The utility of exome sequencing in understanding the genetic basis of chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is characterized by a progressive loss of renal function that can culminate to end stage renal disease (ESRD), requiring renal replacement therapy, which includes hemodialysis and kidney transplant as modalities. CKD has a prevalence of ~11-13% and is associated with significant morbidity and mortality. The prognosis and treatment of CKD cases varies by specific etiologies, which include congenital anomalies of the kidney and urinary tract (CAKUT), steroid-resistant nephrotic syndrome (SRNS), chronic glomerulopathies, cystic kidney disease, autosomal dominant tubulointerstitial kidney disease (ADTKD), nephrolithiasis/nephrocalcinosis, and renal tubulopathies, among others. However, many patients are classified as CKD of unknown etiology. There have been significant and continuing investigations showing the genetic basis of CKD, specifically of monogenic causation (single-gene causing disease). However, current routine practices only use phenotype-driven clinical panel testing, which only evaluates a fraction of known monogenic CKD genes associated with a specific phenotype. Exome sequencing (ES) is thus a beneficial tool for CKD cases that are clinically misdiagnosed, or unknown, rendering them undiagnosed by genetic panel investigations. Although the diagnostic yield of ES has been shown to vary (10-50%), no such study has demonstrated its effectiveness in Canada. As such, this study has examined a cohort of 94 Canadian families who have been undiagnosed by current routine methods of genetic testing through, ES. We have shown that ES has an additional 17% diagnostic rate. Within this group, 58% of cases were categorized as CKDu, but all received a specific clinical diagnosis once solved. Additionally, a molecular diagnosis had a clinical impact for all patients who have been diagnosed, with diagnostic confirmation/resolution/correction, in addition to guidance on family planning, were among the most prevalent clinical benefits of receiving a genetic diagnosis. This study has demonstrated the added benefit of ES, in both the research and clinical settings.

Keywords: chronic kidney disease, monogenic, exome sequencing

Introduction

CKD is defined as a progressive loss of renal function due to abnormalities in either kidney structure or function for more than three months, in addition to either decreased estimated glomerular filtration rate (eGFR) or presence of markers of kidney damage, which includes albuminuria, urine sediment abnormalities, history of kidney transplants, or abnormalities either due to tubular disorders, ones detected via histology, or structural ones detected by imaging[1]. eGFR is commonly used to describe excretory kidney function, and when below 60 mL/min/ 1.73m, indicates a reduction in kidney function[1]. End stage renal disease (ESRD) is the culmination of this progressive disease, which establishes the requirement of renal replacement therapy, either by kidney transplant or dialysis [2]. Globally, CKD has been estimated to have a prevalence of 11-13%, and is associated with high morbidity and mortality [3]. In Canada, this number has been estimated to equate to 12.5%, which represents ~3 million Canadians [4]. CKD is further classified into specific etiologies, which includes congenital anomalies of the kidney and urinary tract (CAKUT), chronic glomerulopathies, cystic kidney disease, autosomal dominant tubulointerstitial kidney disease (ADTKD), nephrolithiasis/nephrocalcinosis, and renal tubulopathies, among others [5]. CKD of unknown etiology (CKDu) is the classification of patients which have CKD with an unknown cause, and this has been estimated to account for 10-36% of cases of this disease [6]. Given that the specific etiology of disease is essential in the determination of interventions as well as patient prognosis, developing methods to diagnose patients with such an etiology is beneficial.

Kidney disease that is known to have a genetic cause is referred to as genetic kidney disease (GKD)[5]. GKD can be further classified by causation, including polygenic - disease causation due to the combined effects of multiple genes - and monogenic - disease causation due

to a singular gene. Within monogenic causation, classification of mode of inheritance can be made. Autosomal dominant (AD) disease refers to the necessity for a singular parental allele to be mutated; autosomal recessive (AR) disease refers to the necessity for both parental alleles to be mutated; and X-linked (XL) disease refers to the necessity for a mutation on the X-chromosome to occur. Each mode of inheritance results in variation in the manner in which a phenotype is expected and is tightly correlated to genotypic changes. Currently, it is estimated that there is a ~30% prevalence of monogenic causation in CKD cases with onset before 25 years of age, with variation dependent on etiologies[5]. Although monogenic causation is more highly established among the pediatric population, given that there is a fraction of adult-onset cases with a positive family history, several studies have evaluated a monogenic causation in these cases. Previous studies by our lab have found that 36% of CKD patients with adult-onset and positive family history have a monogenic cause[7]. Given the contribution of monogenic causation to CKD, as well as the cruciality of understanding case-specific etiologies, a genetic diagnosis is an essential aspect to the care for CKD patients.

While sanger sequencing used to be the preferred method of genetic testing, the advent of next generation sequencing techniques has allowed for increased utility and benefit of genetic testing in clinical practice[8]. Through this method, simultaneous sequencing occurs, either in a particular group of genes known to be associated with a phenotype (targeted-phenotype-associated gene panels), of all known coding regions in the human genome (exome sequencing (ES)), or of the entire human genome (genome sequencing (GS))[8]. In routine clinical practices, targeted-phenotype associated gene panels are employed. However, given that many CKD patients do not receive a clinical diagnosis, or receive a misdiagnosis, and that new genes that are known to be causing CKD are routinely being discovered, ES provides benefits,

since ES analysis can evaluate all genes being interrogated - including those that are considered candidate genes. Using ES, all coding genes of the patient are sequenced, which allow for analysis of all genes known to be causing all forms of CKD at once, and they may be re-evaluated upon rapid updating of known gene lists[8].

Recent studies have established a diagnostic yield of 10-50% using ES [9,10], however no such study has been performed in Canada. Given its high diagnostic yield, in addition to the significant monogenic contribution already established in CKD and the benefits of establishing a genetic diagnosis, we hypothesize that the implementation of ES in routine clinical practice will be advantageous. Therefore, the aim of this study is to describe the prevalence and distribution of genetic disease within each phenotype by understanding the utility of ES as well as its clinical implications by performing this analysis using a curated list of known monogenic causes of CKD, on a cohort of 94 families that were undiagnosed by clinical gene panel investigations, and then by summarizing and evaluating several clinical parameters thereafter.

Materials and Methods

The general workflow of this study is summarized in Figure 1.

Patients

A total of n= 94 families, including n=102 patients were included in this study. This cohort comprised a group of families that were either unable to receive a genetic diagnosis by phenotype-targeted gene panels or did not receive a diagnosis by this method (Fig 1). Reasons for a lack of diagnosis include the broad specificity of symptoms relating to CKD phenotypes, leading to misdiagnosis, as well as only testing in a fraction of known genes by this method. These patients were referred to the genetic clinic at Victoria Hospital according to criteria that

increases suspicion that they have a genetic form of CKD. The cohort is described in Figure 2, and demonstrates the distribution of etiologies (Fig 2).

Genetic clinic

Patients are referred to the renal genetic clinic at Victoria Hospital by their nephrologists, if there is a suspicion that they may have GKD. Although certain criteria for inclusion were established (Fig 1), they were also taken on a case-by-case basis to determine whether there is a risk of GKD. During the consultation, Dr. Connaughton reviews their medical and family history, and determines whether the patient is a candidate for phenotype-targeted gene panels, and if ES is a more suitable alternative, provides them with this option. Patients that are recruited follow consent procedures to participate in research ES. All participants provided informed written consent and the protocol was approved by the research ethics board at Western University.

DNA extraction

Genomic DNA was isolated from whole blood or saliva samples using the following protocols. Upon isolation, samples are stored in the SouthWestern Ontario Disease Genetic Biobank (SWORD-GEN Biobank). n=363 patients have been or are currently being investigated for GKD, either by ES or other methods.

Isolation of genomic DNA from whole blood

Cell Lysis

1. Add 3mls of whole blood to a 15ml centrifuge tube containing 9ml of red blood cell (RBC) lysis solution. Invert to mix and incubate for 5 minutes at room temperature. Invert again at least once during incubation.
2. Centrifuge at 2000x g for 2 minutes to pellet the white blood cells (WBC).

3. Pour off the RBC lysis supernatant leaving behind the WBC pellet and drain tube for at least 10 seconds on clean absorbent paper. Less than 1 µl residual liquid should remain.
4. Vortex the tube vigorously to resuspend the WBCs in the residual liquid.
5. Add 3ml of cell lysis solution to resuspend the cells.
6. To lyse the cells, vortex on high speed for 10 seconds. Usually no incubation is required; however, if cells clumps are visible, incubate at 37◦C until the solution is homogenous. Samples are stable in cell lysis solution for at least 2 years at room temperature.

Protein precipitation

1. Cool samples to room temperature by placing samples on ice for 3 minutes.
2. Add 1 ml of protein precipitation solution to the cell lysate.
3. Vortex at high speed for 20 seconds to mix the protein precipitation solution uniformly with the cell lysate.
4. Centrifuge at 2000x g for 5 minutes. The precipitated protein should form a tight brown pellet. If the protein pellet is not tight, repeat step 3, followed by incubation on ice for 5 minutes and repeat step 4.

DNA precipitation

1. Pour the supernatant containing the DNA (leaving behind the protein pellet) into a clean 15ml centrifuge tube containing 3ml 100% isopropanol (2-propanol).
2. Mix the sample by inverting gently 50 times until the white threads of DNA form visible clumps.
3. Centrifuge at 2000x g for 3 minutes. The DNA will be visible as a small white pellet.

4. Pour off supernatant and drain tube briefly on clean absorbent paper. Add 3ml 70% ethanol and invert tube several times to wash the DNA pellet.
5. Centrifuge at 2000x g for 1 minute. Carefully pour off the ethanol. The pellet may be loose so pour slowly.
6. Invert and drain the tube on clean absorbent paper and allow to air dry for 10-15 minutes.

DNA hydration

1. Add 250µl of DNA hydration solution (250 µl will give a concentration of 400 µg/ml if the total yield is 100µg DNA). Note, DNA hydration solution consists of 10 mM tris, 1 mM EDTA with a pH of 7-8.
2. Rehydrate DNA by incubating at 65◦C for 1 hour or overnight at room temperature. If possible, tap the tube periodically to aid dispersing the DNA.
3. Samples may be centrifuged briefly and then transferred to storage tubes.
4. Store DNA at 4°C or -20 to -80°C for long term storage.

<u>Isolation of genomic DNA from saliva samples (using Orageneâ Discover DNA collection kit)</u>

1. Incubate the spit sample at 50°C overnight.
2. Transfer the sample to a 15ml centrifuge tube.
3. Add 1ml of PrepIT-L2P solution to the tube and invert several times.
4. Place on ice for 10 minutes.
5. Centrifuge at room temperature for 5 minutes at 2000x g.
6. Carefully transfer the clear supernatant containing the DNA to a 15ml centrifuge tube containing 3mls of 100% ethanol. Invert 10 times to precipitate the DNA.

7. Allow the sample to stand at room temperature for 10 minutes to allow the DNA to precipitate.
8. Centrifuge for 2 minutes at 2000x g.
9. Pour off supernatant allowing the DNA pellet to remain.
10. Add 1ml of 70% ethanol and gently invert to wash the DNA pellet. Allow to stand at room temperature for 1 minute.
11. Centrifuge for 2 minutes at 2000x g and pour off excess ethanol.
12. Allow to stand at room temperature for 15 minutes to allow for complete evaporation of the ethanol.
13. Add 100µl of DNA hydration solution to dissolve the DNA pellet. Vortex for 5 seconds to dissolve.
14. Incubate at 37°C overnight on the shaker.
15. Store DNA at 4°C or -20 to -80°C for long term storage.

Exome sequencing, McGill 1-4

Purified genomic DNA was sent to the McGill Genome Centre at McGill University for whole exome sequencing using protocols for library preparation, exome capture, and next generation sequencing, according to the NxSeq AmpFREE low DNA Library Kit. 4 batches were used for this study, each group being numbered according to the batch that they were sent to McGill (1-4). FASTQ files were downloaded and processed using a custom automated workflow in CLC Genomics Workbench version 8.51 (CLC Bio, Aarhus, Denmark) for sequence alignment to our list of 735 genes known to be causing chronic kidney disease compiled via literature review in the lab (mapped to human genome build GRCh37/hg19), variant calling (generation of .VCF files), and target region coverage statistics (generation of .BAM files).

Variant annotation was conducted by using ANNOVAR with a customized Script. ANNOVAR is a functional annotation pipeline for genetic variants that allows for downloading sets of reference databases and *in silico* functional prediction, customize filtering strategies and calculate genetic risk score. Here, downloaded materials included: databases (RefSeq (hg19), dbSNP, gnomAD, ExAC, ESP, HGMD, ClinVar) , *in silico* predictions (PolyPhen-2, SIFT, CADD, Mutation Taster) and ACMG classifications. After processing, variants were filtered in the determination of most likely deleterious variants using the following filtering protocol as well as variant ranking framework.

Known gene lists

Through literature searches, tables were generated to summarize current genes known to be associated with monogenic causation of CKD. The information in these tables were used to (1) generate the curated list of known genes that would function in the exome analysis of patients and (2) to provide reference for the implication of those genes in CKD when analyzing the possible effects of those variants on the onset of patient CKD. These tables were separated into: Cystic kidney diseases (Table S.1); Proteinuric kidney diseases (Table S.2); Isolated CAKUT (Table S.3); Syndromic CAKUT (Table S.4); Tubulopathies (Table S.5); Nephritis (Table S.6); CKD and miscellaneous (Table S.7); Diabetic kidney disease (Table S.8); Hereditary amyloidosis (Table S.9). Each of these tables provides the gene name, protein products, literature reference, mode of inheritance, phenotypes, and OMIM numbers of all known monogenic causes CKD.

Variant filtering in WES analysis

1. Exclude variants with allele frequencies >1% in gnomAD or ExAC databases.
2. Exclude synonymous and intronic variants not located within splice-site regions.

3. Cross reference zygosity of variants with known disease-causing inheritance patterns and exclude variants with unmatched zygosity.
4. Use the gnomAD database to search for allele frequency. Exclude variants with over 10 heterozygous calls if dominant hypothesis, or 2 homozygous calls if recessive hypothesis.

Variant ranking in WES analysis

1. Use web-based bioinformatic tools, PolyPhen-2 (polymorphism phenotyping version 2), SIFT (Sorting Intolerant From Tolerant), and MutationTaster (Berlin, Germany), and CADD (insert program used to determine this) annotated via ANNOVAR to rank the variants based on their likelihood to impact the function of the encoded protein.
2. Classify mutations based on the American College of Medical Genetics and Genomics (ACMG) guidelines to predict pathogenicity of mutation, and whether the variant is pathogenic, likely pathogenic, or variant of uncertain significance (VUS)[11].
3. For each gene selected for further analysis, conduct literature review of the gene and encoded protein, describe the known interactions, analyze structural impacts by examining variant location in protein crystal structure and structure alignment, and consult clinical histories in order to determine the likelihood of variant to cause patient phenotype.
4. Keep likely causative variants, and sanger confirm with segregation if possible.

Results

Exome sequencing was performed in a cohort of 102 people, with 94 families, 98 participants with CKD, and 4 unaffected family members. These families had undergone clinical gene panel testing, but were either undiagnosed by this tool or were unlikely to receive a diagnosis by this method, and were therefore included in this study (Fig 2).

The diagnostic rate of exome sequencing is 17% in 94 families affected by CKD who were unsolved by other means of genetic testing

Exome sequencing solved 16 familial cases of CKD, genetically, generating a diagnostic yield of (16/94) = 17% in this cohort (Fig 3). Here, a solved genetic case refers to a likely pathogenic, or pathogenic finding according to ACMG guidelines that are correlated to patient phenotypes. The causative variant annotations for this group are summarized in Table 1.

Exome sequencing had revealed 22 cases, or (22/94)= 23.4% of this cohort were classified as VUS, that had strong correlations to patient phenotypes (Fig 3). These variant annotations are summarized in Table 2.

The remainder of this cohort (56/94)= 59.6% were grouped as unsolved by exome sequencing. Within this group, two patients were solved by a specific type of testing for causative variants in *MUC1*. The reason for this is variant testing for *MUC1* is not routinely detected by ES and a highly specialized type of long-range PCR is required to detect the known pathogenic variants which are located within a variable number of tandem repeat regions on the *MUC1* gene. One family had a causative variant for familial nephrolithiasis as an incidental but no variants in a gene known to cause CKD was detected. This is therefore classified as an incidental finding for this family since although it did not match the phenotype suspected as initial presentation, on review this family did indeed have a dual diagnosis of nephrolithiasis. This group, both unsolved and those with VUS findings, continue to be evaluated through familial investigations, novel gene evaluations, review of variant classifications, or re-analyses (Fig 3).

The prevalence of genetic kidney disease varied according to etiology in 94 families

Within genetically solved cases of CKD, underlying etiologies, prior to exome sequencing, and after this analysis, were summarized (Fig 4). These results show that a genetic basis for CKD may be variable according to specific etiologies (Fig 4). Among those solved, patients were determined to have the following etiologies, considering their molecular diagnosis: Nephronophthisis, Tubulopathy, Glomerulonephritis, Congenital anomalies of the kidneys and urinary tract (CAKUT), Tubulointerstitial kidney disease (TKD), Cystic kidney disease, and other. Within the other category, includes patients with Atypical hemolytic uremic syndrome (aHUS), Alport syndrome, and Diabetes. Importantly, prior to this analysis, 58% of patients were diagnosed with CKD of unknown etiologies, but every patient that has been solved genetically now received a specific clinical diagnosis (Fig 4).

Molecular diagnosis for CKD had clinical implications for patients and families

Patients who received a molecular diagnosis through exome sequencing, among which received clinical confirmation (n=13), were informed of the genetic basis of their CKD, which led to clinical implications of these findings. Among possible clinical implications, the ones that were recorded included whether the finding led to: diagnostic confirmation, resolution of diagnostic confusion, correction of diagnosis, guidance on family planning, guidance on management in transplant setting, guidance on management for living related donors, genetic counseling, cascade testing in family members, and treatment alterations. Such clinical implications were summarized and quantified according to their percent distribution in this group (Fig 5). Every solved and clinically confirmed patient had some form of clinical implication, where all cases led to diagnostic confirmation and genetic counseling (Fig 5). Following this,

among the most prevalent were diagnostic resolution/correction, while among the least prevalent was effects in the transplant and treatment settings (Fig 5).

Case study: Dent Disease

A 48 year-old male of Italian descent was referred to the Genetic Clinic at Victoria Hospital (P101, Table1). The suspicion of a genetic basis for his CKD was raised due to early onset of CKD and ESRD as well as a positive family history of CKD. He initially presented with symptoms in his early 30s and was diagnosed with CKD at the age of 35. He recalls feeling unwell for a few weeks and after conducting blood work was immediately referred to a nephrologist. He recalls having proteinuria and advanced kidney dysfunction, however, was unsure of other specific details pertaining to his initial diagnosis. Given the small size of his kidneys, he was not a candidate for a kidney biopsy. The patient did not present with extrarenal features, but had a medical history of hypertension prior to a parathyroidectomy, steatosis, and an unprovoked pulmonary embolism. The patient received a renal transplant at the age of 46, after being on dialysis since 35 when he had reached ESRD. The patient has a positive family history of CKD, with a brother who has had a renal transplant, being diagnosed with CKD presumed due to Focal Segmental Glomerulosclerosis (FSGS) in his 40s.

Given the suspicion of a genetic basis for this patient's CKD, with negative FSGS and Alport panels, the patient was advised to receive ES. Upon sequencing, a likely pathogenic variant was found in the *CLCN5* gene (Table 1). The patient had a Guanine to Thymine mutation at position 1723, leading to a truncating variant in this gene, at position 575, on the X chromosome (Table 1). The bioinformatic annotations received through ES for this variant were a CADD score of 43 and disease causing automatic in Mutation Taster (Table 1). Given the

genetic strength of this variant, in addition to the ACMG classification, this variant was further investigated.

Inactivating mutations in the *CLCN5* genes are responsible for Dent disease 1[12]. *CLCN5* encodes a member of the voltage gated chloride ion channel family (CLC-5)[13]. Specifically, it encodes the 746 amino acid protein (CLC-5)[13]. CLC-5 proteins contain homodimers which cross the membrane in opposite directions, although each of those subunits selectively transport hydrogen and chloride ions[14]. The distribution of CLC-5 is significant in that it is mainly expressed in the proximal tubule and collecting ducts of the kidney, but mainly located in early endosomes[16]. Endocytosis through endosome acidification is essential in mediating the resorption process within the proximal tubules[13]. When there is a lack of functional CLC-5, the inhibition of endocytosis impacts the capacity for resorption by the proximal tubules, since it has been shown to play a vital role in this process by driving protons into cells[15]. Many molecules are therefore poorly resorbed[12]. Over 200 mutations in *CLCN5*, including nonsense variants, deletion variants, missense variants, frameshift variants, and intronic splicing variants have been identified to be causative of Dent disease [15]. Dent disease is a renal tubular disorder categorized by gene mutations in either CLCN5 or *OCRL* genes, into Dent Disease 1 and 2, respectively, although diseases may be phenotypically similar[15].

Patients with Dent disease 1 may present with low-molecular weight proteinuria, hypercalciuria, renal calcification, nephrolithiasis, and renal tubular dysfunction[16]. Many patients with Dent disease develop ESRD between the ages 30-50[16].

This mutation has led to the deletion of 172 amino acids at the C-terminus of *CLCN5* (Fig 6). A previous study by Lioyd et al., has shown that truncating variants, even when located upstream of this patient's mutation, leads to the abolishment of its functionality in Xenopus

oocytes[17]. They hypothesized that the protein's C-terminal cytoplasmic domain is essential to its function[17]. Within this C-terminal region, are two known cystathionine-beta synthase (CBS) domains (Fig 7), which have important regulatory function, and have been proposed to play an important role for the trafficking of this protein to the membrane where it is functional[18]. Additionally, previous case reports have reported a pathogenic mutation proximal to that of this patient, in a patient with Dent Disease[19]. Given the functional, population, and genetic data gathered regarding this variant, it was predicted to be causative of this patient's CKD, and was clinically confirmed thereafter.

This genetic diagnosis had clinical impacts for this patient. A genetic diagnosis provided a definitive clinical diagnosis for this patient, where he was previously categorized as having CKDu, and now having Dent Disease 1. He was provided with genetic counseling to explain the implications of this finding. This further prompted cascade testing in at-risk family members, and it was then established that the patient's daughter is a carrier for the condition. The clinical implication was firstly to assist in correcting the diagnosis of this patient's CKD, he was also provided with genetic counseling explaining the impacts of such a diagnosis, and provided assistance in family planning. Further, this diagnosis was able to provide cascade genetic testing in family members. The patient's daughter is now known to be a carrier for this disease, which can have impacts on her decisions in family planning. There have also been implications within the transplant setting. The patient was unaware of his diagnosis at the time of his transplant, and was therefore unable to receive adequate information regarding the possible recurrence rate of the disease. Knowing that his CKD was secondary to Dent disease, could have provided him with the knowledge regarding the recurrence of his CKD following transplant, which can vary by

etiology. Further, if living donors were being considered for transplant, assessing their risk of CKD would have been simplified with the knowledge of this diagnosis.

Discussion

In this study, we have evaluated the utility of ES among a cohort of Canadian families that were referred to the genetic clinic due to a suspicion of having GKD, but did not receive a genetic diagnosis by routine methods. In doing so, we have calculated a diagnostic yield of 17% with clinical implications among those solved.

Studies have demonstrated that ~30% of CKD cases have underlying monogenic causation in young-onset CKD[5], with evidence of a similar prevalence among adult-onset CKD[7] demonstrating significant genetic basis for CKD and searching for a molecular diagnosis among both cohorts of CKD patients. The diagnostic yield of ES within CKD patients has shown variability among studies, ranging from 10-50%[9,10]. Previous studies by our group have found a 38% yield in an Irish cohort. Here, we have shown a diagnostic yield of 17%. While this falls within the expected range, it has not shown to be as effective as other investigations through this study. However, the significant limitation in this study compared to other investigations is that we are evaluating the added benefit of ES, as opposed to its diagnostic capacity. To do this, we have only included families that remained undiagnosed by clinical panel investigations. Therefore, these families would have remained undiagnosed by current routine practice, in the absence of this tool.

Using ES, a clinical diagnosis was established for all solved families. Previous studies by our group have supported the etiological distributions that we have found here, with significant prevalence of patients with cystic kidney disease, CAKUT, and glomerulonephritis phenotypes in an adult cohort[20]. Within this group, 58% of patients had a clinical diagnosis of CKDu. Although

the distribution of etiologies are summarized (Fig 4), this study is not indicative of the specific genetic prevalence in subtypes of CKD, but rather representative of ES benefit in establishing a clinical diagnosis. Importantly, ES was able to provide a specific clinical diagnosis in all solved cases. Providing a patient with CKD with an accurate and specific etiology is crucial to facilitate treatment personalization in addition to establishing the prognosis of disease[5].

In literature, there is significant support for a genetic diagnosis in the pursuit of personalized medicine, as it can conclude effective diagnostic procedures, aids in avoiding unnecessary procedures and treatments, helps with concluding accurate prognosis and follow-up intervals, and allows for genetic counseling for families, as well as risk calculation in the transplant setting, according to recurrence rates as well as living-donor assessments [21]. Here, we have assessed the specific clinical implications of a genetic diagnosis among solved families who remained undiagnosed prior to ES (Fig 5). We have shown that some form of clinical implications occurred in all families, where diagnosis confirmation, confusion resolution, correction, as well as genetic counseling were among the most prevalent (Fig 5). Nevertheless, guidance was provided in the transplant setting and with living related donors, in addition to cascade testing in at-risk family members, in some cases (Fig 5). We have shown through quantification of clinical impacts, that given the variability in prognosis, treatment, and transplant success, both among different etiologies, and within etiologies bearing different mutations, having an accurate molecular diagnosis supports the capacity to effectively treat patients with CKD.

Although there is a significant and growing association of genetic basis of many CKD cases, there are many barriers to genetic testing and hesitation to determine a genetic diagnosis. Rasouley et al., conducted a national survey among nephrologists, and showed that although all

201 nephrologists were treating GKD, 37% of these physicians only reported less than 5 patients for genetic testing[22]. They also demonstrated that a third of these physicians had insufficient knowledge of the genetic basis of CKD [22]. In literature, factors leading to hesitation for genetic testing among CKD patients include a lack of sufficient awareness for inherited diseases, accessibility to genetic testing, as well as concerns for costs [23,24,25]. In addition, among routine genetic testing for CKD patients, phenotype-driven gene panels are used, however these are limited in their capacity to diagnose patients whose etiologies are unknown, or patients who have been misdiagnosed, given the broad manifestations of many CKD etiologies. Here, we have shown that 17/94 families were not genetically diagnosed prior to ES. 11/17 of these families had their clinical diagnosis corrected from CKDu, to a specific etiological description. We have specifically exemplified one such case, in regards to the diagnostic methodologies as well as the clinical implications, although such an analysis was performed for every patient included in this study. Given the importance of accurate and precise diagnosis to treat patients with CKD, ES has proven to be a useful tool, where currently implemented tools are failing.

Many limitations must be considered when evaluating the results of this study. Firstly, the cohort that have been evaluated here are those who have been unable to receive a genetic diagnosis via currently implemented tools, and therefore do not represent the capacity for ES to diagnose patients with CKD as a whole, nor the prevalence of genetic causation in CKD. Further, ES is limited to the genes that are being evaluated, and as such, is only as effective as the list of genes that we have selected through literature to be valuable in searching for monogenic causation of CKD. Finally, when classifying variants according to ACMG guidelines, we have used online tools that may not have considered specific conditions which could have altered their score otherwise, such as the necessity of familial testing to accurately predict score[11]. As such,

many VUS variants may be classified differently, leading to a differential genetic diagnosis, if each factor in its calculation were recorded and determined specifically.

In this study, we have demonstrated the utility of ES in determining a molecular and consequently clinical diagnosis among 94 families that were undiagnosed otherwise. Given its diagnostic yield and advantages, along with the impacts that such diagnoses have had clinically, it has shown to be advantageous in routine clinical practice. Future studies should investigate whether the utility of ES can be altered with differences in the cohort, gene lists, bioinformatic tools, and altered approaches to determining variant classification via ACMG. If studies can investigate more effective methods of variant ranking/classification, as well as its utility in a broader cohort, then it can establish the importance of ES implementation in routine clinical practice, to provide a genetic diagnosis for CKD patients.

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Figures/tables

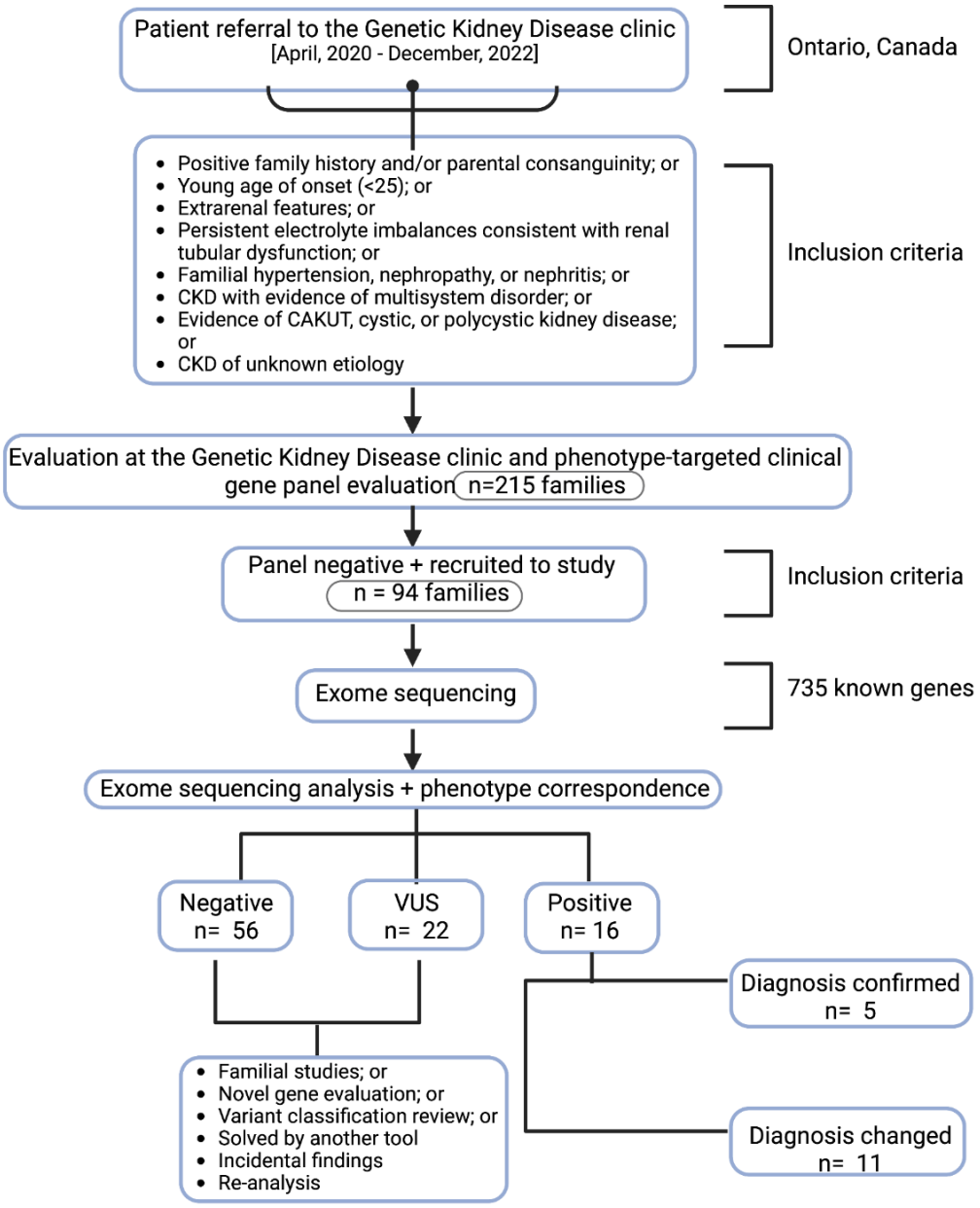

Figure 1. Diagnostic workflow of families being evaluated for a genetic cause to their CKD using exome sequencing as an additional tool. Families that were referred to the genetic kidney disease clinic on suspicion of having a genetic cause to their kidney disease. This study included families that remained undiagnosed following routine clinical gene panel analysis, to evaluate the added benefit of exome sequencing in these cases. After evaluation, families were sorted into whether they were solved, whether they had a clinically significant variant of uncertain significance (VUS) and whether they were negative. Those that were solved had clinical implications, and those with VUS or negative testing continue to be evaluated by other means.

Variables	Subjects
Cohort size (n)	102
Unaffected family members (n)	4
Families (n)	94
CKD patients (n)	98
ESRD (n)	39
Hemodialysis (n)	23
Renal transplant (n)	16
Mean age (years)	47.5
Mean age of CKD onset (years)	34.3
Mean age of ESRD onset (years)	38.1
Ethnicity, n(%)	
Caucasian	52(51.0)
Asian	7(6.9)
Middle Eastern	2(2.0)
Black or African Canadian	1(1.0)
Indigenous	1(1.0)
Hispanic	3(2.9)
Unknown	36(37.2)

Variables	Subjects
CKD Etiology, n(%)	
Unknown	52(53.1)
Known	46(46.9)
Presumed CKD Etiology, n(%)	
Tubulopathy	2(2.0)
Tubulointerstitial kidney disease	3(3.1)
Cystic kidney disease	9(9.2)
Glomerulonephritis	12(12.2)
CAKUT	8(8.2)
Diabetic nephropathy	3(3.1)
Other	9(9.2)

Figure 2. Details of a Canadian cohort being assessed for chronic kidney disease by exome sequencing who were previously undiagnosed. A group of n=102 people, including 98 chronic kidney disease patients undergoing exome sequencing analysis were described by being a patient or unaffected family member, whether they have reached end stage renal disease (ESRD), ESRD modality, mean current age and age of onset, etiological descriptions, and ethnicities.
CKD: chronic kidney disease; CKD etiology unknown: at the time of referral to genetic kidney disease clinic, cause of CKD was unclear; CAKUT; congenital anomalies of the kidney and urinary tracts

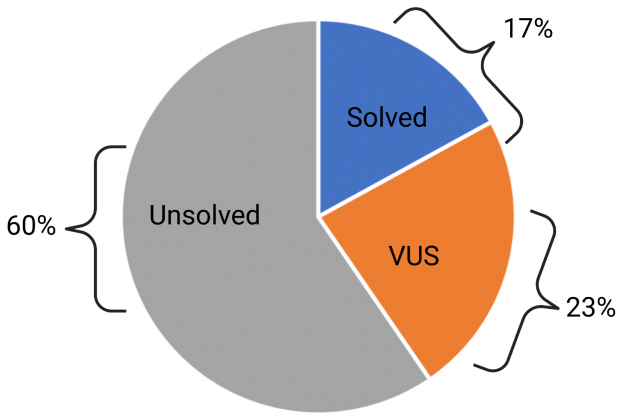

Figure 3. Exome sequencing diagnostic yield in n=94 families undiagnosed by clinical gene panel evaluations. In a group of 94 families that were unable to receive a genetic diagnosis by phenotype-targeted clinical gene panel, exome sequencing analysis was performed and its diagnostic yield was quantified. Solved is defined as having a pathogenic or likely pathogenic variant according to ACMG

guidelines that corresponds to the participant's phenotype. A variant of uncertainty (VUS) diagnosis is one that has an unknown risk associated with disease causation but is clinically relevant. Unsolved are families that were not solved genetically by this analysis.

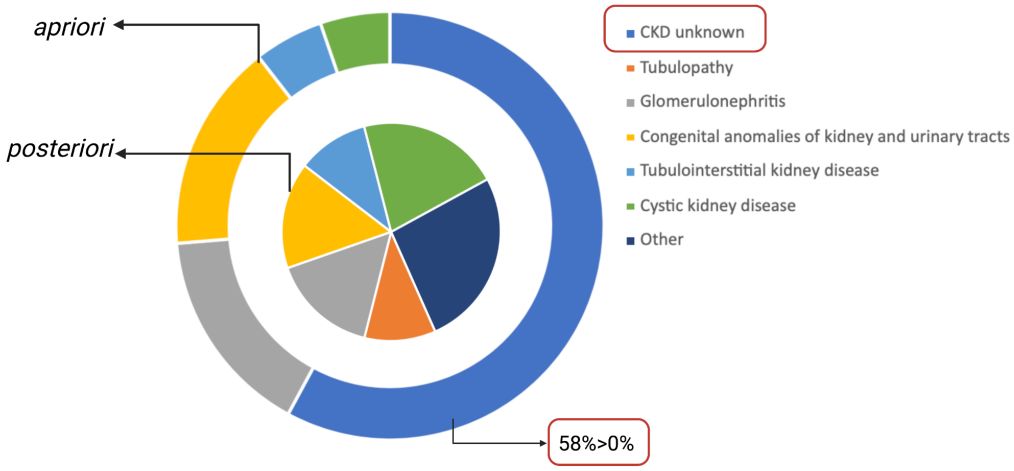

Figure 4. Etiological distribution of CKD patients that were genetically solved by exome sequencing analysis (n=16). In a group of 94 families that were unable to receive a genetic diagnosis by phenotype-targeted clinical gene panel, exome sequencing analysis was performed. For genetically solved cases (n=16), etiological distributions of CKD were summarized prior to, and following, exome sequencing analysis. In the "other" group, includes patients with Alport syndrome, Diabetes, and Atypical hemolytic uremic syndrome

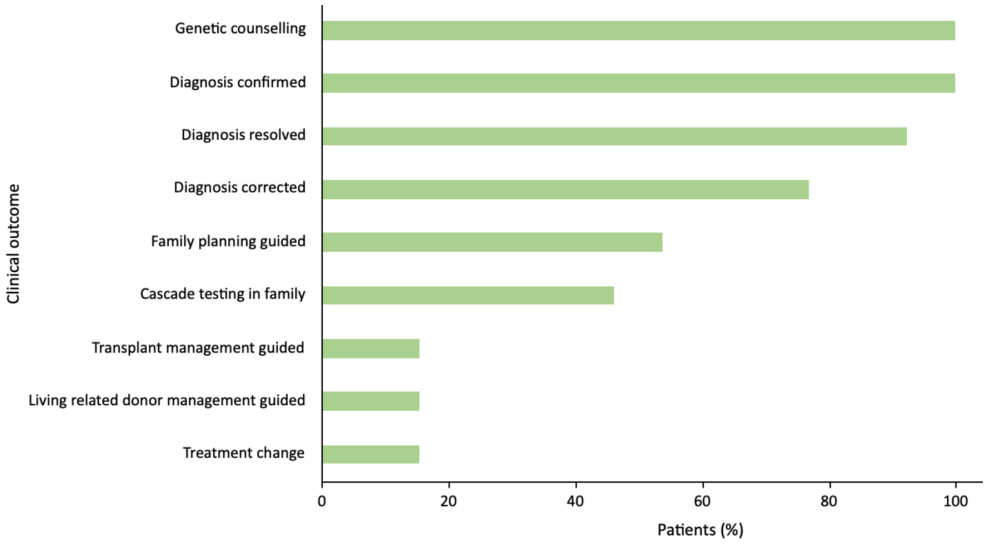

Figure 5. Prevalence of clinical implications in clinically confirmed genetic diagnoses by exome sequencing n=13. In a group of 94 families that were unable to receive a genetic diagnosis by

phenotype-targeted clinical gene panel, exome sequencing analysis was performed. For genetically solved and clinically confirmed cases (n=13) clinical outcomes were recorded and % distribution were summarized.

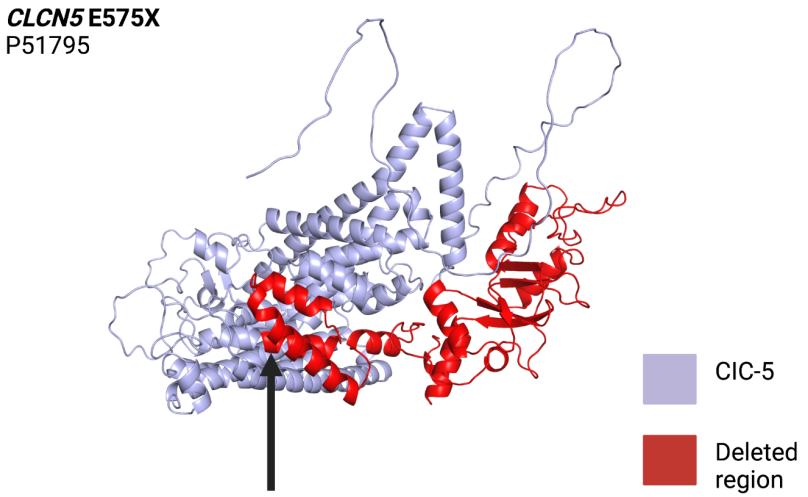

Figure 6. Representation of a nonsense mutation at position 575 of the *CLCN5* gene product. Voltage-gated chloride ion channel 5 (CIC-5) with a premature stop codon at position 575 is shown, where the protein is coloured purple, and the deleted region is coloured in red. The specific mutation location is shown with an arrow. This figure was generated using Pymol, with PDB file P5179.

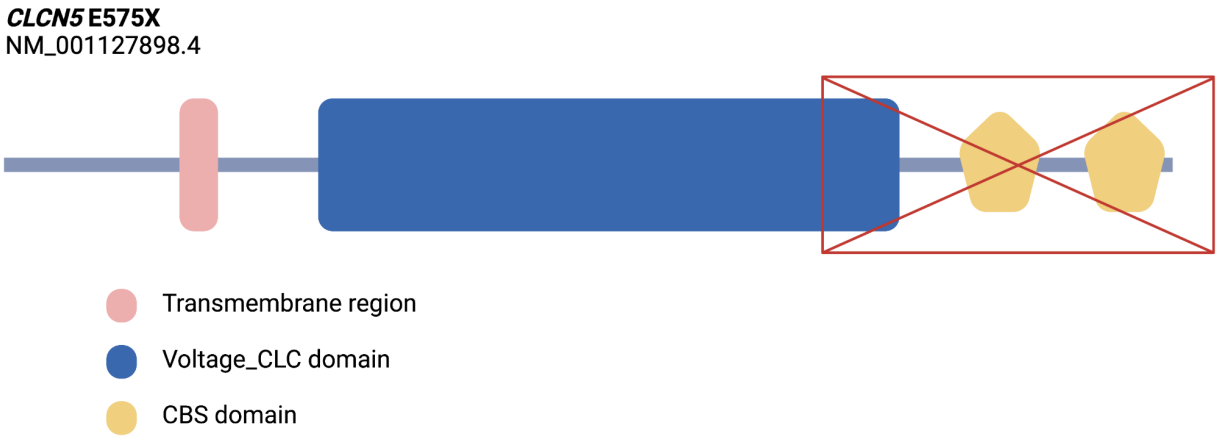

Figure 6. Representation of a nonsense mutation at position 575 of *CLCN5* and the effects on known domain regions of its gene product. Voltage-gated chloride ion channel 5 (CIC-5) with a premature stop codon at position 575 is shown, with known domain regions demonstrated. Its transmembrane, catalytic (Voltage_CLC domain) and cystathionine beta synthase (CBS) domain are shown, where the mutation causes deletion to the C-terminal end of the catalytic domain along with both CBS domains. This figure was adapted from ENSEMBL, using the transcript number NM_001127898.4 (ENST00000376088.7)

Table 1: Genetic annotations of variants found to be causative of CKD in n=17 families that were solved through exome sequencing analysis.

Patient #	Family #	Gene	hg19 Pos	Transcript	c.Change	Exon	Zygosity	p.Change	CADD	Poly2	SIFT	MutTaster	ACMG	SNP ID	Allele Freq.	ExAC	gnomAD	Count	Cover
P0071	F0048	CFH	chr1: 196646682	NM_000186	C504G	5	Het	Y168X	23.7	//	//	A	LP	//	//	//	//	12	27
P0012	F0009	COL4A3	chr2: 228142227	NM_000091	G2083A	28	Het	G695R	25	D	D	D	LP	rs200287952	//	0.0002	0.0002	6	16
P00089	F0058	NPHP1	2q13	//	127 kb deletion	//	Hom	//	//	//	//	//	//	//	//	//	//	//	//
P0075	F0051	UMOD	chr16: 20360421	NM_001008389	G202A	3	Het	E68K	27.9	D	D	D	LP	//	//	//	//	18	44
P0090	F0059	NPHP1	//	//	Deletion	//	Het	//	//	//	//	//	P	//	//	//	//	//	//
P0115	F0078	COL4A3	chr2: 228142227	NM_000091	G2083A	28	Het	G695R	25	D	D	D	LP	rs200287952	//	0.0002	0.0002	6	12
P00117	F0080	NPHP1	//	//	106.4kb deletion	//	Hom	//	//	//	//	//	P	//	//	//	//	//	//
P0091	F0060	PKD1	chr16: 2161729	NM_000296	3437_3439del	15	Het	1146_1147del	//	//	//	//	LP	rs1320867301	//	//	//	12	29
P0128	F0049	UMOD	chr16: 20360057	NM_003361.4	A665G	3	Het	Y222C	21.2	T	D	N	LP	rs1159216039	//	//	//	44	89
P0140	F0097	CLCN5	chrx:49845266	NM_000084	410dupT	5	Het	I137fs	//	//	//	//	P	//	//	//	//	14	14
P0144	F0099	PAX2	chr10: 102539327	NM_000278	483delT	4	Het	P161fs	//	//	//	//	P	//	//	//	//	10	23
P0101	F0067	CLCN5	chrx:49854961	NM_000084	G1723T	10	Het	E575X	43	//	//	A	LP	//	//	//	//	18	18
P0136	F0095	ORAI1	chr12: 122064779	NM_032790	132delA	31	Hom	P44fs	//	//	//	//	LP	//	//	//	//	16	16
P0064	F0047	PODXL	chr7:131191443	NM_005397	C1048T	5	Het	R382X	35	//	//	A	LP	rs1351659066	0/1/31386	//	3.23E-05	25	42

P0183	F0125	CDKN1C	chr11:29062 05	NM_000076	514_515insG	1	Het	P172fs	//	//	//	//	LP	//	//	//	//	6	10
P0231	F0166	CEP164	chr11:11728 2575	NM_0012719 33	c.C4213T	31	Het	p.Q1405X	40	//	//	A	P	rs1473 98904	0/230/28 2374	0.0008	0.0008	31	64

Shown are patient numbers, family numbers, gene name, position on the human reference genome (Hg19pos), transcript number, nucleotide change (c.change), exon number, zygosity of the variant, amino acid change indicated by one-letter code (p.change), bioinformatic prediction tools (CADD, Poly2, Mutationtaster), ACMG classification, SNP identification, allele frequencies as per GnomAD, ExAC and GnomAD frequencies, count, and coverage of the sequencing. Abbreviations: chr=chromosome; del=deletion; ins=insertion; fs=frameshift; [bioinformatic scoring: D=deleterious; T=tolerated; A=disease causing automatic; N=polymorphism]; X=nonsense mutation; [ACMG: P=pathogenic, LP=likely pathogenic].

Table 2: Genetic annotations of clinically significant variants of unknown significance in n=22 families with CKD that were analyzed by exome sequencing

Patient #	Family #	Gene	hg19 Pos	Transcript	c.Change	Exon	Zygosity	p.Change	CADD	Poly2	SIFT	MutTaster	ACMG	SNP ID	Allele Freq.	ExAC	gnomAD	Count	Cover
P0015	F0012	JAG1	chr20:10639368	NM_000214	C442T	4	Het	P148S	10.73	B	T	D	VUS	rs1355919795	//	//	//	10	16
P0025	F0020	ARHGAP24	chr4:86916056	NM_001346093	C670G	6	Het	P224A	22.8	B	T	D	//	rs35521695	//	0.0113	0.0099	23	47
P0026	F0021	REN	chr1:204128683	NM_000537	C533T	5	Het	T178M	26.3	D	T	D	VUS	rs147436851	//	6.59E-05	3.23E-05	9	35
P0088	F0057	FN1	chr2:216279564	NM_001306129	G1937A	13	Het	R646K	15.89	B	T	D	VUS	//	//	//	//	17	31
P0103	F0068	CFI	chr4:110685820	NM_000204	G355A	3	Het	G119R	22.3	D	D	N	VUS	rs141853578	//	0.0005	0.0005	18	40
P0099	F0065	UMOD	chr16:20360277	NM_001008389:	G346C	3	Het	G116R	23.5	D	D	N	VUS	rs139042757	//	//	//	33	70
P0200	F0140	TTC21B	chr2:166786721	NM_024753	G1048T	9	Het	A350S	28.6	D	T	D	VUS	//	0/16/251082	7.42E-05	//	13	28
P202	F0141	COL4A5	Chr2:228172594	NM_000091	T4421C	48	Het	L1474P	23.4	D	D	D	VUS	//	//	0.0028	0.0022	13	30

P202	F0141	KCNJ11	Chr11:17409548	NM_000522	C91T	1	Het	R31W	//	//	//	//	VUS	//	0	//	//	29	60
P0185	F0127	TBC1D8B	chrX:106117191	NM_017752	c.T3359G	21	Het	p.M1120R	17.24	B	D	N	VUS	//	//	//	//	16	16
P0028	F0023	APOE	chr19:45409886	NM_000041	A5G	2	Het	K2R	20.7	B	T	N	VUS	//	//	//	//	18	41
P0021	F0016	CYP11B1	chr8:143958612	NM_000497	G422A	3	Het	R141Q	26.8	D	D	D	VUS	rs267601810	0/3/281926	9.00E-06	6.47E-05	14	35
P0047	F0033	SLC12A3	chr16:56920296	NM_000339	C1946T	16	Het	T649M	32	D	D	D	VUS	rs145337602	//	0.0000498	0.00000647	3	11
P0054	F0037	KLHL3	chr5:136961453	NM_001257195	G1478A	12	Het	R493Q	35	D	D	D	LP	//	//	//	//	12	35
P0095	F0062	SLC6A19	chr5:121067676	NM_001003841	C461T	3	Het	P154L	27.6	D	D	D	VUS	rs771980756	0/9/281662	4.18E-05	3.23E-05	35	77
P0059	F0042	ATXN1	6:16327865	NM_000332.4	677_678insGCA	8	Hom	Q225dup	//	//	//	//	VUS	//	321/915/100840	//	//	//	//
P0059	F0042	ATXN1	6:16327916	NM_000332.4	621_626dupGCAGCA	8	Het	Q207_Q208dup	//	//	//	//	VUS	//	3/6/18242	//	//	//	//
P0107	F0070	LAMC1	chr1:183096481	NM_002293	A3065G	17	Het	N1022S	23.8	D	D	D	VUS	rs147794601	0/42/282870	0.0001	9.69E-05	12	28
P0109	F0072	SLC6A19	chr5:12125505	NM_001003841	C569T	4	Het	S190L	26.2	P	D	D	VUS	//	//	2.478E-05	//	38	71
P0121	F0084	NPHP3	chr3:132416142	NM_153240.5	G2050T	14	Hom	E684X	44	//	//	A	VUS	//	//	//	//	4	12
P0135	F0094	TSC1	chr9:135800991	NM_000368	T346G	5	Het	L116V	22.7	D	T	D	VUS	rs199620268	0/113/282648	0.0003	0.0005	21	44
P0168	F0115	GATA3	chr10:8100480	NM_001002295	A454C	3	Het	T152P	23	P	T	D	VUS	//	//	//	//	35	77
P0234	F0169	ABCC6	chr16:16259743	NM_001171	c.C3043T	23	Het	p.R1015W	26.4	D	T	N	VUS	//	0/7/281098	1.687E-05	3.234E-05	11	29

P0186	F0128	BICC1	chr10:60546719	NM_001080512	A424G	5	Het	T142A	25.8	D	D	D	VUS	//	//	//	//	9	23
P0186	F0128	FN1	chr2:216285470	NM_001306129	G1601A	11	Het	R534H	35	D	D	D	VUS	rs142165052	0/60/2828 00	0.0002	0.0003	7	16

Shown are patient numbers, family numbers, gene name, position on the human reference genome (Hg19pos), transcript number, nucleotide change (c.change), exon number, zygosity of the variant, amino acid change indicated by one-letter code (p.change), bioinformatic prediction tools (CADD, Poly2, Mutationtaster), ACMG classification, SNP identification, allele frequencies as per GnomAD, ExAC and GnomAD frequencies, count, and coverage of the sequencing. Abbreviations: chr=chromosome; del=deletion; ins=insertion; fs=frameshift; dup=duplication; [bioinformatic scoring: B= benign; D=deleterious; T=tolerated; N=polymorphism]; X=nonsense mutation; [ACMG: VUS=variant of unknown significance].

Supplemental Items

Supplementary Table S1: genes that represent monogenic causes of human cystic kidney disease or nephronophthisis, if mutated.

Gene	*Alias*	*Protein*	*Reference*	*Mode of inheritance*	*Phenotype*	*OMIM number*
ALMS1	*ALMS*	*Alstrom Syndrome Protein 1*	*Collin Nat Genet AR 31(1):74, 2002*		*Alstrom syndrome*	*# 203800*
ALG9		*ALG9 alpha-1,2-mannosyltransferase*	*Weinstein Am. J. Med. Genet. 136A: 194-197, 2005*	AR	*Congenital disorder of glycosylation, type Il*	*#606941*
B9D1	*MKS9*	*B9 domain containing protein 1*	*Romani Orphanet J Rare Dis 9:72, 2014*	AR	*Meckel syndrome 9, Joubert syndrome 27*	*# 614209, # 617120*
B9D2	*MKS10*	*B9 domain containing protein2*	*Dowdle AJHG 89(1):94, 2011*	AR	*Meckel syndrome 10, Joubert syndrome 34*	*# 614175*
BBS1		*Bardet-Biedl Syndrome 1*	*Mykytyn Nat Genet 31(4):435, 2002*	AR	*Bardet-Biedl syndrome 1*	*# 209900*
BBS2		*Bardet-Biedl Syndrome 2*	*Katsanis Science 293(5538):2256, 2001*	AR	*Bardet-Biedl syndrome 2*	*# 615981*
BBS3	*ARL6*	*Meckel syndrome, type 1*	*Chaddour Hum Mutat 28(5), 523, 2007*	AR	*Bardet-Biedl syndrome 3*	*# 600151*
BBS4		*Bardet-Biedl Syndrome 4*	*Mykytyn Nat Genet 32(2):188, 2001*	AR	*Bardet-Biedl syndrome 4*	*# 615982*
BBS5		*Bardet-Biedl Syndrome 5*	*Tieder Int J Pediatr Nephrol 3(3):199, 1982*	AR	*Bardet-Biedl syndrome 5*	*# 615983*
BBS6	*MKKS*	*Bardet-Biedl Syndrome 6*	*Katsanis Nat Genet 26(1):67, 2000*	AR	*Bardet-Biedl syndrome 6*	*# 605231*

BBS7		Bardet-Biedl Syndrome 7	Badano AJHG 72(3),AR 50, 2003	Bardet-Biedl syndrome 7	615984
BBS8	TTC8	Bardet-Biedl Syndrome 8	Stoetzel J Hum GenetAR 1(1):81, 2005	Bardet-Biedl syndrome 8	615985
BBS9	PTHB1	Bardet-Biedl Syndrome 9	Nishimura AJHGAR 7(6):1021, 2005	Bardet-Biedl syndrome 9	615986
BBS10		Bardet-Biedl Syndrome 10	Stoetzel Nat GenetAR 8(5):521, 2006	Bardet-Biedl syndrome 10	615987
BBS11	TRIM32	Bardet-Biedl Syndrome 11	Chiang PNASAR 03(16):6287,2006	Bardet-Biedl syndrome 11	615988
BBS12		Bardet-Biedl Syndrome 12	Stoetzel AJHG 80(1):1,AR 007	Bardet-Biedl syndrome 12	615989
BBS15	WDPCP	WD repeat-containing planar cell polarity effector	Stone Nat GenetAR 5(1):79, 2000	Bardet-Biedl syndrome 15	615992
BBS17	LZTFL1	Bardet-Biedl syndrome 17	Marion J Med GenetAR 9(5):317, 2012	Bardet-Biedl syndrome 17	615994
BBS18	BBIP1	Bardet-Biedl syndrome 18	Scheidecker J MedAR Genet 51(2):132, 2014	Bardet-Biedl syndrome 18	615995
BBS20	FT27	Bardet-Biedl Syndrome 20	Schaefer J Med GenetAR 1(5):447 2016	Bardet-Biedl syndrome 19	615996
C2CD3	OFD14	Orofaciodigital syndrome 14	Thauvin-Robinet AR Nature Genet 6(8):905, 2014.	Orofaciodigital syndrome IV	615948
CCDC28B		Coiled-coil domain containing protein 28B	Cardenas-Rodriguez AR/DR Hum Genet 132(1):91, 013	Bardet-Biedl syndrome 1, modifier of	209900
CCDC41	CEP83	Coiled-coil domain containing 41	Tailler AJHGAR 4(6):905, 2014	Nephronophthisis 18	615862
CCND1		Cyclin D1	Wu The Journal ofAD rology, 172(6 Pt 1), 410–2413, 2004	Renal cell carcinoma	168461
CDC73		Cell division cycle 73	Teh J. Clin. Endocr.AD Metab. 81: 4204-4211, 996	Parathyroid adenoma with cystic changes	607393
CEP120	SRTD13	Centrosomal protein 20kDa	Shaheen Hum MolAR Genet 24(5):1410, 015	Short-rib thoracic dysplasia 13 with or without polydactyly, Joubert syndrome 31	616300, 617761
CEP41	TSGA14	Centrosomal protein 41kDa	Lee Nat GenetAR 4(2):193, 2012	Joubert syndrome 15	614464

COL4A1		Collagen, type IV, alpha-1	Plaisier New Eng. J. Med. 357: 2687-2695, 2007	AD	Angiopathy, hereditary, with nephropathy, aneurysms, and muscle cramps; hematuria, renal cysts	120130
CPT2		Carnitine	Zinn Pediat. Res. 29 (suppl.): 73A only, 1991	AD/AR	CPT II Deficiency	600650
ODDX59	OFD5	Orofaciodigital syndrome	Shamseldin AJHG 93(3):555, 2013	AR	Orofaciodigital syndrome V	174300
DYNC2H1	SRTD3	Dynein cystoplasmic 2 heavy chain	El Hokayem J Med Genet 49(4):227, 2012	AR	Short-rib thoracic dysplasia 3 with or without polydactyly	613091
FAN1	MTMR15	FANCI-associated nuclease 1	Zhou Nat Genet 44(8):910, 2012	AR	Interstitial nephritis, karyomegalic	614817
GANAB		Glucosidase, alpha, neutral AB	Porath Am. J. Hum. Genet. 98: 1193-1207, 2016	AD	Polycystic kidney disease 3	104160
GLIS3		GLIS family zinc finger protein 3	Taha Am. J. Med. Genet. 122A: 269-273, 2003	AR	Diabetes mellitus, neonatal, with congenital hypothyroidism	610192
HOXA4		Heomobox A4	Acampora Nucleic Acids Res 17(24):10385, 1985	AD	NA	142953
HOXB6		Heomobox B6	Kaur J Exp Zool 264(3):323, 1992	AD	NA	142961
HSD17B4		17-Beta-Hydroxysteroid dehydrogenase IV	Ferdinandusse Am. J. Hum. Genet. 78: 112-124, 2006	AR	D-bifunctional protein deficiency; renal cysts, adrenal cortex atrophy	601860
IFT43	CED3	Intraflagellar transport 43	Gilissen AJHG 87(3):418, 2010	AR	Cranioectodermal dysplasia 3	614099
IFT52	SRTD	Intraflagellar Transport 52	Girisha Clin Genet 90(6):536, 2016	AR	Short-rib thoracic dysplasia 16 with or without polydactyly	617102
IFT57		Intraflagellar Transport 57	Bruel J Med Genet 54(6):371, 2017	AR	Orofaciodigital syndrome XVIII	617927
IFT80	SRTD2	Intraflagellar Transport 80	Beales Nat Genet 39(6):727 2007	AR	Short-rib thoracic dysplasia 2 with or without polydactyly	611263
IFT81	CDV-1	Intraflagellar Transport 81	Perrault J Med Genet 52(10):657, 2015	AR	Short-rib thoracic dysplasia 19 with or without polydactyly	605489

FT122	CED1	ntraflagellar transport 122	Valczak-Sztulpa 36(6):949, 2010	AJHG	Cranioectodermal lysplasia 1	# 218330
FT140	SRTD9	ntraflagellar transport 140	Perrault 90(5):864, 2012 Senum AJHG 109(1):136-135	AJHG	Short-rib thoracic lysplasia 9 with or without polydactyly utosomal dominant olycystic idney-spectrum	# 266920 n/a
BTS1	NPP5E	nositol olyphosphate-5-phosphat se	Bielas Nat Genet 41(9):1032, 2009	NatR	oubert syndrome 1	# 213300
BTS2	TMEM216	ransmembrane Protein 16	dvardson 36(1):93, 2010	AJHG	Meckel syndrome 2, oubert syndrome 2	# 603194 # 608091
BTS3	tHI1	tbelson Helper ntegration Site 1	Parisi J Med Gen 43(4):334 ,2005	NatR	oubert syndrome 3	# 608629
BTS8	tRL13B	tDP-ribosylation actot-like 13B	Cantagrel 43(2):170, 2008	AJHG	oubert syndrome 8	# 612291
BTS9	C2D2A	Coiled-coil and C2 lomains-containing rotein 2A	Noor 82(4):1011, 2008	AJHG	oubert syndrome 9 Meckel syndrome 6 COACH syndrome	# 612285, # 612284, # 216360
BTS12	KIF7	Kinesin family member 7	Putoux Nat Genet 43(6):601, 2011	NatR	crocallosal syndrome oubert syndrome 12	# 200990
BTS13	CTN1	ectonic family member 1	Garcia-Gonzalo Nat Genet 43(8):776, 2011	NatR	oubert syndrome 13	# 614173
BTS14	TMEM237	ransmembrane protein 37	Huang 89(6):713, 2011	AJHG	oubert syndrome 14	# 614424
BTS16	TMEM138	ransmembrane protein 38	ee Science 335(6071):66, 2012	NatR	oubert syndrome 16	# 614465
BTS17	C5orf42	Chromosome 5 open eading frame 42	rour AJHG 90(4):693, 012	AJHG	oubert syndrome 17	# 614615
BTS18	CTN3	ectonic family member 3	Thomas 91(2):372, 2012	AJHG	oubert syndrome 18	# 614815
BTS20	TMEM231	ransmembrane protein 31	rour J Med Genet 49:636-641, 2012	NatR	oubert syndrome 20 Meckel syndrome 11	# 614970, # 615397
BTS21	CSPP1	Centrosome spindle ole-associated protein 1	kizu AJHG 94(1):80, 014	AJHG	oubert syndrome 21	# 615636
BTS22	PDE6D	Phosphodiesterase 6D	Thomas Hum Mutat 35(1):137, 2014	NatR	oubert syndrome 22	# 615665

BTS23	KIAA0586	ALPID 3, chicken omolog of	Bachmann-Gagescu R Hum Mutat 36(9):831, 2015	oubert syndrome 23	# 616490
BTS24	TCTN2	ectonic family member 2	Huppke Eur J Hum Genet 23(5):616, 2015	oubert syndrome 24	# 616654
BTS25	CEP104	entrosomal protein 1kDa	Korvatska Am J Med Genet B Neuropsychiatr Genet 156B(3):303, 2011	oubert syndrome 25	# 616781
BTS26	KIAA0556	atanin-intereacting rotein	Saunders Genome Biol 16:293, 2015	oubert syndrome 26	#614175
KIAA0753	OFD15	rofaciodigital syndrome 15	Thevrier Hum Mol Genet 25(3):497, 2016	rofaciodigital syndrome V	# 617127
KIF14	MKS12	inesin family member 14	Filges Clin Genet 86(3):220, 2013	Meckel syndrome 12	# 616258
MKS1		Meckel syndrome, type 1	Kyttälä Nat Genet 38(2):155, 2006	Meckel syndrome 1 oubert syndrome 28 Bardet-Biedl syndrome 13	# 249000, # 617121, # 615990
NEK1	SRTD6	NIMA Related Kinase 1	Thiel AJHG 88(1):106, 2011	Short-rib thoracic ysplasia 6 with or without polydactyly	# 263520
NPHP1		Nephrocystin 1	Hildebrandt Nat Genet 17(2):149, 1997	uvenile nephronophthisis oubert syndrome 4 Senior-Loken syndrome-1	# 256100 # 609583 # 266900
NPHP2	INVS	nversin	Otto Nat Genet 34(4):413, 2003	nfantile nephronophthisis	# 602088
NPHP3		Nephrocystin 3	Olbrich Nat Genet 34(4):455, 2003	Nephronophthisis 3 Meckel syndrome Renal-hepatic-pancreatic ysplasia 1	# 604387 # 267010 # 208540
NPHP4		Nephronophthisis 4	Otto AJHG 71(5):1161, 2002	Nephronophthisis 4 Senior-Loken syndrome 4	# 606966
NPHP5	IQCB1	Q motif containing B1	Otto Nat Genet 37(3):282, 2005	Senior-Loken syndrome 5	# 609254
NPHP6	CEP290	entrosomal protein 290kDa	Sayer Nat Genet 38(6):674, 2006	oubert syndrome 5 Bardet-Biedl syndrome 14 Meckel syndrome 4	# 610188 # 615991 # 610189
NPHP7	GLIS2	GLIS Family Zinc Finger 2	Attanasio Nat Genet 39(8):1018, 2007	Nephronophthisis 7	# 611498

NPHP8	RPGRIP1 L	RPGRIP1 Like	Arts Nat Genet 39(7):882, 2007	R	Meckel syndrome 5 Joubert syndrome 7 COACH syndrome	# 611561, # 611560, # 216360
NPHP9	NEK8	NIMA (never in mitosis gene a) - related kinase 8	Otto JASN 19(3):587, 2008	R	Renal-hepatic-pancreatic dysplasia 2 Nephronophthisis 9	# 615415 # 613824
NPHP10	SDCCAG8	Serologically Defined Colon Cancer Antigen 8	Otto Nat Genet 42(10):840, 2010	R	Bardet-Biedl syndrome 16 Senior-Loken syndrome 7	# 615993 # 613615
NPHP11	TMEM67	Transmembrane Protein 67	Otto J Med Genet 46(10):663, 2009	R	COACH syndrome, Nephronophthisis 11	# 216360 # 613550
NPHP12	TTC21B	Tetratricopeptide Repeat Domain 21B	Davis Nat Genet 43(3):189, 2011	R	Nephronophthisis 12	# 613820
NPHP13	WDR19	WD repeat domain 19	Bedrup AJHG 89(5):634, 2011	R	Nephronophthisis 13 Senior-Loken syndrome 8	# 614377 # 616307
NPHP14	ZNF423	Zinc finger protein 423	Chaki Cell 150(3):533, 2012	R	Nephronophthisis 14 Joubert syndrome 19	# 614844
NPHP15	CEP164	Centrosomal protein 164kDa	Chaki Cell 150(3):533, 2012	R	Nephronophthisis 15	# 614845
NPHP16	ANKS6	Ankyrin repeat and sterile alpha motif domain containing 6	Hoff Nat Genet 45(8):951, 2013	R	Nephronophthisis 16	# 615382
NPHP17	IFT172	Intraflagellar transport 172 homolog, (Chlamydomonas)	Halbritter AJHG 93(5):915, 2013	R	Short-rib thoracic dysplasia 10 with or without polydactyly	# 615630
NPHP19	DCDC2	Double-cortin domain containing protein 2	Schueler AJHG 96(1):81, 2015	R	Nephronophthisis 19	# 616217
NPHP20	MAPKBP 1	Mitogen activated protein kinase-binding protein 1	Macia AJHG 100(2):323, 2017	R	Nephronophthisis 20	# 617271
NPHPL1	GPNPEP3	Glycyl-prolyl aminopeptidase 3	O'Toole J Clin Invest 120(3):791, 2010	R	Nephronophthisis-like nephropathy 1	# 613159
PKHD1	ARPKD	PKHD1, Fibrocystin/Polyductin	Bergmann Kidney Int 67(3):829 2005	R	Polycystic kidney disease 1 with or without hepatic disease	# 263200
POC1B		Cone rod dystrophy 20	Roosing AJHG 95(2):131, 2014	R	Cone-rod dystrophy 20	# 615973
SCLT1	OFD9	Orofaciodigital syndrome 9	Idly Hum Mutation 35(1): 36, 2013	R	Orofaciodigital syndrome X	# 258865
SLC41A1		Solute carrier member family 41, member 1	Hurd JASN 24(6):967, 2013	R	NA	# 610801

TMEM107	MKS13	Transmembrane Protein 107	Shasheen Hum Mol Genet 24(18):5211, 2015	AR	Meckel syndrome 13 Joubert syndrome 29	617562
TRAF3IP1	ILS9	TNF receptor-associated factor 3-interacting protein 1	Serbari Dev Biol 360(1):66, 2011	AR	Senior-Loken syndrome 9	616629
USH2A		Usherin 2A	Smith Genomics 14(4):995, 1992	AR	Usher syndrome type 2A	276901
VDR34	SRTD11	VD Repeat Domain 34	Schmidts AJHG 93(5):932, 2013	AR	Short-rib thoracic dysplasia 11 with or without polydactyly	615633
VDR35	CED2	VD repeat domain 35	Gilissen AJHG 87(3):418, 2010	AR	Cranioectodermal dysplasia 2	613610
VDR60	SRTD8	VD Repeat Domain 60	McInerney-Leo AJHG 93(3): 515, 2013	AR	Short-rib thoracic dysplasia 8 with or without polydactyly	615503
ALG5		ALG5 Dolichyl-Phosphate Beta-Glucosyltransferase	Lemoine Am J Hum Genet 109:1484, 2022	AD	Polycystic Kidney Disease 7	620056
LRP5		Low density lipoprotein receptor-related protein 5	Gnossen proc Natl Acad Sci U S A 111:5343, 2014	AD	Polycystic liver disease 4 with or without kidney disease	617875
MBTPS2		Membrane-bound transcription Factor Protease, Site 2	Zeligman Arch Dermatol 80:413, 1959	AD	FAP Syndrome 1, with or without Bresheck Syndrome	308205
SEC63		SEC63 Homolog, Protein Translocation regulator	Gnossen Orphant J Rare Dis 1:69, 2014	AD	Polycystic liver disease 2	617004
PRKCSH		Protein Kinase C Substrate, 80-KD, Heavy Chain	Gerrebi Clin Genet 21:342, 1982	AD	Polycystic liver disease 1	174050
TBC1D32		TBC1 Domain Family Member 32	Idly Hum Mutat 35:36, 2014	AD	NA	615867
EVC		EvC Ciliary Complex Subunit 1	Ruiz-Perez Nat Genet. 24(3):283, 2000	AR/AD	Ellis-van Creveld Syndrome	225500
EVC2		EvC Ciliary Complex Subunit 2	Xurian Indian J Dent Res. 18(1):31, 2007	AR/AD	Ellis-van Creveld Syndrome	225500
OFD1		Orofaciodigital syndrome	Feather Hum Mol Genet 6(7):1163, 1997	XLD	Orofaciodigital syndrome	311200

*AR, autosomal recessive; AD, autosomal dominant; DR, digenic recessive; NA, not available; OMIM, Online Mendelian Inheritance in Man; XLD; X-linked dominant; XL; X-linked; #, phenotype MIM number; * gene/ locus MIM number if not phenotype MIM number available.*

Supplementary Table S2: genes that represent monogenic causes of human nephrotic syndrome, if mutated.

Gene	*Protein*	*Reference*	*Mode of inheritance*	*Phenotype*	*OMIM number*
ADCK4	*ActarF domain containing kinase 4*	*Ashraf J Clin Invest 123:5179, 2013*	*AR*	*Nephrotic syndrome, type 9*	*# 615567*
ALG1	*ALG1, Chitobiosyldiphosphodolichol Beta-Mannosyltransferase*	*Harshman Pediatr Int 58:785, 2016*	*AR*	*Congenital disorder of glycosylation type Ik*	*# 608540*
ARHGDIA	*Rho GDP dissociation inhibitor (GDI) alpha*	*Gee J Clin Invest 123:3243, 2013*	*AR*	*Nephrotic syndrome, type 8*	*# 615244*
AVIL	*Advillin*	*Rao J Clin Invest 127:4257, 2017*	*AR*	*NA*	** 613397*
CD2AP	*CD2 associated protein*	*Kim Science 300:1298, 2003*	*AR*	*Glomerulosclerosis, focal segmental, 3*	*# 607832*
COQ2	*Coenzyme Q2 4-hydroxybenzoate polyprenyltransferase*	*Diomedi-Camassei JASN 18:2773, 2007*	*AR*	*Primary coenzyme Q10 deficiency 1*	*# 607426*
COQ6	*Coenzyme Q6 monooxygenase*	*Heeringa J Clin Invest 121:2013, 2011*	*AR*	*Primary coenzyme Q10 deficiency 6*	*# 614650*
CUBN	*Cubilin (intrinsic factor-cobalamin receptor)*	*Ovunc JASN 22:1815, 2011*	*AR*	*Megaloblastic anemia-1, Finnish type*	*# 261100*
CRB2	*Crumbs, Drosphilia, Homolog of 2*	*Ebarasi AJHG 96: 153-161, 2015*	*AR*	*Focal segmental glomerulosclerosis 9*	*# 616220*
DGKE	*Diacylglycerol kinase epsilon*	*Lemaire Nat Genet 45: 531, 2013*	*AR*	*Nephrotic syndrome, type 7*	*# 615008*
EMP2	*Epithelial membrane protein 2*	*Gee AJHG 94:884, 2014*	*AR*	*Nephrotic syndrome, type 10*	*# 615861*
FAT1	*Fat tumor suppressor, Drosphila, homolog of, 1*	*Gee Nat Commun 7:10822, 2016*	*AR*	*NA*	** 600976*
ITGA3	*Integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)*	*Falcin Hum Mol Genet 24:3679, 2015*	*AR*	*Congenital interstitial lung disease, nephrotic syndrome, and epidermolysis bullosa*	*# 614748*

ITGB4	Integrin, beta 4	Kambham AJKD 36:190, 2000	AR	Epidermolysis bullosa	# 226730
KANK1	KN motif and ankyrin repeat domain-containing protein 1	See J Clin Invest 125:2375, 2015	AR	Cerebral palsy, spastic quadriplegic,	# 612900
KANK2	KN motif and ankyrin repeat domain-containing protein 2	See J Clin Invest 125:2375, 2015	AR	Nephrotic syndrome, type 16	# 617783
KANK4	KN motif and ankyrin repeat domain-containing protein 3	See J Clin Invest 125:2375, 2015	AR	NA	* 614612
LAGE3	L antigen family member 3	Braun Nat Genet 49:1529, 2017	AR	Galloway-Mowat syndrome 2, X-linked	# 301006
LAMB2	Laminin, beta 2	Zenker Hum Mol Genet 12:2625, 2004	AR	Nephrotic syndrome, type 5, with or without ocular abnormalities	# 614199
LCAT	Lecithin-Cholesterol Acyltransferase	Taramelli Hum Genet 85:195, 1990	AR	Norum disease	# 245900
MAGI2	Membrane-associated guanylate kinase, WW and PDZ domains-containing 2	Sierzynska JASN 28:1614, 2017	AR	Nephrotic syndrome, type 15	# 617609
MYO1E	Homo sapiens myosin IE (MYO1E)	Mele NEJM 365:295, 2011	AR	Glomerulosclerosis, focal segmental, 6	# 614131
NEU1	Neuraminidase 1	Mütze Genet Metab Rep 10:1-4, 2016	AR	Sialidosis	# 256550
NPHS1	Nephrin	Kestila Mol Cell 1:575, 1998	AR	Nephrotic syndrome, type 1	# 256300
NPHS2	Podocin	Boute Nat Genet 24:349, 2000	AR	Nephrotic syndrome, type 2	# 600995
NUP107	Nucleoporin, 107-KD	Miyake AJHG 97:555, 2015	AR	Nephrotic syndrome, type 11	# 616730
NUP133	Nucleoporin 133-KD	Braun Nat Gene 48:457, 2016	AR	NA	* 607613
NUP205	Nucleoporin, 205-KD	Braun Nat Gene 48:457, 2016	AR	Nephrotic syndrome, type 13	# 616893
NUP85	Nucleoporin 85-KD	Braun Nat Gene 48:457, 2016	AR	NA	* 170285
NUP93	Nucleoporin, 93-KD	Braun Nat Gene 48:457, 2016	AR	Nephrotic syndrome, type 12	# 616892
OSGEP	O-sialoglycoprotein endopeptidase	Braun Nat Genet 49:1529, 2017	AR	Galloway-Mowat syndrome 3	# 617729
PDSS2	Prenyl (decaprenyl) diphosphate synthase, subunit 2	Lopez AJHG 79:1125, 2006	AR	Primary coenzyme Q10 deficiency 3	# 614652

PLCE1	Phospholipase C, epsilon 1	Hinkes Nat Genet 38:1397, 2006	AR	Nephrotic syndrome, type 3	610725
PTPRO	Protein tyrosine phosphatase, receptor type, O	Ozaltin AJHG 89:139, 2011	AR	Nephrotic syndrome, type 6	614196
SCARB2	Scavenger receptor class B, member 2	Wadhwar Brain 127: 2173, 2004	AR	Epilepsy, progressive myoclonic 4, with or without renal failure	254900
SGPL1	Sphingosine 1 phosphate lyase 1	Lovric J Clin Invest 127: 912, 2017	AR	Nephrotic syndrome, type 14	617575
SMARCAL1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a-like 1	Boerkoel Nat Genet 30:215, 2002	AR	Schimke immunoosseous dysplasia	242900
TP53RK	TP53-regulating kinase	Braun Nat Genet 49:1529, 2017	AR	Galloway-Mowat syndrome 4	617730
TPRKB	TP53RK binding protein	Braun Nat Genet 49:1529, 2017	AR	Galloway-Mowat syndrome 5	617731
TTR	Transthyretin	Indo Biochem Biophys Res Commun 211:354, 1995	AR	Hereditary transthyretin-related amyloidosis	105210
VPS33B	VPS33B, Late Endosome and Lysosome Associated	Gissen Nat Genet 38:1214, 2006	AR	NA	608552
WDR73	WD repeat-containing protein 73	Colin AJHG 95:637, 2014	AR	Galloway-Mowat syndrome 1	251300
XPO5	Exportin 5	Braun Nat Genet 48:457, 2016	AR	NA	607845
ACTN4	Actinin, alpha 4	Kaplan Nat Genet 24(3):251, 2000	AD	Glomerulosclerosis, focal segmental 1	603278
ANLN	Actin-binding protein anillin	Gbadegesin JASN 25:1991, 2014	AD	Focal segmental glomerulosclerosis 8	616032
APOA1	Apolipoprotein A-1	Nichols Genomics 8:318, 1990	AD	Multiple classifications	107680
ARHGAP24	Rho GTPase activating protein 24	Akilesh J Clin Invest 121:4127, 2011	AD	NA	610586
INF2	Inverted formin, FH2 and WH2 domain containing	Brown Nat Genet 42:72, 2010	AD	Glomerulosclerosis, focal segmental, 5	613237
LMX1B	LIM Homeobox Transcription Factor 1 Beta	Dreyer Nat Genet 19:47 1998	AD	Nail-patella syndrome	161200
MEFV	MEFV Innate Immunity Regulator, Pyrin	Bergman Am J Med 45:601, 1968	AD	Familial Mediterranean fever, AD	134610

MYH9	Myosin heavy chain 9, nonmuscle	Heath AJHG 69:1033, 2001	AD	Macrothrombocytopenia and granulocyte inclusions with or without nephritis or sensorineural hearing loss	# 155100
PODXL	Podocalyxin	Barua Kidney Int 85:124, 2014	AD	NA	* 602632
SLC37A4	Solute Carrier Family 37 (Glucose-6-Phosphate Transporter), Member 6	Nordlie J Biol Chem 258:9739, 1983		Glycogen storage disease Ic	# 232240
TRPC6	Transient receptor potential cation channel, subfamily C, member 6	Winn Science 308:1801, 2005	AD	Glomerulosclerosis, focal segmental, 2	# 603965
WT1	Wilms Tumor 1	Melo J Clin Endocrinol Metab 87:2500, 2002	AD	Frasier syndrome	# 136680
IKBKAP	Inhibitor of kappa light polypeptide gene enhancer in B cells, kinase complex associated protein	Anderson AJHG 68:753, 2001	AR/AD	Familial dysautonomia	# 223900
NXF5	Nuclear RNA export factor 5	Esposito Hum Mol Genet 12:3654, 2013	XL	NA	* 300319
APOE	Apolipoprotein E	Oikawa JASN 8:820, 1997	CL	Multiple classifications	* 107741
APOL1	Apolipoprotein L-1	Parsa NEJM 369:2183, 2013	Unknown	Susceptibility to nondiabetic end-stage renal disease, Susceptibility to focal segmental glomerulosclerosis 4	# 612551
GPC5	Glypican 5	Okamoto Nat Genet 43:459, 2011	Unknown	NA	* 602446
SYNPO	Synaptopodin	Bierzynska Kidney Int 91:937, 2017	Unknown	NA	* 608155
LPIN1	Lipin1	Christensen Danish Med. Bull. 30: 112-115, 1983	AR	Myoglobinuria, acute recurrent, autosomal recessive; renal failure	
KCNJ5	Potassium channel, inqardly rectifying, subfamily J, member 5	Mulatero Hypertension 59:235-240, 2012	AD	Hyperaldosteronism, familial, type III	600734
AMN	Amnion-associated transmembrane protein	De Filipo Ital. J. Pediat. 39: 58, 2013	AR	Amerslund-Grasbeck syndrome 2	605799

APOC2	Apolipoprotein C-II	Kashyap Atherosclerosis, 35(1), 9–40, 1980	AR	Nephrotic syndrome 8	608083
G6PC1	Glucose-6-Phosphatase Catalytic Subunit 1	Karthi Gene, 700, 7–16, 2019	AR	Glycogen storage disease Ia	NA
COQ8B	Coenzyme Q8B	Ashraf J. Clin. Invest. 123: 5179-5189, 2013	AR	Nephrotic syndrome, type 9	615567
ALG13	ALG13 UDP-N-Acetylglucosaminyltransferase subunit	Esposito Human molecular genetics, 22(18), 3654–3666, 2013	XLR	Focal segmental glomerulosclerosis	300776
C6	Complement component 6	Leddy J. Clin. Invest. 53: 544-553, 1974	AR	C6 deficiency	217050
ELP1	Elongator complex protein 1	Anderson Am J Hum Genet. 68(3):753–758, 2001	AD/AR	Dysautonomia, familial	603722

*AR, autosomal recessive; AD, autosomal dominant; Unknown, mode of inheritance not clearly characterized; NA, not available; OMIM, Online Mendelian Inheritance in Man; XL; X-linked; #, phenotype MIM number; * gene/ locus MIM number if not phenotype MIM number available; +, gene and phenotype combined.*

Supplementary Table S3: genes that represent monogenic causes of human isolated CAKUT, if mutated.

Gene	Protein	Reference	Mode of inheritance	Phenotype	OMIM #
ACE	Angiotensin I-converting enzyme	Gribouval Nat Genet 37:964, 2005	AR	Renal tubular dysgenesis	# 267430
AGT	Angiotensinogen	Gribouval Nat Genet 37:964, 2005	AR	Renal tubular dysgenesis	# 267430
AGTR1	Angiotensin II receptor, type 1	Gribouval Nat Genet 37:964, 2005	AR	Renal tubular dysgenesis	# 267430
CHRM3	Muscarinic acetylcholine receptor M3	Weber AJHG 19:634, 2011	AR	Prune belly syndrome	# 100100
ETV4	ETS translocation variant 4, E1A enhancer binding protein	Chen IJPCH 4:61, 2016	AR	NA	* 600711
FRAS1	Extracellular matrix protein FRAS1	Kohl JASN 25:1917, 2014	AR	Fraser syndrome 1	# 219000
FREM1	FRAS1 related extracellular matrix protein 1	Kohl JASN 25:1917, 2014	AR	Manitoba oculotrichoanal syndrome	# 248450
FREM2	FRAS1 related extracellular matrix protein 2	Kohl JASN 25:1917, 2014	AR	Fraser syndrome 2	# 617666
GRIP1	Glutamate receptor interacting protein 1	Kohl JASN 25:1917, 2014	AR	Fraser syndrome 3	# 617667
HPSE2	Heparanase 2 (Inactive)	Bulum Nephron 130:54, 2015	AR	Urofacial syndrome 1	# 236730

ITGA8	Integrin α8	Humbert AJHG 89:1260, 2014	Renal hypodysplasia/ aplasia 1	# 191830
REN	Renin	Gribouval Nat Genet 47:964, 2005	Renal tubular dysgenesis	# 267430
TRAP1	Heat-shock protein 75 (also known as TNF receptor-associated protein 1)	Chaisawat Kid Int 85:880, 2014	NA	* 606219
FGF20	Fibroblast Growth Factor 20	Barak Dev Cell 22:1191, 2012	Renal hypodysplasia/ aplasia 2	# 615721
BMP4	Bone morphogenic protein 4	Weber JASN 19:891, 2008	Microphthalmia, syndromic 6	# 607932
CHD1L	Chromodomain helicase DNA binding protein 1-like	Brockschmidt NDT 27:2355, 2012	NA	* 613039
CRKL	CRK Like Proto-Oncogene, adaptor protein	Lopez-Rivera NEJM 376:742, 2017	NA	* 602007
DSTYK	Dual serine/threonine and tyrosine protein kinase	Ganna-Cherchi NEJM 369:621, 2013	Congenital anomalies of kidney and urinary tract 1	# 610805
EYA1	Eyes absent homolog 1	Abdelhak Nat Genet 15:157, 1997	Branchiootorenal syndrome 1, with or without cataracts	# 113650
GATA3	GATA binding protein 3	Pandolfi Nat Genet 11:40, 1995; Van Esch Nature 406:419, 2000	Hypoparathyroidism, sensorineural deafness, and renal dysplasia	# 146255
GREB1L	Growth Regulation By Estrogen In Breast Cancer 1 Like	Trophy Genetics 2017, 07:215, Ganna-Cherchi AJHG 101:1034, 2017	Renal hypodysplasia/ aplasia 3	# 617805
HNF1B	HNF homeobox B	Lindner Hum Mol Genet 4:263, 1999	Renal cysts and diabetes syndrome	# 137920
MUC1	Mucin 1	Kirby Nat Genet 45:299, 2013	Medullary cystic kidney disease 1	# 174000
NFIA	Nuclear Factor 1/A	Rao Eur J Med Genet 57:65, 2014	Brain malformations with or without urinary tract defects	# 613735

NRIP1	Nuclear Receptor Interacting Protein 1	Tivante JASN 28:2364, 2017	NA	# 602490
PAX2	Paired box 2	Sanyanusin Hum Mol Genet 4:2183, 1995	Papillorenal syndrome	# 120330
PBX1	PBX Homeobox 1	Heidet JASN 28:2901, 2017	Congenital anomalies of kidney and urinary tract syndrome with or without hearing loss, abnormal ears, or developmental delay	# 617641
PPP3CA	Protein Phosphatase 3, Catalytic Subunit, Alpha Isoform	Mizuguchi Hum Mol Genet 27:1421, 2018	Arthrogryosis, cleft palate, craniosynostosis, and impaired intellectual development	
RET	Proto-oncogene tyrosine-protein kinase receptor Ret	Skinner AJHG 82:344, 2008	Multiple OMIM classifications	# 164761
ROBO2	Roundabout, axon guidance receptor, homolog 2 (Drosophila)	Hwang Hum Genet 134:905, 2015; Lu AJHG 80:616, 2007	Vesicoureteral reflux 2	# 610878
SALL1	Sal-like protein 1 (also known as Spalt-like transcription factor 1)	Kohlhase Nat Genet 18:81, 1998	Townes-Brocks syndrome 1	# 107480
SIX1	SIX homeobox 1	Ruf PNAS 101: 8090, 2004	Branchio-otic syndrome 3	# 608389
SIX2	SIX homeobox 2	Weber JASN 19:891, 2008	NA	# 604994
SIX5	SIX homeobox 5	Hoskins AJHG 80:800, 2007	Branchiootorenal syndrome 2	# 610896
SLIT2	Slit homolog 2	Hwang Hum Genet 134:905, 2015	NA	# 603746
SOX17	Transcription factor SIX-17	Gimelli Hum Mut 31:1352, 2010	Vesicoureteral reflux 3	# 613674
SRGAP1	SLIT-ROBO Rho GTPase activating protein 1	Hwang Hum Genet 134:905, 2015	NA	# 606523
TBX18	T-Box transcription factor	Tivante AJHG 97:291, 2015	Congenital anomalies of kidney and urinary tract 2	# 143400

TNXB	*Tenascin XB*	*Gbadegesin JASN 24:1313, 2013*	*Vesicoureteral reflux 8*	*615963*
JPK3A	*Jroplakin 3A*	*Jenkins JASN 16:2141, 2005*	*NA*	*611559*
WNT4	*Protein Wnt-4*	*Biason-Lauber NEJM 351:792, 2004; Mandel AJHG 82:39, 2008; Vivante JASN 24:550, 2013*	*Mullerian aplasia and hyperandrogenism*	*158330*
KAL1	*Anosmin 1*	*Hardelin PNAS 89:8190, 1992*	*Hypogonadotropic hypogonadism 1 with or without anosmia Kallmann syndrome 1)*	*308700*
FAM58A	*Family with Sequence Similarity 58 Member A*	*Unger Nat Genet 40:287, 2008*	*Toe Syndactyly, Telecanthus, and Anogenital and Renal Malformations*	*300707*

*AR, autosomal recessive; AD, autosomal dominant; NA, not available; OMIM, Online Mendelian Inheritance in Man; XL; X-linked; #, phenotype MIM number; * gene/ locus MIM number if not phenotype MIM number available.*

Supplementary Table S4: genes that represent monogenic causes of human syndromic CAKUT, if mutated.

Gene	Protein	Reference	Mode of inheritance	Phenotype	OMIM number
B3GALTL	Beta 3-Glucosyltransferase	Lesnik Oberstein *AJHG* 79:562, 2006	AR	Peters-plus syndrome	# 261540
BSCL2	BSCL2, Seipin Lipid Droplet Biogenesis Associated	Haghighi *Clin Genet* 89:34, 2016	AR	Multiple classifications	# 608594 # 269700 # 600794 # 615924 # 270685
CD151	CD151 Molecule (Raph Blood Group)	Karamatic *Blood* 104:2217, 2004	AR	NA	* 602243
CD96	CD96 Molecule	Kaname *AJHG* 81:835, 2007	AR	C syndrome	# 211750
CHRNG	Cholinergic Receptor Nicotinic Gamma Subunit	Vogt *J Med Genet* 49:21, 2012	AR	Escobar syndrome	# 265000
CISD2	CDGSH Iron Sulfur Domain 2	Amr *AJHG* 81:673, 2007	AR	Wolfram syndrome 2	# 604928

CTU2	Cytosolic Thiouridylase, subunit 2	Shaheen *AJMG* 170:3222, 2016	AR	Microcephaly, facial dysmorphism, renal agenesis, and ambiguous genitalia syndrome	618142
CYP21	Cytochrome P450 Family 21	Martul *Arch Dis Child* 55:324, 1980	AR	Hyperandrogenism, nonclassic type, due to 21-hydroxylase deficiency	201910
DACH1	Dachshund Family Transcription Factor 1	Schild *NDT* 28:227, 2013	AR	NA	603803
DHCR7	7-Dehydrocholesterol Reductase	Löffler *AJHG* 13;95:174, 2000	AR	Smith-Lemli-Opitz syndrome	270400
DIS3L2	DIS3 Like 3'-5' Exoribonuclease 2	Astuti *Nat Genet* 44:277, 2012	AR	Perlman syndrome	267000
EMG1	EMG1, N1-Specific Pseudouridine Methyltransferase	Armistead *AJHG* 84:728, 2009	AR	Bowen-Conradi syndrome	211180
ERCC8	Excision repair cross-complementing, group 8	Bertola *J Hum Genet* 51:701, 2006	AR	Cockayne syndrome, type A	216400
ESCO2	Establishment Of Sister Chromatid Cohesion N-Acetyltransferase 2	Vega *J Med Genet* 47:30, 2010	AR	Roberts syndrome	268300
ETFA	Electron Transfer Flavoprotein Alpha Subunit	Lehnert *Eur J Pediatr* 39:56, 1982	AR	Glutaric acidemia IIA	231680
ETFB	Electron Transfer Flavoprotein Beta Subunit	Lehnert *Eur J Pediatr* 39:56, 1982	AR	Glutaric acidemia IIB	231680
ETFDH	Electron Transfer Flavoprotein Dehydrogenase	Lehnert *Eur J Pediatr* 39:56, 1982	AR	Glutaric acidemia IIC	231680
FANCA	Fanconi Anemia Complementation Group A	Joenje & Patel *Nat Rev Genet* 2:466, 2001	AR	Fanconi anemia, complementation group A	227650
FANCB	Fanconi Anemia Complementation Group B	McCauley *AJMG* 55A:2370, 2011	AR	Fanconi anemia, complementation group B	300514
FANCD2	Fanconi Anemia Complementation Group D2	Kalb *AJHG* 80:895, 2007	AR	Fanconi anemia, complementation group D2	227646
FANCE	Fanconi Anemia Complementation Group E	Wegner *Clin Genet* 50:479, 1996	AR	Fanconi anemia, complementation group E	600901

FANCI	Fanconi Anemia Complementation Group I	Savage *AJMG* 170A:386, 2015	AR	Fanconi anemia, complementation group I	609053
FANCL	Fanconi Anemia Complementation Group L	Petro *Hum Mutat* 36:562, 2015	AR	Fanconi anemia, complementation group L	614083
FAT4	FAT Atypical Cadherin 4	Alders *Hum Genet* 33:1161, 2014	AR	Van Maldergem syndrome 2	615546
FOXP1	Forkhead Box P1	Bekheirnia *Genet Med* 9:412, 2017	AR	NA	605515
HES7	Hes Family BHLH Transcription Factor 7	Sparrow *Hum Mol Genet* 17:3761, 2008	AR	NA	608059
HYLS1	HYLS1, Centriolar And Ciliogenesis Associated	Paetau *J Neuropathol Exp Neurol* 67:750, 2008	AR	Hydrolethalus syndrome	236680
ICK	Intestinal cell kinase	Lahiry *AJHG* 84:822, 2009	AR	NA	612325
IFT46	Intraflagellar Transport 46	Lee *Dev Biol* 400:248, 2015	AR	Short-rib thoracic dysplasia 16 with or without polydactyly	617102
IFT74	Intraflagellar Transport 74	Cevik *PLoS Genet* 9:e1003977, 2013	AR	Bardet-Biedl syndrome 20	617119
ITGA3	Integrin Subunit Alpha 3	Falcin *Hum Mol Genet* 24:3679, 2015	AR	Interstitial lung disease, nephrotic syndrome, and epidermolysis bullosa, congenital	614748
JAM3	Junctional Adhesion Molecule 3	Mochida *AJHG* 0;87:882, 2010	AR	Hemorrhagic destruction of the brain, subependymal calcification, and cataracts	613730
LMNA	Lamin A/C	Klupa *Endocrine* 36:518, 2009	AR	Multiple OMIM classification	150330
LRIG2	Leucione rich repeats and Immunoglobulin like domains containing protein 2	Stuart *AJHG* 92:259, 2013	AR	Urofacial syndrome 2	615112
LRP2	LDL Receptor Related Protein 2	Kantarci *Nat Genet* 39:957, 2007	AR	Donnai-Barrow syndrome	222448
LRP4	LDL Receptor Related Protein 4	Li Am *J Hum Genet* 86:696, 2010	AR	Cenani-Lenz syndactyly syndrome	212780

MESP2	Mesoderm Posterior BHLH Transcription Factor 2	George-Abraham *AJMG* A 158A:1971, 2012	AR	NA	605195
MKS3	Meckel Syndrome Type 3 Protein	Baala *AJHG* 80:186, 2007	AR	Meckel syndrome	607361
PEX5	Peroxisomal Biogenesis Factor 5	Sundaram *Nat Clin Pract Gastroenterol Hepatol* :456, 2008	AR	Peroxisome biogenesis disorder 2A Zellweger)	214110
PMM2	Phosphomannomutase 2	Horslen *Arch Dis Child* 6:1027, 1991	AR	Congenital disorder of glycosylation, type a	212065
POC1A	POC1 centriolar protein	Shaheen *AJHG* 91:330, 2012	AR	Short stature, onychodysplasia, facial dysmorphism, and hypotrichosis	614813
PRODH	Proline dehydrogenase 1	Perry *Ann Hum Genet* 1:401, 1968	AR	Hyperprolinemia, Type 1	239500
PROK2	Prokineticin 2	Madan *Mol Genet Metab Rep* 12:57, 2017	AR	Hypogonadotropic hypogonadism 4 with or without anosmia	610628
RAD51C	RAD51 Paralog C	Vaz *Nat Genet* 42:406, 2010	AR	Fanconi Anemia, Complementation Group O	613390
RECQL4	RecQ Like Helicase 4	Siitonen *Eur J Hum Genet* 7:151, 2009	AR	Baller-Gerold syndrome	218600
RMND1	Required for Meiotic Nuclear Division 1 Homolog	Taylor *JAMA* 312:68, 2014	AR	Combined Oxidative Phosphorylation Deficiency 11	614922
ROR2	Receptor Tyrosine Kinase Like Orphan Receptor 2	Viens *Clin Genet* 37:481, 990	AR	Robinow syndrome	268310
RPS19	Ribosomal Protein S19	Hoefele *Pediatr Nephrol* 5:1255, 2010	AR	NA	603474
SCARF2	Scavenger Receptor Class F Member 2	Anastasio *AJHG* 87:553, 2010	AR	Van den Ende-Gupta syndrome	600920
STRA6	Stimulated By Retinoic Acid 6	Golzio *AJHG* 80:1179, 2007	AR	Microphthalmia, syndromic 9	601186

				Microphthalmia, solated, with oloboma 8	
TMCO1	Transmembrane And Coiled-Coil Domains 1	Kin	*PNAS* 107:258, 2010	AR	Craniofacial lysmorphism, keletal anomalies, nd mental etardation yndrome	213980
UBR1	Ubiquitin Protein Ligase E3 Component N-Recognin 1	anlieferinghen	*Genet Couns* 14:105, 2003	AR	ohanson-Blizzard yndrome	243800
PEX1	Peroxisomal Biogenesis Factor 1	Crane	*Hum Mutat* 26:167, 005	AR	Peroxisome iogenesis lisorder 1A Zellweger)	214100
PIGL	Phosphatidylinositol Glycan Anchor Biosynthesis Class L	chnur	*AJMG* 72:24, 997	AR	CHIME syndrome	280000
PIGO	Phosphatidylinositol Glycan Anchor Biosynthesis Class O	rawitz	*AJHG* 91:146, 012	AR	Hyperphosphatasi with mental etardation yndrome 2	614749
PIGN	Phosphatidylinositol Glycan Anchor Biosynthesis Class N	Ohba	*Neurogenetics* 5:85, 2014	AR	Multiple ongenital nomalies-hypoto ia-seizures yndrome 1	614080
PIGT	Phosphatidylinositol Glycan Anchor Biosynthesis Class T	Nakashima	*Neurogenetics* 5:193, 2014	AR	Multiple ongenital nomalies-hypoto ia-seizures yndrome 3	615398
PIGV	Phosphatidylinositol Glycan Anchor Biosynthesis Class V	Horn	*Eur J Hum Genet* 2:762, 2014	AR	NA	610274
PIGY	Phosphatidylinositol Glycan Anchor Biosynthesis Class Y	lkovski	*Hum Mol Genet* 4:6146, 2015	AR	Hyperphosphatasi with mental etardation yndrome 6	616809
PTF1A	Pancreas Specific Transcription Factor, 1a	Gurung	*Mol Med Rep* 2:1579, 2015	AR	NA	607194
SLX4	SLX4 Structure-Specific Endonuclease Subunit	Stoepker	*Nat Genet* 3:138, 2011	AR	Fanconi anemia, complementation group P	613951
TXNL4A	Thioredoxin-Like 4A	Hing	*Am J Med Genet A* 40:804, 2006	AR	Burn-McKeowen Syndrome	608572

WFS1	Wolframin ER Transmembrane Glycoprotein	Salih *Acta Paediatr Scand* 80:567, 1991	AR	Wolfram syndrome 1	222300
WNT3	Wnt Family Member 3	Niemann *AJHG* 74:558, 2004	AR	Tetra-amelia syndrome 1	273395
XRCC4	X-Ray Repair Cross Complementing 4	Murray *Am J Hum Genet* 96:412, 2015	AR	Short Stature, Microcephaly, And Endocrine Dysfunction	616541
ZMPSTE24	Zinc Metallopeptidase STE24	Chen *AJMG A* 149A:1550, 2009	AR	Restrictive dermopathy, lethal	275210
ACTB	Actin Beta	Rivière *Nat Genet* 44:440, 2012	AD	Baraitser-Winter syndrome 1	243310
ACTG1	Actin Gamma 1	Rivière *Nat Genet* 44:440, 2012	AD	Baraitser-Winter syndrome 1	243310
AIFM3	Apoptosis Inducing Factor, Mitochondria Associated 3	Lopez-Rivera *NEJM* 376:742, 2017	AD	NA	617298
ARID1B	AT-Rich Interaction Domain 1B	Levy *J Med Genet* 28, 991	AD	Coffin-Siris syndrome 1	135900
ATXN10	Ataxin 10	Matsuura *Nat Genet* 26:191, 2000	AD	Spinocerebellar ataxia 10	603516
BICC1	BicC Family RNA Binding Protein	Kraus *Hum Mutat* 33:86, 2012	AD	Renal cystic/dysplasia	601331
BMP7	Bone Morphogenetic Protein 7	Hwang *Kidney Int* 85:1429, 2014	AD	NA	112267
BRAF	B-Raf Proto-Oncogene, Serine/Threonine Kinase	Sarkozy *Hum Mutat* 30:695, 2009	AD	Cardiofaciocutaneous syndrome	115150
CDC5L	Cell Division Cycle 5 Like	Groenen *Genomics* 59:218, 1998	AD	NA	602868
CREBBP	CREB Binding Protein	Kanjilal *J Med Genet* 29:669, 1992	AD	Rubinstein-Taybi syndrome 1	180849
DACT1	Dishevelled Binding Antagonist Of Beta Catenin 1	Webb *Hum Mutat* 38:373, 2017	AD	Townes-Brocks syndrome 2	617466
EP300	E1A Binding Protein P300	Roelfsema *AJHG* 76:572, 2005	AD	Rubinstein-Taybi syndrome 2	613684
ESRRG	Estrogen Related Receptor Gamma	Harewood *PLoS One* 5:e12375, 2010	AD	NA	602969
FBN1	Fibrillin 1	Tokhmafshan *Pediatr Nephrol* 32:565, 2017	AD	Marfan syndrome	154700

FGFR1	Fibroblast growth factor receptor 1	Farrow *AJHG* 140A:537, 2006	AD	Multiple OMIM classifications	615465 147950 123150 166250 101600 190440
FGFR3	Fibroblast growth factor receptor 3	Rohmann *Nat Genet* 38:495, 2006	AD	CADD syndrome	149730
FGF10	Fibroblast Growth Factor 10	Milunsky *Clin Genet* 69:349, 2006; Bamforth *AJMG* 43:932, 1992	AD	CADD syndrome	149730
FGF8	Fibroblast Growth Factor 8	Falardeau *J Clin Invest* 118:2822 2008	AD	Hypogonadotropic hypogonadism 6 with or without anosmia	612702
FGFR2	Fibroblast Growth Factor Receptor 2	LeHeup *Eur J Pediatr* 154:130, 1995	AD	Multiple OMIM classifications	176943
FGFRL2	Forkhead Box C1	LeHeup *Eur J Pediatr* 154:130, 1995	AD	Antley-Bixler syndrome without genital anomalies or disordered steroidogenesis	207410
FMN1	Formin 1	Dimitrov *J Med Genet* 47:569, 2010	AD	NA	136535
FOXF1	Forkhead Box F1	Hilger *Hum Mutat* 36:1150, 2015	AD	Alveolar capillary dysplasia with misalignment of pulmonary veins	265380
GDF3	Growth Differentiation Factor 3	Caraca *AJMG A* 167A:2795, 2015	AD	Klippel-Feil syndrome 3	613702
GDNF	Glial cell line derived neurotrophic factor	Pini Prato *Medicine (Baltimore)* 88:83, 2009	AD	Susceptibility Hirschsprung Disease	613711
GFRA1	GDNF Family Receptor Alpha 1	Chatterjee *Hum Genet* 131:1725, 2013	AD	NA	601496
GLI2	GLI Family Zinc Finger 2	Carmichael *J Urol* 190:1884, 2013	AD	Culler-Jones syndrome, Holoprosencephaly 9	615849 610829
HOXA13	Homeobox A13	Halal *AJMG* 30:793, 1998	AD	Hand-foot-uterus syndrome	140000
HOXD13	Homeobox D13	Garcia-Barceló *AJMG* 1146A:3181, 2008	AD	NA	142989

JAG1	agged 1	Kamath *Nat Rev Nephrol* AD 9:409, 2013	Alagille syndrome	118450
KAT6B	Lysine Acetyltransferase 6B	Campeau *AJMG* 90:282, AD 2012	Genitopatellar syndrome	606170
KCTD1	Potassium Channel Tetramerization Domain Containing 1	Marneros *AJMG* 92:621, AD 2013	Scalp-ear-nipple syndrome	181270
KCNH2	Potassium Voltage-Gated Channel Subfamily H Member 2	Caselli *AJMG* 146A:1195, AD 2008	Scalp-ear-nipple syndrome	152427
KRAS	KRAS Proto-Oncogene, GTPase	Schubbert *Nat Gene* AD 38:331, 2006	Noonan syndrome	609942
LMX1B	LIM Homeobox Transcription Factor 1 Beta	Dreyer *Nat Genet* 19:47, AD 998	Nail-patella syndrome	161200
LPP	LIM Domain Containing Preferred Translocation Partner In Lipoma	Hernández-García *AJMG* AD t 158A:1785, 2012	NA	600700
MAP2K1	Mitogen-activated protein kinase kinase 1	Schulz *Clin Genet* 73:62, AD 2007	Cardiofaciocutaneous syndrome 3	615279
MAP2K2	Mitogen-activated protein kinase kinase 2	Schulz *Clin Genet* 73:62, AD 2007	Cardiofaciocutaneous syndrome 4	615280
MLL2/ KMT2D	Myeloid/Lymphoid Or Mixed-Lineage Leukemia Protein 2	Banka *Eur J Hum Genet* AD 20:381, 2012	Kabuki syndrome	147920
MNX1	Motor Neuron and Pancreas Homeobox 1	Ashcraft J Pediatr Surg AD 9:691, 1974	Currarino Syndrome	176450
MYCN	MYCN Protooncogene, bHLH Transcription Factor	Marcelis *Hum Mut* AD 29:1125, 2006	Feingold syndrome 1	164280
NOTCH2	Notch 2	Kamath *Nat Rev Nephrol* AD 9:409, 2013	Alagille syndrome, Hajdu-Cheney syndrome	610205, 102500
PKD1	Polycystin 1, Transient Receptor Potential Channel Interacting	Rossetti *JASN* 18:2143, AD 2007	Polycystic kidney disease 1	173900
PKD2	Polycystin 2, Transient Receptor Potential Cation Channel	Rossetti *JASN* 18:2143, AD 2007	Polycystic kidney disease 2	613095
PROKR2	Prokineticin Receptor 2	Sarfati *Front Horm Res* AD 39:121, 2010	Hypogonadotropic hypogonadism 3 with or without anosmia	244200
PTPN11	Protein Tyrosine Phosphatase, Non-Receptor Type 11	Bertola *AJMG* 130A:378, AD 2004	LEOPARD syndrome 1	151100
RAF1	Raf-1 Proto-Oncogene, Serine/Threonine Kinase	Razzaque *Nat Genet* AD 39:1013, 2007	Noonan syndrome	611553
RAI1	Retinoic Acid Induced 1	Vilboux *PLoS One* AD 6:e22861, 2011	Smith-Magenis syndrome	182290

RPL26	Ribosomal protein L26	Gazda *Hum Mutat* 33:1037, 2012	AD	Diamond-Blackfa n anemia 11	614900
RPS26	Ribosomal protein S26	Gripp *Am J Med Genet A* 64A:2240, 2014	AD	Diamond-Blackfa n anemia 10	613309
SALL4	Spalt Like Transcription Factor 4	Kohlhase *GeneReviews®Book Section,* 1993	AD	Duane-radial ray yndrome	607323
SEMA3A	Semaphorin 3A	Young *Hum Reprod* 27:1460, 2012	AD	Hypogonadotropic ypogonadism 16 vith or without nosmia	614897
SEMA3E	Semaphorin 3E	Lalani *J Med Genet* 41:e94, 2004	AD	CHARGE yndrome	214800
SETBP1	SET Binding Protein 1	Schinzel *AJMG* 1:361, 978	AD	Schinzel-Giedion nidface retraction yndrome	269150
SHH	Sonic Hedgehog	Lurie *AJMG* 35:286, 1990	AD	Holoprosencephal 3	142945
SF3B4	Splicing Factor 3b Subunit 4	Bernier *AJMG* 90:925, 2012	AD	Acrofacial lysostosis 1, Nager type	154400
SNAP29	Synaptosome Associated Protein 29	Lopez-Rivera *NEJM* 376:742, 2017	AD	Di George yndrome	604202
SOS1	SOS Ras/Rac Guanine Nucleotide Exchange Factor 1	Ferrero *Eur J Med Genet* 51:566, 2008	AD	Noonan syndrome	610733
SOX9	SRY-Box 9	Airik *Hum Mol Genet* 19:4918, 2010	AD	Campomelic ysplasia	114290
SRCAP	Snf2 Related CREBBP Activator Protein	Hood *AJHG* 90:308, 2012	AD	Floating-Harbor yndrome	136140
TBX1	T-Box 1	Kujat *AJMG A* 140:1601, 2006	AD	Di George yndrome	188400
TBX3	T-Box 3	Meneghini *Eur J Med Genet* 49:151, 2006	AD	Ulnar-mammary yndrome	181450
TFAP2A	Transcription Factor AP-2 Alpha	Milunsky *AJHG* 82:1171, 2008	AD	Branchiooculofaci l syndrome	113620
TP63	Tumor Protein P63	Celli *Cell* 99:143, 1999	AD	Multiple OMIM lassifications	603273
TRPS1	Zinc finger transcription factor; Trichorhinophalangeal syndrome	Fasic *Ren Fail* 36:619, 2014	AD	Trichorhinophalan geal syndrome	190350 190351
TSC1	Tuberous Sclerosis 1	Curatolo *Lancet* 372:657, 2008	AD	Tuberous clerosis-1	191100

TSC2	Tuberous Sclerosis 2	Kumar *Hum Mol Genet* 4:1471, 1995	AD	Tuberous clerosis-2	613254
TWIST2	Twist Family BHLH Transcription Factor 2	Stevens *AJMG* 107:30, 2002	AD	Ablepharon-macrotomia syndrome	200110
WNT5A	Wnt Family Member 5A	Roifman *Clin Genet* 87:34, 2015; Person *Dev Dyn* 239:327, 2010	AD	Robinow syndrome	180700
GDF6	Growth Differentiation Factor 6	Tassabehji *Hum Mutat* 29:1017, 2008	AD/ AR	Multiple OMIM classifications	601147
GLI3	GLI Family Zinc Finger 3	Cain *PLoS One* 4:e7313, 2009	AD/ AR	Multiple OMIM classifications	165240
PCSK5	Proprotein Convertase Subtilisin & Kexin Type 5	Nakamura *BMC Res Notes* 8:228, 2015	AD/ AR	NA	600488
PTEN	Phosphatase And Tensin Homolog	Reardon *J Med Genet* 38:820, 2001	AD/ AR	Multiple OMIM classifications	601728
RPS24	Ribosomal Protein S24	Vetgin *Turk J Pediatr* 36:239, 1994	AD/ AR	Aase-Smith syndrome	602412
VANGL1	VANGL Planar Cell Polarity Protein	Bartsch *Mol Syndromol* 2:76, 2012	AD/ AR	Caudal regression syndrome	600145
AXIN1	Axin 1	Oates *AJHG* 79:155, 2006	*de novo*	Caudal duplication anomaly	607864
H19	H19, Imprinted Maternally Expressed Transcript (Non-Protein Coding)	Hur *PNAS* 113:10938, 2016	*de novo*	Beckwith-Wiedemann syndrome	130650
KCNQ1OT1	KCNQ1 Opposite Strand & Antisense Transcript 1 (Non-Protein Coding)	Chiesa *Hum Mol Genet* 21:10, 2012	*de novo*	Beckwith-Wiedemann syndrome	130650
NIPBL	NIPBL, Cohesin Loading Factor	Rohatgi *AJMG* 152A:1641, 2010	*de novo*	Cornelia de Lange syndrome 1	122470
CDKN1C	Cyclin Dependent Kinase Inhibitor C	Mussa *Pediatr Nephrol* 27:397, 2012	*de novo*	Beckwith-Wiedemann syndrome	130650
CHD7	Chromodomain Helicase DNA Binding Protein 7	Janssen *Hum Mutat* 33:1149 2012	*de novo*	CHARGE syndrome	214800
AMER1	APC Membrane Recruitment Protein 1	Pellegrino *AJMG* 16:159, 1997	XL	Osteopathia striata with cranial sclerosis	300373
ATP7A	ATPase Copper Transporting Alpha	Vulpe *Nat Genet* 3:7, 1993	XL	Menkes disease	309400
BCOR	BCL6 Corepressor	Ng *Nat Genet* 36:411, 2004	XL	Microphthalmia, syndromic 2	300166

DLG3	Disc large, drosphilia, homologue of	Philips *Orphanet J Rare Dis* 9:49, 2014	XL	Mental retardation, X-linked 90	300850
FAM58A	Family With Sequence Similarity 58 Member A	Green *J Med Genet* 33:594, 1996; Unger *Nat Genet* 40:287, 2008	XL	STAR syndrome	300707
FLNA	Filamin A	Robertson *AJMG* A 40:1726, 2006	XL	Multiple OMIM classifications	300017
GPC3	Glypican 3	Cottereau *AJMG* C *Semin Med Genet* 163:92, 2013	XL	Simpson-Golabi-Behmel syndrome, type 1	312870
MID1	Midline 1	Preiksaitiene *Clin Dysmorphol* 24:7, 2015	XL	Opitz GBBB syndrome, type I	300000
NAA10	N-Alpha -Acetyltransferase 10, NatA Catalytic Subunit	Lenz Z Kinderheilkd 77:384, 1955	XL	Microphthalmia, syndromic 1	309800
NSDHL	NAD(P) Dependent Steroid Dehydrogenase-Like	König *J Am Acad Dermatol* 46:594, 2002	XL	CHILD syndrome	308050
PIGA	Phosphatidylinositol Glycan Anchor Biosynthesis Class A	Johnston *AJHG* 90:295, 2012	XL	Multiple congenital anomalies-hypotonia-seizures syndrome 2	300868
PORCN	Porcupine O-Acyltransferase	Suskan *Pediatr Dermatol* 7:283, 1990	XL	Focal dermal hypoplasia	305600
SMC1A	Structural Maintenance Of Chromosomes 1A	Deardorff *GeneReviews® [Book Section Seattle(WA),* 993	XL	Cornelia de Lange syndrome 2	300590
UPF3B	UPF3B, Regulator Of Nonsense Mediated MRNA Decay	Lynch *Eur J Med Genet* 55:476, 2012	XL	NA	300298
ZIC3	Zic Family Member 3	Chung *AJMG* 155:1123, 2011	XL	VACTERL Association	314390
ODSR1	Odd-Skipped Related Transciption Factor 1	Zhang *Hum Mol Genet* 20:4167, 2011	Unknown	NA	608891
PALB2	Partner and Localizer of BRCA2	Xia *Nat Genet* 39:159, 2007	Unknown	Fanconi Anemia, Complementation Group N	610832
PIK3CA	Phosphatidylinositol 3-kinase Catalytic, Alpha	Ahmad *Clin Dysmorphol* 18:1, 2009		CLOVE syndrome	612918
SH2B1	SH2B Adaptor Protein 1	Sampson *AJMG* 152:2618, 2010	Unknown	NA	608937

ATN1	Atrophin 1	Palmer *Am. J. Hum. Genet.* 104: 542-552, 2019	AD	Congenital hypotonia, epilepsy, developmental delay, and digital anomalies	607462
B3GLCT	Beta-3-glucosyltransferase	Dassie-Ajdid *Clin Genet*	AR	Peter-Plus syndrome	610308
FANCD2	Fanconi Anemia Group D2	Kalb *Am. J. Hum. Genet.* 80: 895-910, 2007	AR	Fanconi anemia, complementation group D2	613984
FANCE	FA Complementation Group E	Wegner *Clin. Genet.* 50: 479-482, 1996	AR	Fanconi anemia, complementation group E	613976
CYP11B1	Cytochrome P450, Subfamily XIB, Polypeptide 1	Glenthoj *Acta Endocr.* 93: 94-99, 1980 ;	AR/AD	Adrenal hyperplasia, congenital, due to 11-beta-hydroxylase deficiency	610613
DLL4	Delta Like Canonical Notch Ligand 4	Shutter *Genes Dev.* 14: 313-1318, 2000	AD	Adams-Oliver syndrome 6	605185
ZMYM2	Zinc Finger	Connaughton *Am. J. Hum. Genet.* 107: 727-742, 2020	AD	Neurodevelopmental-craniofacial syndrome with variable renal and cardiac abnormalities	602221
PTK7	Protein-tyrosine kinase	Chan *eLife*, 11, e74777, 2022	AR	Posterior urethral valve	601890
AFF3	AF4/FMR2 Transcription Elongation Factor 3	Shimizu *J. Hum. Genet.* 64: 1041-1044, 2019	AD	KINSSHIP syndrome	601464
CFAP418	Cilia-and-Flagella-Associated Protein 418	Heon *Hum. Molec. Genet.* 25: 2283-2294, 2016	AR	Bardet-Biedl syndrome 21	614477
CENPF	Centromeiric protein	Filges *Hum. Mutat.* 37: 359-363, 2016	AR	Stromme syndrome	600236
CHRNA3	Cholinergic receptor, neuronal nicotinic, alpha polypeptide 3	Mann *Am. J. Hum. Genet.* 105: 1286-1293, 2019	AR	Bladder dysfunction, autonomic, with impaired pupillary reflex and secondary CAKUT	18503

EBP	Emopamil-binding protein	Milunsky Am. J. Med. Genet. 116A: 249-254, 2003	XLD/XLR	Chondrodysplasia punctata, X-linked dominant; MEND syndrome	300205
ERCC4	ERCC Excision repair endonuclease catalytic subunit	Niedernhofer *Nature* 444: 1038-1043, 2006	AR	XFE progeroid syndrome	133520
FANCG	FA Complementation Group G	le winter Nature Genet. 20: 281-283, 1998	AR	Fanconi anemia, complementation group G	602956
HSPA9	Heat-shock 70-KD protein 9	Royer-Bertrand *Sci. Rep.* 5: 17154, 2015	AD/AR	Even-plus syndrome	600548
KANSL1	KAT8 Regulatory NSL complex, subunit 1	Koolen *Nature Genet.* 38: 999-1001, 2006	AD	Koolen-De Vries syndrome	612452
COX14	Cytochrome c oxidase assembly factor COX14	Veraarpachai Am. J. Hum. Genet. 90: 142-151, 2012	AR	Mitochondrial complex IV deficiency, nuclear type 10	614478
EDNRA	Endothelial receptor type A	Gordon *Am. J. Hum. Genet.* 96: 519-531, 2015	AD	Mandibulofacial dysostosis with alopecia	131243
FANCC	FA Complementation Group C	NA	AR	Fanconi anemia, complementation group C	613899

*AR, autosomal recessive; AD, autosomal dominant; NA, not available; OMIM, Online Mendelian Inheritance in Man; XL; X-linked; #, phenotype MIM number; Unknown, mode of inheritance not clearly characterized; * gene/ locus MIM number if not phenotype MIM number available.*

Supplementary Table S5: genes that represent monogenic causes of human autosomal dominant tubulo-interstitial kidney disease, if mutated. (Sorted alphabetically by mode of inheritance).

Gene	Protein	Reference	Mode of inheritance	Phenotype	OMIM number
HNF1B	Hepatocyte nuclear factor 2	Lindner *Hum Mol Genet* 24:263, 1999	AD	Renal cysts and diabetes syndrome	137920
MUC-1	Mucin-1	Kirby *Nat Genet* 45:299, 2013	AD	Medullary cystic kidney disease 1	174000
REN	Renin	Zivna *AJHG* 85: 204, 2009	AD	Familial juvenile hyperuricemic nephropathy 2	613092
SEC61A1	SEC61 complex, alpha 1	Bolar *AJHG* 99:174, 2016	AD	Familial juvenile hyperuricemic nephropathy 4	617056

UMOD	Uromodulin	Hart *J Med Genet* 39(12):882, 2002	AD	Familial juvenile hyperuricemic nephropathy 1	162000

AD, autosomal dominant; OMIM, Online Mendelian Inheritance in Man; XL; X-linked; #, phenotype MIM number.

Supplementary Table S6: genes that represent monogenic causes of human chronic glomerulopathies, if mutated.
(Sorted alphabetically by mode of inheritance)

Gene	Protein	Reference	Mode of inheritance	Phenotype	OMIM number
ADAMTS13	ADAM metallopeptidase with thrombospondin type 1 motif 13	Levy *Nature* 413: 488, 2001	AR	Familial thrombotic thrombocytopenic purpura	274150
COL4A4	Collagen type IV alpha 4 chain	Mochizuki *Nat Genet* 8:77, 1994	AR	Alport syndrome	203780
EIF2AK3	Eukaryotic Translation Initiation Factor 2 Alpha Kinase 3	Delepine *Nature Genet* 25:406, 2000	AR	Wolcott-Rallison syndrome	226980
PLG	Plasminogen	Schuster *Blood* 93:3457, 1999	AR	Plasminogen Deficiency, Type 1	217090
CFHR5	Complement factor H related 5	Gale *Lancet* 376:794, 2010	AD	Nephropathy due to CFHR5 deficiency	614809
FN1	Fibronectin	Castelletti *PNAS* 105:2538, 2008	AD	Glomerulopathy with fibronectin deposits 2	601894
FOXC2	Forkhead Box C2	Mildirim-Toruner *AJMG* 131A:281, 2004	AD	Lymphedema-distichiasis syndrome with renal disease and diabetes mellitus	153400
GSN	Gelsolin	Maury *FEBS* Lett 260:85, 1990	AD	Amyloidosis, Finnish type	105120
LYZ	Lysozyme	Pepys *Nature* 362:553, 1993	AD	Renal amyloidosis	105200
THBD	Thrombomodulin	Delvaeye *NEJM* 361:345, 2009	AD	Susceptibility to atypical hemolytic uremic syndrome 6	612926
SLC37A4	Solute Carrier Family 37 Glocose-6-Phosphate Transporter), Member 4	Wilson *JIMD Rep* 58:122, 2021	AD	Congenital disorder of glycosylation, type Iw	619525

SOX18	SRY-Box 18	Sherwood *Arch Dis Child* 62:1278, 1987	AD	Hydrotrichosis-Lymph edema-Telangiectasia-Renal Defect Syndrome	137940
SPRY2	Sprouty RTK Signaling Antagonist 2	Milillo *Europ J Hum Genet* 23:1673, 2015	AD	Susceptibility to IgA nephropathy 3	616818
C3	Complement C3	Fremeaux-Bacchi *Blood* 112:4948, 2008	AR/AD	C3 deficiency, Susceptibility to hemolytic uremic syndrome, atypical 5	613779 612925
CD46	CD46 molecule	Noris *Lancet* 362:1542, 2003	AR/AD	Atypical hemolytic-uremic syndrome, type 2	612922
CFB	CFB	Goicoechea de Jorge *PNAS* 104:240, 2007	AR/ AD	Complement factor B deficiency, Susceptibility to hemolytic uremic syndrome, atypical 4	615561 612924
CFH	Complement factor H	Edelsten *Arch Dis Child* 53:255, 978	AR/AD	Complement factor H deficiency, Susceptibility to hemolytic uremic syndrome, atypical 1	609814 235400
CFHR1	Complement factor H elated 1	Zipfel *PLoS* Genet 3:e41, 2007	AR/AD	Susceptibility to hemolytic uremic syndrome, atypical	235400
CFI	Complement factor I	Fremeaux-Bacchi *J Med Genet* 41: 84, 2004	AR/ AD	Complement factor I deficiency, Hemolytic uremic syndrome, atypical	610984 612923
CFHR3	CFHR3	Zipfel *PLoS* Genet 3: e41, 2007	AR/ AD	Susceptibility to hemolytic uremic syndrome, atypical	235400
COL4A3	Collagen type IV alpha chain	Lemmink *Hum Mol Genet* 3:1269, 994	AR/AD	Alport syndrome Benign familial hematuria	203780 104200
COL4A5	Collagen type IV alpha chain	Antignac *J Clin Invest* 93:1195, 994	XL	X-linked Alport syndrome	301050
COL4A6	Collagen type IV alpha chain	Zenieri *Hum Mutat* 4:195, 1994	XL	NA	303631

DNASE1L3	Deoxyribonuclease -like-3	Al-Mayouf *Nature Genet.* 43:AR 186-1188, 2011		Systemic lupus erythematosus 16	602244

*AR, autosomal recessive; AD, autosomal dominant; NA, not available; OMIM, Online Mendelian Inheritance in Man; XL; X-linked; #, phenotype MIM number; * gene/ locus MIM number if not phenotype MIM number available.*

Supplemental Table S7: Genes that represent monogenic causes of chronic kidney disease (other), if mutated.

Gene	*Protein*	*Reference*	*Mode of Inheritance*	*Phenotype*	*OMIM#*
KYNU	*Kynureninase*	*Christensen J Inherit Metab Dis 30:248, 2007*	*AR*	*Hydroxyknureninuria*	*236800*
LDHA	*Lactate dehydrogenase A*	*Maekawa Am J Hum Genet 39:232, 1986*	*AR*	*Glycogen storage disease XI*	*612933*
MEFV	*MEFV Innate Immunity Regulator, Pyrin*	*Benson Ann Intern Med 87:31, 1977*	*AR*	*Familial Mediterranean fever, AR*	*249100*
MMACHC	*Metabolism of Cobalamin Associated C*	*Lerner-Ellis Nat Genet 38:93, 2006*	*AR*	*Methylmalonic aciduria and homocystinuria, cdlC type*	*277400*
MMUT	*Methylmalonyl-Co A Mutase*	*Ledley Bioessays 12:335, 1990*	*AR*	*Methylmalonic aciduria, mut(0) type*	*251000*
MVK	*Melcalonate Kinase*	*Prietsch AR Pediatrics 111:258, 2003*		*Mevalonic aciduria*	*610377*
PCBD1	*Pterin-4-alpha-carbinolamine Dehydratase 1*	*Ferrè J Am Soc Nephrol 25:574, 2014*	*AR*	*Hyperphynylalanine mia, BH4-Deficient, D*	*264070*
PET100	*PET100 Cytochrome c Oxidase Chaperone*	*Lim Am J Hum Genet 94:209, 2014*	*AR*	*Mitochondrial Complex IV Deficincy, Nuclear Type 12*	*619055*
SARS2	*Seryl-tRNA Synthetase 2*	*Belostotsky Am J Hum Genet 88:193, 2011*	*AR*	*Hyperuricemia, Pulmonary Hypertension, Renal Failure, and Alkalosis Syndrome*	*613845*

SLC5A1	*Solute Carrier Family 5 (Sodium/Glucose Cotransporter), Member 1*	*Abdullah JAR Pediatr Gastroenterol Nut 23:561, 1996*	*Glucose/Galactose Malabsorption*	*606824*
UQCC2	*Ubiquiinol-Cytochrome C Reductase Complex Assembly Factor 2*	*Tucker PLoSAR Genet 9:e1004034, 2013*	*Mitochonrial Complex III Deficiency, Nuclear Type 7*	*615824*
NLRP3	*NLR Family Pyrin Domain-Containing 3*	*Hoffman Am JAD Hum Genet 66:1693, 2000*	*Famalial cold inflammatory syndrome 1*	*120100*
NLRP3	*NLR Family Pyrin Domain-Containing 3*	*Dodé Am J Hum Genet 70:1498, 2022*	*Muckle Wells syndrome*	*AD 191900*
NSD1	*Nuclear Receptor-binding set domain protein 1*	*Sotos N Engl J Med 271:109, 1964*	*Sosto Syndrome*	*AD 117550*
SLC47A1	*Solute Carrier Family 47, Member 1*	*Greenberg Am J Med Genet 62:247, 1996*	*Smith-Magenis Syndrome*	*AD 182290*
STX16	*Syntaxin 16*	*Levine Am J Med 74:545, 1983*	*Pseudohypoparathyroidism Type IB*	*AD 603233*
PGK1	*Phosphoclycerate Kinase 1*	*Rosa Blood 60:84, 1982*	*Phosphoglycerate Kinase 1 Deficiency*	*XLR 300653*
WAS	*Wasp Actin Nucleation Promoting Factor*	*Standen Q J Med 59:401, 1986*	*Wiskott-Aldrich Syndrome*	*XLR 301000*
PLA2R1	*Phospholipase A2 Receptor 1*	*Debiec N Engl J Med 346:2053*	*Membranous Nephropathy*	*Unknown 614692*
SACS	*Sacsin*	*Criscuolo AR Neurology 62: 100-102, 2004*	*Spastic ataxia, Charlevoix-Saguenay type*	*604490*
UQCRQ	*Ubiquinol-cytochrome c reductase, complex III subunit VII*	*Barel Am. J. Hum. Genet. 82: 1211-1216, 2008*	*Mitochondrial complex III deficiency, nuclear type 4*	*AR 612080*
ADA2	*Adenosine deaminase*	*Zhou New Eng. J. Med. 370: 911-920, 2014*	*Vasculitis, autoinflammation, immunodeficiency, and hematologic defects syndrome*	*AR 607575*

C5	*Complement component 5*	*Nishimura New Eng. J. Med. 370: 632-639, 201*	*AD/AR*	*Eculizumab, poor response to*	*120900*
FOXP3	*Forkhead box P3*	*Misra Gene 25;581(1):57-65, 2016*	*XLR*	*Susceptibility to ESRD*	*300292*
HPS1	*HPS1 Biogenesis of lysosomal organelles complex3, subunit 1*	*O'Brian Journal of internal medicine, 290(1), 129–140, 2021*	*AR*	*Hermansky-Pudlak syndrome 1; renal failure*	*604982*
ITGA6	*Integrin, alpha 6*	*Ruzzi J. Clin. Invest. 99: 2826-2831, 1997*	*AR*	*Epidermolysis bullosa, junctional 6, with pyloric atresia*	*147556*
KCNA1	*Potassium channel, voltage-gated, shaker-related subfamily, member 1*	*Chan Neurogenetics 8: 131-135, 2007*	*AD*	*Episodic ataxia/myokymia syndrome*	*176260*
SDHB	*Succinate dehydrogenase complex, subunit B, iron sulfur protein*	*Fairchild JAMA 242: 2210-2211, 1979*	*AD*	*Pheochromocytoma*	*185470*
SDHD	*Succinate dehydrogenase complex, subunit D, integral membrane protein*	*Fairchild JAMA 242: 2210-2211, 1979*	*AD*	*Pheochromocytoma*	*602690*
TMEM127	*Transmembrane protein 27*	*Fairchild JAMA 242: 2210-2211, 1979*	*AD*	*Pheochromocytoma*	*613403*
CACNA1H	*Calcium channel, voltage-dependent, T type, alpha-1H subunit*	*Scholl eLife 4: e06315, 2015*	*AD*	*Hyperaldosteronism, familial, type IV*	*607904*
CCND1	*Cyclin D1*	*Yu The Journal of urology, 172(6 Pt 1), 2410–2413, 2004*	*AD*	*Von Hippel-Lindau Syndrome*	*168461*
CLCN2	*Chloride channel 2*	*Scholl Nature Genet. 50: 349-354, 2018*	*AD*	*Hyperaldosteronism, familial, type II*	*600570*

CYP11B2	*Cytochrome P450, subfamily XIB, polypeptide*	*Chen and applied pharmacology, 279(2), 95–102, 2014*	*Toxicology*	*AR*	*Hypoaldosteronism, congenital, due to CMO I deficiency / Hypoaldosteronism, congenital, due to CMO II deficiency*	*124080*
HNF1A	*HNF1 Homeobox A*	*Reibouissou Hum. Molec. Genet. 14: 603-614, 2005*		*AD/AR*	*Renal cell carcinoma*	*142410*
KCNJ18	*Potassium channel, inwardly rectifying, subfamily J, member 18*	*Ryan Cell 140: 88-98, 2010*		*AD*	*Thyrotoxic periodic paralysis, susceptibility to, 2*	*613236*
FGF3	*Fibroblast growth factor 3*	*Vasei Cancer Genet Cytogenet 194:88-95, 2009*		*AR*	*Wilms tumour*	*164950*
UBE3A	*Ubiquitin-protein ligase E3A*	*Wu Genet Mol Res 15:gmr15049023, 2016*		*AD*	*Angelman syndrome*	*601623*
NTN1	*Netrin-1*	*Ranganathan Mediators Inflamm 2014:525891, 2014*	*AD*		*Acute kidney injury/CKD*	*601614*
PERM1	*PPARGC1- and ESRR-induced regulator muscle, 1*	*N/A*		*AD*	*N/A*	*615921*
COA8	*Cytochrome C Oxidase Assembly Factor*	*N/A*		*AD*	*N/A*	*N/A*
COX20	*Cytochrome c oxidase assembly factor COX20*	*Szklarczyk Hum. Molec. Genet. 22: 656-667, 2013*		*AR*	*Mitochondrial complex IV deficiency, nuclear type 11; lactic acidosis*	*614698*
COX8A	*Cytochrome c oxidase, subunit 8A*	*Hallman Brain 139: 338-345, 2016*		*AR*	*Mitochondrial complex IV deficiency, nuclear type 15*	*123870*
FANCM	*FA Complementation Group M*	*Kim Genes (Besel) 17;12(5):751l, 2021*		*AR*	*Hypertensive kidney disease*	*609644*

FASTKD2	*Fast kinase domain 2*	*Ghezzi Am. J. Hum. Genet. 83: 415-423, 2008*	*AR*	*Combined oxidative phosphorylation deficiency 44*	*612322*
KCNK3	*Potassium channel, subfamily K, member 3*	*Ma New Eng. J. Med. 369: 351-361, 2013*	*AD*	*Pulmonary hypertension, primary, 4*	*603220*
BMPR2	*Bone morphogenetic protein receptor, type II*	*Rigelsky Am. J. Med. Genet. 146A: 2551-2556, 2008*	*AD*	*Pulmonary hypertension, familial primary, 1, with or without HHT; Pulmonary hypertension, primary, fenfluramine or dexfenfluramine-associated; Pulmonary venoocclusive disease 1*	*600799*
HBB	*Hemoglobin—beta locus*	*Monk Prenatal Diag. 13: 45-53, 1993*	*AD*	*Sickle cell anemia*	*141900*
HSD3B2	*3-Beta-hydroxysteroid dehydrogenase 2*	*Bongiovanni Clin. Invest. 41: 2086-2092, 1962*	*AR*	*Adrenal hyperplasia, congenital, due to 3-beta-hydroxysteroid dehydrogenase 2 deficiency*	*613890*

*AR, autosomal recessive; AD, autosomal dominant; NA, not available; OMIM, Online Mendelian Inheritance in Man; XL; X-linked; #, phenotype MIM number; * gene/ locus MIM number if not phenotype MIM number available.*

Supplementary Table S8: Genes that represent monogenic causes of human diabetic kidney disease, if mutated.

Gene	*Protein*	*Reference*	*Mode of Inheritance*	*Phenotype*	*OMIM#*
C7	*Compliment component 7*	*Chen J Cell Biochem 123:481, 2021*	*AR*	*DKD*	
CCR2	*Chemokine, CC Motif, Receptor 2*	*Chen J Cell Biochem 123:481, 2021*	*AR*	*DKD*	

GPR158	*G Protein-coupled receptor 158*	*Sandholm Diabetologia 65:1495, 2022*	*AR*	*DKD*
LSM14A	*LSM14A mRNA Processing Body Assembly Factor*	*Sandholm Diabetologia 65:1495, 2022*	*AR*	*DKD*
MFF	*Mitochondrial Fission Factor*	*Sandholm Diabetologia 65:1495, 2022*	*AR*	*DKD*
MOXD1	*Monooxygenase, DBH-like 1*	*Sandholm Diabetologia 65:1495, 2022*	*AR*	*DKD*
PYCARD	*PYD and CardDomain-containing Protein*	*Chen J Cell Biochem 123:481, 2021*	*AR*	*DKD*
COL1A2	*Collagen of Skin, Tendon, and Bone, Alpha-2 Chain*	*Chen J Cell Biochem 123:481, 2021*	*AD*	*DKD*
COL6A3	*Collagen Type 6, Alpha-3*	*Chen J Cell Biochem 123:481, 2021*	*AD*	*DKD*
COL20A1	*Collagen Type XX, Alpha-1*	*Sandholm Diabetologia 65:1495, 2022*	*AD*	*DKD*
DCLK1	*Doublecortin-like Kinase 1*	*Sandholm Diabetologia 65:1495, 2022*	*AD*	*DKD*
EIF4E	*Eukaryotic Translation Initiation Factor 4E*	*Sandholm Diabetologia 65:1495, 2022*	*AD*	*DKD*
PAX4	*Paired Box Gene 4*	*Plengvidhya J Clin Endocrinol Metab 92:2821, 2007*		*MODY type IX 612225*

NEUROD1	*Neurogenic Differentiation 1*	*Malecki Nat Genet 23:323, 1999*	*Unknown*	*MODY 6* *606394*
PDX1	*Pancreas/Duodenum Homeobox Protein 1*	*Fajans N Engl J Med 345:971, 2001*	*Unknown*	*MODY type IV* *606392*
GREM1	*Gremlin 1 homolog, cystine knot superfamily*	*McKnight Journal of the American Society of Nephrology : JASN, 21(5), 773–781, 2010*	*AR*	*Diabetic nephropathy* *603054*
CEL	*Carboxyl-ester lipas*	*Raeder Nature Genet. 38: 54-62, 2006*	*AD*	*Maturity-onset diabetes of the young, type VIII* *114840*
CYP11A1	*Cytochrome P450, subfamily XIA, polypeptide 1*	*Pagotto Mol Cell Endocrinol 15:111170, 2021*	*AR*	*Adrenal insufficiency, congenital, with 46XY sex reversal, partial or complete* *118485*
GCK	*Glucokinase*	*Njolstad New Eng. J. Med. 344: 1588-1592, 2001*	*AD/AR*	*Diabetes mellitus, noninsulin-dependent, late onset; Diabetes mellitus, permanent neonatal 1* *138079*

INS	*Insulin*	*N/A*	*AD/AR*	*Diabetes mellitus, insulin-dependent, 2; Diabetes mellitus, permanent neonatal 4; Hyperproinsulinemia; Maturity-onset diabetes of the young, type 10*	*176730*
KCNJ11	*Potassium channel, inwardly rectifying subfamily J, member 11*	*Yorifuji J. Clin. Endocr. Metab. 90: 3174-3178, 2005*	*AD/AR*	*Diabetes mellitus, transient neonatal 3; Diabetes, permanent neonatal 2, with or without neurologic features; Hyperinsulinemic hypoglycemia, familial, 2; Maturity-onset diabetes of the young, type 13; Diabetes mellitus, type 2, susceptibility to*	*600937*

KLF11	*Kruppel-like-factor 11*	*Neve Proc. Nat. Acad. Sci. 102: 4807-4812, 2005*	*Maturity-onset diabetes of the young, type VII*	*Maturity-onset diabetes of the young, type VII*	*603301*

*AR, autosomal recessive; AD, autosomal dominant; NA, not available; OMIM, Online Mendelian Inheritance in Man; XL; X-linked; #, phenotype MIM number; * gene/ locus MIM number if not phenotype MIM number available.*

Supplementary Table S9: genes that represent monogenic causes of hereditary amyloidosis, if mutated. (Sorted alphabetically by mode of inheritance).

Gene	Protein	Reference	Mode of inheritance	Phenotype	OMIM number
APOC2	Apolipoprotein C2	Zucfova *J Clin Pathol* 71:687, 2018	AR	Apolipoprotein C-II Deficiency	207750
APOA1	Apolipoprotein A1	Zucfova *J Clin Pathol* 71:687, 2018	AD	Amyloidosis, 3 or more types	105200
APOA2	Apolipoprotein A2	Zucfova *J Clin Pathol* 71:687, 2018		Hereditary amyloidosis	
APP	Amyloid beta Precursor Protein	Zucfova *J Clin Pathol* 71:687, 2018	AD	Cerebral amyloid angiopathy, PRNP-related	105714
B2M	Beta-2-Microglobulin	Zucfova *J Clin Pathol* 71:687, 2018	AD	Amyloidosis, familial visceral	105200
CST3	Cystatin C	Zucfova *J Clin Pathol* 71:687, 2018	AD	Cerebral Amyloid Angiopathy, CST3-related	105150
FGA	Fibrinogen Alpha Chain	Zucfova *J Clin Pathol* 71:687, 2018	AD	Amyloidosis, familial visceral	105200

GSN	Gelsolin	Kufova *J Clin* AD *Pathol* 71:687, 2018	Amyloidosis, Finnish Type	05120
TM2B	ntegral Membrane Protein 2B	Kufova *J Clin Pathol* 71:687, 2018	Amyloidosis	
LYZ	Lysozyme	Kufova *J Clin* AD *Pathol* 71:687, 2018	Amyloidosis, renal	05200
PRNP	Prion Protein	Kufova *J Clin* AD *Pathol* 71:687, 2018	Cerebral amyloid angiopathy, PRNP-related	37440
TTR	Transthyretin	Kufova *J Clin* AD *Pathol* 71:687, 2018	Amyloidosis, hereditary, transthyretin-related	05210
B2M	Beta-2-microglobulin	Valleix *New Eng. J. Med.* 366: 2276-2283, 2012	AD	Amyloidosis, familial visceral	09700
FGA	Fibrinogen, A Alpha Polypeptide	Benson *Nature Genet.* 3: 252-255, 1993	AD	Amyloidosis, familial visceral	34820

*AR, autosomal recessive; AD, autosomal dominant; NA, not available; OMIM, Online Mendelian Inheritance in Man; XL; X-linked; #, phenotype MIM number; * gene/ locus MIM number if not phenotype MIM number available.*