable to consanguineous families.

N/A, not applicable; WES, whole exome sequencing

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Table 4

Thirty six genes that cause monogenic-CAKUT if mutated

Gene	Protein	Reference
Autosomal dominant		
BMP4	Bone Morphogenetic Protein 4	102
CHD1L	Chromodomain Helicase DNA Binding Protein 1-Like	103
DSTYK	Dual Serine/Threonine And Tyrosine Protein Kinase	41
EYA1	EYA Transcriptional Coactivator And Phosphatase 1	104
GATA3	GATA Binding Protein 3	105,106
HNF1B	HNF1 Homeobox B	107
MUC1	Mucin 1, Cell Surface Associated	108
PAX2	Paired Box 2	109
RET	Ret Proto-Oncogene	110
ROBO2	Roundabout, Axon Guidance Receptor, Homolog 2 (Drosophila)	111
SALL1	Spalt-Like Transcription Factor 1	112
SIX1	SIX Homeobox 1	113
SIX2	SIX Homeobox 2	102
SIX5	SIX Homeobox 5	114
SOX17	SRY (Sex Determining Region Y)-Box 17	115
SRGAP1	SLIT-ROBO Rho GTPase Activating Protein 1	116
TBX18	T-Box 18	19
TNXB	Tenascin XB	117
UMOD	Uromodulin	118
UPK3A	Uroplakin 3A	119
WNT4	Wingless-Type MMTV Integration Site Family, Member 4	120,121,122
Autosomal recessive		
ACE	Angiotensin I Converting Enzyme	123
AGT	Angiotensinogen (Serpin Peptidase Inhibitor, Clade A, Member 8)	123
AGTR1	Angiotensin II Receptor, Type 1	123
CHRM3	Cholinergic Receptor, Muscarinic 3	124
FGF20	Fibroblast Growth Factor 20	125
FRAS1	Fraser Extracellular Matrix Complex Subunit 1	40,126
FREM2	FRAS1 Related Extracellular Matrix Protein 2	40
FREM1	FRAS1 Related Extracellular Matrix 1	40
GRIP1	Glutamate Receptor Interacting Protein 1	40
HPSE2	Heparanase 2 (Inactive)	127
ITGA8	Integrin, Alpha 8	40,128
LRIG2	Leucine-Rich Repeats And Immunoglobulin-Like Domains 2	129

Gene	Protein	Reference
REN	Renin	123
TRAP1	TNF Receptor-Associated Protein 1	7
X-Linked		
KAL1	Anosmin 1	130

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Table 5

Thirty nine monogenic genes that cause steroid-resistant nephrotic syndrome (SRNS) if mutated (marked with "*" are genes sequenced in Sadowski et al)

Autosomal recessive		
ADCK4*	AarF domain containing kinase 4	58
ARHGDIA*	Rho GDP dissociation inhibitor (GDI) alpha	59
CD2AP*	CD2-associated protein	80,131
CFH*	Complement factor H	132
COQ2*	Coenzyme Q2 4-hydroxybenzoate Polyprenyltransferase	85,56
COQ6*	Coenzyme Q6 monooxygenase	57
CRB2	Crumbs homolog 2	8
CUBN*	Cubilin (intrinsic factor-cobalamin receptor)	133
DGKE*	Diacylglycerol kinase, epsilon	134
EMP2	Epithelial membrane protein 2	84
FAT1	FAT tumor suppressor homolog 1	Gee, in press
ITGA3*	Integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)	135
ITGB4*	Integrin, beta 4	136
KANK1	KN motif and ankyrin repeat domain containing protein 1	60,137
KANK2	KN motif and ankyrin repeat domain containing protein 2	60,137
KANK4	KN motif and ankyrin repeat domain containing protein 4	60,137
LAMB2*	Laminin, β2	83
MTTL1	Mitochondrially encoded tRNA leucine 1	
MYO1E*	Homo sapiens myosin IE (MYO1E)	138
NPHS1*	Nephrin	15
NPHS2*	Podocin	79
NUP93	Nucleoporin 93 kDa	Braun, submitted
NUP107	Nucleoporin 107 kDa	139
NUP205	Nucleoporin 205 kDA	Braun, submitted
PDSS2*	Prenyl (decaprenyl) diphosphate synthase, subunit 2	140
PLCE1*	Phospholipase C, epsilon 1	62
PTPRO*	Protein tyrosine phosphatase, receptor type, O	141
SCARB2*	Scavenger receptor class B, member 2	142
SMARCAL1*	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a like 1	143
WDR73	WD repeat domain 73	144–146
XPO5	Exportin 5	Braun, submitted
Autosomal dominant		
ACTN4*	Actinin, alpha 4	81
ANLN	Anillin, actin binding protein	147

Autosomal recessive		
ARHGAP24*	Rho GTPase activating protein 24	[148]
INF2*	Inverted formin, FH2 and WH2 domain containing	[82]
LMX1B*	LIM homeobox transcription factor 1, beta	[149]
MYH9	Myosin heavy chain 9	[150]
TRPC6*	Transient receptor potential cation channel, subfamily C, member 6	[151,152]
WT1*	Wilms tumor 1	[153]

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Table 6

Ten genes that cause monogenic chronic glomerulo-nephritis if mutated.

Gene	Protein	Disease	Reference
Autosomal recessive			
COL4A4 *	Collagen, type IV, alpha 4	Alport	154
CFH	Complement factor H	MPGN	96
Autosomal Dominant			
CFI	Complement factor I	MPGN	155
CFHR5* **	Complement factor H-related 5	MPGN	156, 98157,158
FN1	Fibronectin 1	GFND	159
Autosomal dominant/recessive			
COL4A3 *	Collagen, type IV, alpha 3	Alport	154
CD46	CD46 molecule, complement regulatory protein (MCP)	MPGN	160
C3	Complmenet component 3	MPGN	97
X-linked			
COL4A5	Collagen, type IV, alpha 5	Alport	161
COL4A6	Collagen, type IV, alpha 6	Alport with LM	162

Alport: Alport's syndrome; aHUS: atypical HUS; TMA: thrombotic microangiopathy; GFND: glomerulopathy with giant fibronectin deposits; FMF: familial Mediterranean fever; LM: leiomyomatosis.

*Both, COL4A3 and COL4A4 can independently lead to autosomal dominant or autosomal recessive forms of Alport syndrome[163]

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Table 7

Sixteen frequent and 66 infrequent monogenic causes of nephronophthisis-related ciliopathies (NPHP-RC).

Gene	Protein	References
NPHP1 (JBTS4)	Nephrocystin-1	[164,165]
INVS (NPHP2)	Inversin	[166]
NPHP3	Nephrocystin-3	[167]
NPHP4	Nephroretinin	[168,169]
IQCB1 (NPHP5)	IQ motif containing B1	[170]
CEP290 (NPHP6)	Centrosomal protein 290 kDa	[171]
GLIS2 (NPHP7)	GLIS family zinc finger 2	[172]
RPGRIP1L (NPHP8)	RPGRIP1-like/FTM	[173]
NEK8 (NPHP9)	NIMA (never in mitosis gene A)- related kinase 8	[174]
SDCCAG8 (NPHP10)	Serologically defined colon cancer antigen 8	[175]
TMEM67 (NPHP11)	Transmembrane protein 67	[176]
TTC21B (NPHP12)	Tetratricopeptide repeat domain 21B	[177]
WDR19 (NPHP13)	WD repeat domain 19	[178]
ZNF423 (NPHP14)	Zinc finger protein 423	[179]
CEP164 (NPHP15)	Centrosomal protein 164 kDa	[179]
ANKS6 (NPHP16)	Ankyrin repeat and sterile alpha motif domain containing 6	[180]

Monogenic (recessive) mutations in the following additional 66 genes also cause the nephronophthisis-related ciliopathies (NPHP-RC) Meckel syndrome, Senior-Loken syndrome, Joubert syndrome, or Bardet-Biedl syndrome, but less frequently:

XPNPEP3, ATXN10, FAN1, SLC41A1, HNF1B, CLDN16, CLDN19, BSND, 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*.

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Table 8

Thirty monogenic genes that cause urinary stone disease (USD) if mutated.

Gene	Protein	Disease entity	Mode of inheritance	Reference
ADCY10/SAC	adenylate cyclase 10 (soluble)	Hypercalciuria, Calcium oxalate nephrolithiasis	AD	181
AGXT	alanine-glyoxylate aminotransferase	Primary hyperoxaluria, type 1	AR	182
APRT	adenine phosphoribosyltransferase	Adenine phosphoribosyltransferase deficiency, Urolithiasis (DHA stones), renal failure	AR	183
ATP6V0A4	ATPase, H+ transporting, lysosomal V0 subunit a4	dRTA	AR	184
ATP6V1B1	ATPase, H+ transporting, lysosomal 56/58kDa, V1 subunit B1	Distal renal tubular acidosis (dRTA) with deafness	AR	185
CA2	carbonic anhydrase II	Osteopetrosis + d/pRTA	AR	186
CASR	calcium-sensing receptor	Hypocalcemia with Bartter syndrome/hypocalcemia, autosomal dominant	AD	187
CLCN5	chloride channel, voltage-sensitive 5	Dent disease/Nephrolithiasis, type 1	XR	188
CLCNKB	chloride channel, voltage-sensitive Kb	Bartter syndrome, type 3	AR	189
CLDN16	claudin 16	Familial hypomagnesemia with hypercalciuria & nephrocalcinosis, FHHNC	AR	190
CLDN19	claudin 19	Familial hypomagnesemia with hypercalciuria & nephrocalcinosis with ocular abnormalities	AR	191
CYP24A1	cytochrome P450, family 24, subfamily A, polypeptide 1	1,25-(OH) D-24 hydroxylase deficiency, infantile Hypercalcemia	AR	192
FAM20A	family with sequence similarity 20, member A	Enamel-Renal syndrome, amelogenesis imperfect and nephrocalcinosis	AR	193
GRHPR	glyoxylate reductase/hydroxypyruvate reductase	Primary hyperoxaluria, type 2	AR	194
HNF4A	hepatocyte nuclear factor 4, alpha	MODY + Fanconi syndrome + Nephrocalcinosis	AD	195
HOGA1	4-hydroxy-2-oxoglutarate aldolase 1	Primary hyperoxaluria, type 3	AR	196
HPRT1	Hypoxanthine phosphoribosyltransferase 1	Kelley-Seegmiller syndrome, partial HPRT deficiency, HPRT-related gout	XR	197
KCNJ1	potassium inwardly-rectifying channel, subfamily J, member 1	Bartter syndrome, type 2	AR	198
OCRL	oculocerebrorenal syndrome of Lowe	Lowe syndrome/Dent disease 2	XR	199
SLC12A1	solute carrier family 12, member 1	Bartter syndrome, type 1	AR	200
SLC22A12	solute carrier family 22 (organic anion/urate transporter), member 12	Renal hypouricemia, RHUC1	AD/AR	201
SLC2A9	solute carrier family 2 (facilitated glucose transporter), member 9	Renal hypouricemia, RHUC2	AD/AR	202
SLC34A1	solute carrier family 34 (sodium phosphate), member 1	Hypophosphatemic nephrolithiasis/osteoporosis-1, NPHLOP1/Fanconi renotubular syndrome 2	AD/AR	203
SLC34A3	solute carrier family 34 (sodium phosphate), member 3	Hypophosphatemic rickets with hypercalciuria	AR	204
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	205
SLC4A1	solute carrier family 4, anion exchanger, member 1 (erythrocyte membrane protein band 3, Diego blood group)	Primary distal renal tubular acidosis, dominant/recessive	AD/AR	206

Gene	Protein	Disease entity	Mode of inheritance	Reference
SLC7A9	solute carrier family 7 (glycoproteinassociated amino acid transporter light chain, bo,+ system), member 9	Cystinuria, type B	AD/AR	207
SLC9A3R1	solute carrier family 9, subfamily A (NHE3, cation proton antiporter 3), member 3 regulator 1	Hypophosphatemic nephrolithiasis/osteoporosis-2, NPHLOP2	AD	208
VDR	vitamin D (1,25- dihydroxyvitamin D3) receptor	Idiopathic hypercalciuria	AD	209
XDH	xanthine dehydrogenase	Xanthinuria, type 1	AR	210

AD, autosomal dominant; AR, autosomal recessive

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