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Genetics of Kidney Disease: The Unexpected Role of Rare Disorders

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Abstract

Hundreds of different genetic causes of chronic kidney disease are now recognized, and while individually rare, taken together they are significant contributors to both adult and pediatric diseases. Traditional genetics approaches relied heavily on the identification of large families with multiple affected members and have been fundamental to the identification of genetic kidney diseases. With the increased utilization of massively parallel sequencing and improvements to genotype imputation, we can analyze rare variants in large cohorts of unrelated individuals, leading to personalized care for patients and significant research advancements. This review evaluates the contribution of rare disorders to patient care and the study of genetic kidney diseases and highlights key advancements that utilize new techniques to improve our ability to identify new gene–disease associations.

INTRODUCTION

MAF: minor allele frequency

ES: exome sequencing

CAKUT: congenital anomalies of the kidney and urinary tract

ADPKD: autosomal dominant polycystic kidney disease

CHIP: clonal hematopoiesis of indeterminate potential

Chronic kidney disease (CKD) is a complex condition that encompasses many individual diseases characterized by abnormalities in kidney structure or function (1). Globally, kidney disease is common, with an estimated prevalence of 9%, and is a major contributor to morbidity and mortality (2). Similar to other common diseases, CKD has relatively high heritability, with broad-sense heritability estimates ranging from 19% to 54% depending on the biomarker utilized (3–5).

Genetic variation can be broadly dichotomized into common variants, present in more than 1% of the alleles of the population [a minor allele frequency (MAF) of >0.01], and rare variants (MAF<0.01) (6–8). The role of common variants in kidney disease has been assessed using genome-wide association studies (GWAS), which have explained only 20% of an estimated 54% heritability in creatinine-based estimated glomerular filtration rate (4). On the other side of the spectrum, rare pathogenic variants are responsible for most Mendelian (monogenic) diseases. There are over 600 Mendelian forms of kidney disease, responsible for 50% of childhood-onset kidney disease; the majority of the causative variants are very rare or private within a specific family (9, 10). Although present at a lower frequency, Mendelian kidney diseases are identified in approximately 10% of adult patients, with the specific diagnostic yield of testing varying based on the individual's type of kidney disease, family history, age at onset, and extra-renal manifestations (11). Similar to pediatric cases, rare and private variants drive most diagnoses in adult cases. The data on the impact of rare disorders in CKD are now emerging and are consistent with analyses of other complex traits, which have demonstrated that a significant amount of missing heritability is explained by rare protein-altering variants that are not well captured by current genotyping and imputation techniques but can be analyzed using massively parallel sequencing of the exome (exome sequencing, ES) or genome (12, 13).

The rare variants implicated in kidney disease are diverse in their class, inheritance, affected gene, and clinical phenotype. For example, rare structural variants and variations in gene copy number have been linked to the development of congenital anomalies of the kidney and urinary tract (CAKUT), and single-nucleotide variants and small insertions and deletions (indels) have been linked to kidney diseases across the phenotypic spectrum (14, 15). Rare somatic variants have been implicated as a second hit in cyst development in autosomal dominant polycystic kidney disease (ADPKD) and as the driver variants in clonal hematopoiesis of indeterminate potential (CHIP), an age-associated non-malignant condition that may cause increased risk of kidney failure and complications of CKD (16, 17). Rare mosaic variants also impact the severity of X-linked Alport syndrome, suggesting further complexity in determining the effect of a variant (18).

In this review, we describe the role rare variants play in the genetics of kidney disease. We examine their central place in diagnostic studies, including the implications for patient care and the use of genetic testing in prognostication and treatment. We then explore the typical approaches employed to identify and validate new rare variant associations with disease. We conclude with the investigation of large data sets and the integration of clinical data from electronic health records, which offer opportunities to evaluate genetic effects at a scale that was previously impossible.

CLINICAL DIAGNOSTIC SETTINGS

Genetic kidney disease is an umbrella term that captures hundreds of rare disorders with an identified genetic cause. To date, over 600 monogenic disorders with kidney and urologic phenotypes have been identified (**Figure 1**) (19). Almost all these genetic conditions are seen in fewer than 1 in 2,000 people, but cumulatively they represent the fifth most common cause of kidney failure (20). While a few monogenic disorders account for a large fraction of cases, the remaining cases are attributable to a large number of rare disorders. This long tail in the distribution of

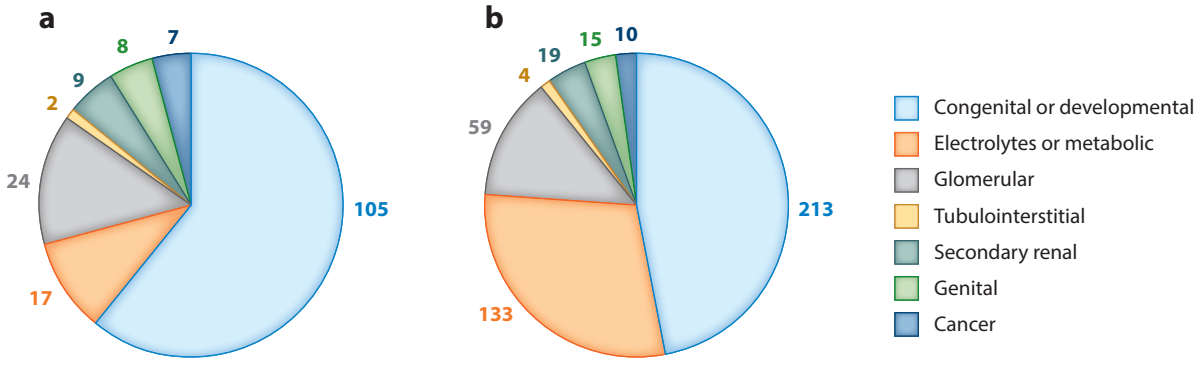

Figure 1

Monogenic kidney and urogenital disorders. The number of genes for dominant (*a*) and recessive (*b*) kidney and urogenital disorders with corresponding clinical categories is shown. Figure adapted from Reference 19 with permission.

monogenic kidney diseases has important implications for clinical diagnostic algorithms and for gene discovery efforts. Several diagnostic studies have been performed to better define the diagnostic yield and clinical implications of genetic testing in different patient populations with kidney disease. One of the key findings across these studies is that the majority of identified pathogenic variants are very rare, with a maximum (max) MAF of less than 1×10^{-4}, or private within a single family.

Pediatric Conditions

Genetic diseases were originally thought to be mostly pediatric, so earlier diagnostic studies focused on evaluating pediatric patients (11, 21). One such study used ES to evaluate 187 pediatric patients with steroid-resistant nephrotic syndrome and identified a genetic cause in 49 (26%) cases and 77 diagnostic variants (22). Interestingly, despite the recessive inheritance of these conditions, all variants were extremely rare; 32 (42%) were absent from the literature, 39 (51%) were absent from Exome Aggregation Consortium (ExAC), and a further 25 (32%) had a max MAF of less than 1×10^{-4}. One exception is pediatric steroid-resistant nephrotic syndrome caused by variants in *NPHS2*, which offers an interesting example of the interaction of common and rare variants in disease. *NPHS2* p.R229Q is the most commonly identified pathogenic variant in this patient population, with a max MAF in ExAC of 0.029. However, the *NPHS2* p.R229Q variant does not cause disease when present in the homozygous state and is only pathogenic when paired with certain other rare *NPHS2* variants (23). In the cited study, the deleterious variants found in trans to *NPHS2* p.R229Q in affected individuals were always rare and often private, with *NPHS2* p.E264Q being the most common in ExAC, having a max MAF of 0.003. Similarly, the evaluation of genetic causes of CAKUT in 232 families identified 32 different causative variants in 32 cases (14%) affecting 22 genes with 16 (50%) of these variants absent from the literature and 28 (88%) very rare or absent from the Genome Aggregation Database (gnomAD) (24).

Broadening to Adult Patients

ES has been used to evaluate diverse patient populations with kidney disease, including individuals with adult-onset disease. The largest study to do so included 3,315 individuals with CKD from any cause, of whom 2,144 had developed kidney failure and 2,837 were adults at study entry (15). This study identified a molecular diagnosis in 307 individuals (9.1%) leading to the diagnosis of 66 different Mendelian kidney diseases. The study identified 343 diagnostic variants, of which 340

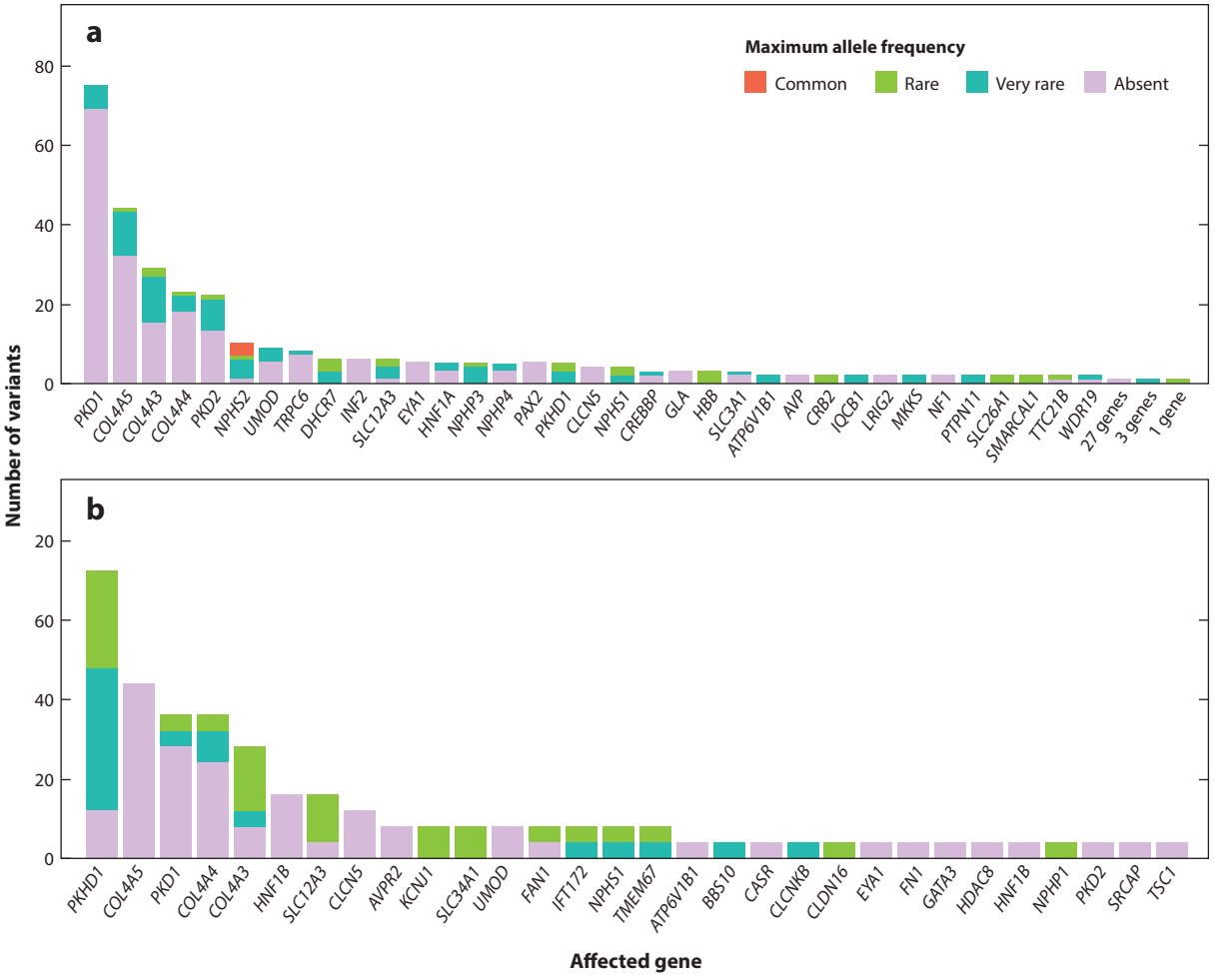

Figure 2

Maximum minor allele frequency (max MAF) of diagnostic variants assessed per gene. A variant is categorized as common if its max MAF is ≥0.01, rare if the max MAF is 0.01–0.0001, very rare if the variant is present in the Genome Aggregation Database (gnomAD) but the max MAF is <0.0001, and absent if it is not found within gnomAD. (*a*) Data from Groopman et al. (15), where genes with a single variant were collapsed into a single bar by max MAF. (*b*) Data from Jayasinghe et al. (25).

(99%) are rare in gnomAD. Most variants were either very rare, with a max MAF of less than 1×10^{-4} ($n = 84$, 24%), or private ($n = 229$, 67%) (**Figure 2*a***).

Impacts of a Genetic Diagnosis

One of the key findings of diagnostic studies is that most genetic diagnoses directly impact patient care, even with the limited number of targeted treatments currently available. Groopman et al. (15) found that a genetic diagnosis led to a clinical impact in 89% of cases, including in 76% of cases where a genetic kidney disease was suspected prior to testing. These clinical impacts were retrospectively assessed and ranged from informing prognosis to changing transplant and treatment decisions. Importantly, a genetic diagnosis in patients with CKD of unknown etiology clarified the cause of kidney disease in all cases, carried prognostic implications for 77%, initiated

targeted subspecialty care for 77%, and changed therapy for 62%. Prospective data supporting the clinical utility of genetic testing for kidney disease were recently published on 204 patients with suspected genetic kidney disease who underwent ES. A direct clinical impact was reported for 47 (59%) probands with a genetic diagnosis and for 73 (91%) families (25). Clinical impacts included the prevention of 10 kidney biopsies, changes to treatment plans in 16 cases, and altered surveillance in 35 that were again driven by rare variants (**Figure 2*b***).

Prognosis

The variability in the clinical presentation of genetic forms of kidney diseases has complicated the provison of prognostic information to patients, even when a genetic cause is identified. In addition, the majority of pathogenic variants associated with kidney disease are very rare or private within a family, which limits our ability to provide prognosis based on individual variants. Nevertheless, genotype–phenotype correlations have been part of human genetics since its inception, often using generalizable variant characteristics such as the type of effect on the protein, the properties of the altered amino acid, or the position of the variant within the protein. In nephrology, the two most mature applications of this approach look at ADPKD and Alport syndrome. For patients with ADPKD, the PROPKD (predicting renal outcomes in polycystic kidney disease) scoring system has been developed and validated to predict an individual's median age at kidney failure by integrating clinical and variant data (26). Truncating variants in *PKD1* carry the highest risk of kidney failure, followed by nontruncating *PKD1* variants, then variants in *PKD2*, and it also appears that nontruncating in-frame insertions and deletions in *PKD1* that alter the protein length carry a higher risk than missense variants (27). Similarly, for patients with Alport syndrome, nonsense variants carry the most severe prognosis, while splicing and missense variants portend intermediate and mild phenotypes, respectively. Other factors such as the position of the variant within the gene, its position relative to noncollagenous interruptions, and the substituting amino acid have also been shown to impact patient prognosis (28–30). Future tools may also include predictive information from both common and rare variants to improve their power (31). Availability of larger data sets would allow integration of more variants, and ideally more distinct families with the same variants, into the development of robust prognostic tools to allow for better predictions. Such tools could significantly impact clinical trials, as participants could be stratified based on the expected progression of their disease.

Treatment

Diagnostic studies have shown that obtaining a genetic diagnosis can have a direct impact on treatment (**Table 1**). Examples include the use of high-dose coenzyme Q10 (CoQ10) supplementation for patients with nephrotic syndrome and diagnostic variants within the CoQ10 pathway (*COQ2*, *COQ6*, *ADCK2/COQ8B*, *PDSS2*, *MTTL1*) and the use of xanthine oxidase inhibitors for patients with APRT (adenine phosphoribosyltransferase) deficiency (32, 33). A genetic diagnosis can limit exposure to ineffective treatments; for example, when a genetic cause of nephrotic syndrome is identified, immunosuppression is usually not used, as the majority of genetic nephrotic syndrome cases will not respond and these treatments carry significant risks (34). Future studies should assess the benefits of avoided adverse effects, such as reduced infection and cancer risks from limiting immunosuppression due to genetic testing. Moreover, the ability to detect undiagnosed patients with monogenic diseases can help with risk stratification in clinical trials to optimize power and reduce exposure to side effects.

An ultimate goal is to develop curative treatments. One of the most advanced examples in nephrology is the application of gene therapy for Fabry disease (35). Fabry disease is caused by

Table 1 Some examples of kidney-relevant monogenic disorders with disease-specific therapies

Syndrome	Gene(s)	Therapy
Liddle syndrome	*SCNN1A*, *SCNN1B*, or *SCNN1G*	Amiloride
Pseudohyperaldosteronism, type II	*KCNJ5*	Thiazide diuretics
Corticosteroid remediable aldosteronism	*CYP11B2/CYP11B1* gene fusion	Glucocorticoids
Familial hyperaldosteronism, type II	*CLCN2*	Aldosterone antagonists
Familial hyperaldosteronism, type III	*KCNJ5*	Aldosterone antagonists
Fabry disease	*GLA*	α-Galactosidase enzyme replacement, chaperone therapy, gene therapy[a]
COQ10 deficiency	*COQ2*, *COQ6*, *ADCK2/COQ8B*, *PDSS2*, or *MTTL1*	CoQ10 replacement
Primary hyperoxaluria 1	*AGXT*	RNAi therapy
APOL1-associated kidney disease	*APOL1*	Small-molecule inhibitors,[a] RNAi[a]
Amyloidosis, hereditary, transthyretin-related	*TTR*	RNAi, CRISPR-Cas9 therapy[a]

[a]Under investigation.

over 1,000 different variants in the *GLA* gene, most very rare or private, that lead to reduced α-galactosidase A activity and the accumulation of glycosphingolipids (36). The standard treatment for this disease is enzyme replacement therapy (ERT), which requires regular infusions and can lead to treatment limiting anti-drug antibodies. However, in a pilot safety study, five males with classical Fabry disease due to very rare missense variants who were stably treated with ERT were treated with gene therapy (35). They underwent lentivirus-mediated ex vivo gene therapy where hematopoietic stem/progenitor cells were transduced with a functional *GLA* gene, then reintroduced via an autologous hematopoietic stem cell transplant. These patients demonstrated a durable normalization of leukocyte α-galactosidase A activity and stable glycosphingolipid levels that allowed three (60%) of them to discontinue their ERT, with a reasonable adverse event profile. This study gives us hope that with further refinement, curative treatments may be available for more of our patients.

Fabry disease also provides other interesting examples of personalized therapy, including chaperone therapy and treatment decisions for female patients. A common mechanism of disease in this condition is altered protein trafficking leading to a reduction in enzyme activity. Migalastat is a chaperone molecule that restores enzyme function and shows clinical efficacy similar to ERT in the 35–50% of individuals with an amenable variant but has no effect in individuals with non-amenable variants (37, 38). This variant specificity makes genetic testing a key step in optimizing therapy for patients with Fabry disease. It was long thought that, due to the X-linked nature of the disease, females were unaffected carriers; however, it is now clear that many females are affected and that there is a complex interplay between the specific variant characteristics and skewed X inactivation that leads to highly heterogeneous clinical presentations (39). This has complicated the decision of when and how to treat female Fabry disease patients, as some individuals clearly benefit from therapy but we lack tools to predict response before patients are symptomatic, highlighting an area in need of further research.

Other targeted therapies are becoming available for patients with genetic kidney diseases, using new techniques like RNA interference (RNAi), antisense-oligonucleotides (ASO), and CRISPR-Cas9. RNAi has shown great promise for the treatment of genetic kidney diseases, with positive phase III trials using patisiran to treat hereditary transthyretin amyloidosis due to *TTR* variants and lumasiran to treat primary hyperoxaluria type 1 due to *AGT* variants (40, 41). These treatments have been designed to be variant agnostic, allowing them to be used to treat individuals with

a variety of different rare variants. CRISPR-Cas9 has been studied in a small cohort of individuals with transthyretin amyloidosis and was shown to reduce serum TTR production through targeted gene knockdown using an in vivo delivery technique (42). Exon-skipping ASO treatment of truncating *COL4A5* variants has been shown in mice to induce clinical and histologic improvements by altering the protein effect to an in-frame exon deletion (43). This may become a treatment option for patients with a variety of rare truncating *COL4A5* variants that typically cause severe disease but have yet to be studied in humans. Therapeutic approaches for *APOL1*-associated nephropathy include using ASO treatments to reduce *APOL1* expression and the use of small-molecule inhibitors of *APOL1* to reduce its function (44). These targeted and personalized therapies are likely to be applied to different genetic diseases and offer our patients hope for better treatments in the future.

FSGS: focal segmental glomerulosclerosis

APPROACHES FOR IDENTIFYING NEW ASSOCIATIONS

Finding new gene–disease associations is important as they can improve diagnostic evaluations and patient care. Identification of novel genes can provide a more accurate understanding of kidney structure and physiology, with the ultimate goal of developing novel therapies. However, the long tail in the distribution of genetic kidney diseases (**Figure 2**) indicates that a discovery of new monogenic kidney diseases will require access to cohorts of patients with rare disorders, or require novel approaches for large-scale phenotyping to identify rare subsets.

Family-based Studies

Despite early knowledge of the existence and inheritance patterns of genetic causes of kidney disease, the identification of the genes associated with specific conditions did not occur until the 1990s, when the first maps of the genome became available. Linkage analysis and homozygosity mapping enabled positional cloning of genes underlying classic Mendelian disorders (45, 46). One of the first genetic kidney diseases with a defined molecular cause was Alport syndrome. Cloning of *COL43*, *COL4A4*, and *COL4A5*, the type IV collagen genes expressed in the glomerular basement membranes, led to the identifications of variants in X-linked and autosomal forms of Alport syndrome (47, 48). In recent years, variants in these genes have been shown to contribute to many different forms of kidney disease, highlighting the importance of the type IV collagen component of the glomerular basement membrane in maintenance of kidney function (15, 28–30, 47, 48).

Similarly, gene mapping efforts led to the identification of the first gene for ADPKD, which was caused by variants in *PKD1* (49). This discovery relied on a family that carried an unusual and rare translocation of chromosome 22 onto chromosome 16, leading to a disruption of *PKD1* that segregated within the family. Investigators then screened other individuals with highly similar clinical presentations and identified three further probands with variants in *PKD1*, including two with rare structural variants and a private canonical splice site variant causing an in-frame deletion that segregated through three generations of a large family. Following the positional cloning of *PKD2* as the second major gene for ADPKD, there was no additional gene discovery for many years (50). Recently, ES of *PKD1/PKD2*-negative cases identified other genes that each account for a small fraction of the remaining cases (51).

Another example of the utility of identifying a rare variant in a large family is the discovery of *TRPC6* as a cause of autosomal dominant focal segmental glomerulosclerosis (FSGS) (52). A novel missense variant c.335C>A, p.P112Q, was identified through direct sequencing after haplotype analysis identified the minimal candidate region in a large family and showed perfect segregation with disease through 21 individuals. Investigators then demonstrated functional differences in *TRPC6* channel function induced by the missense change, suggesting a gain-of-function mechanism. Since then, *TRPC6* has been commonly implicated in sporadic and familial cases of

FSGS. However, FSGS has proven to be highly heterogeneous, with over 30 genes discovered to date (53).

Many other studies have used homozygosity mapping in consanguineous families to identify variants for rare diseases such as nephronophthisis or nephrotic syndrome. This approach has led to the identification of multiple genes for nephronophthisis despite very high genetic heterogeneity, implicating defects in the primary cilia and the centrosome in the pathogenesis (54, 55).

One of the challenges with family-based studies is the requirement for large families with multiple affected members alive and available for both phenotyping and genetic testing. Investigators have identified the molecular basis for disease for the majority of large families segregating monogenic disorders, and most unsolved cases involve small families with few affected individuals or singletons with unaffected parents, complicating gene identification. Since demonstration of a causal link between a gene and disease requires identification of independent variants, other approaches have been developed. As an alternative to gene mapping based on families with multiple affected individuals, one can search for de novo variants in trios of unaffected parents with an affected child (56). This approach enables identification of variants with large effects that impact reproductive fitness and are typically well suited to studying developmental disorders. Based on the relatively low mutation rate in the coding region of the human genome, recurrent de novo variants in the coding region of the same gene and pathway are likely to be disease causing. This study design has led to the identification of genes for many neuropsychiatric disorders, intellectual disability, and congenital heart disease but has not been systematically undertaken to study kidney developmental disorders (57–61).

Because of the significant genetic heterogeneity, gene discovery efforts often yield suggestive signals in candidate genes that require confirmation through identification of independent mutations. Tools like matchmaker exchange have been successful in connecting different centers with data on separate individuals with similar phenotypes to confirm new gene-disease associations and will likely continue to grow in influence in the future (62). These matchmaking services rely on researchers to collect comprehensive clinical information, as the indications leading to the sequencing are usually biased by the researcher's interest. Often, extra-renal manifestations are key for linking syndromic cases that may go unrecognized because of researchers' ascertainment bias (63, 64).

Case-Control Studies

Another approach applied to the identification of new gene–disease associations relies on comparing genetic data from a set of cases, often defined by a specific clinical phenotype, to a set of controls. These studies can utilize microarray data with imputation or massively parallel sequencing to capture variants implicated in disease. As most of the variants implicated in Mendelian kidney disease are very rare or private, single-variant association studies are underpowered. Hence, variants are often aggregated or collapsed by gene, or within a gene set that contains genes within a shared pathway or network (65). Variants are typically filtered and stratified prior to aggregation based on MAF cut-offs and in silico tools to select variants predicted to be the most damaging. In practice, many different models are tested with subsequent correction for multiple hypothesis testing.

In the nephrology field, few gene-based collapsing analyses for rare disorders have been performed. One study compared ES data from 195 cases affected by renal hypodysplasia to 6,905 unaffected controls (66). They identified a suggestive signal in *GREB1L* driven by private protein truncating and predicted deleterious missense variants ($p = 4.1 \times 10^{-6}$). After integrating familial segregation data to improve the statistical power, they demonstrated exome-wide significance ($p = 2.3 \times 10^{-7}$). *GREB1L*'s status as a susceptibility gene for renal hypodysplasia and its role in kidney morphogenesis were then validated using a zebrafish model.

However, most case-control studies utilizing gene-level collapsing analysis have not led to the identification of novel kidney disease genes. The major limitation of this approach seems to be the high genetic heterogeneity of kidney diseases. When large cohorts of patients with diverse clinical presentations are combined, only the known genes contributing to the more common monogenic diseases are statistically significant (67). When only individuals with a specific presentation are included, the number of cases is not sufficient (68). Additionally, these analyses require stringent variant filtering because 1–5% of the control population may carry predicted deleterious variants in a kidney disease–associated gene (19, 68).

Integration of Large Data Sets

The approaches outlined above have focused on cohorts collected for research purposes that range in size from single families to a few thousand individuals. Multiple efforts are underway to produce biomedical databases that link genetic sequencing data to participant data for hundreds of thousands to millions of individuals such as the UK Biobank (UKB), All of Us, the Million Veteran Program, and Geisinger Health System's DiscovEHR. These large data sets allow many different genetic and phenotypic features to be assessed simultaneously at large scale with the goal of discovering signals that would not be possible with smaller sample sizes. Results from these large biobanks are beginning to be published, and one of the most interesting data sets includes 281,104 ES results integrated with International Classification of Diseases (ICD-10)-based phenotyping and lab data from the UKB (69). This study presented a high-level overview of the cohort and analyses performed with large amounts of data available within the supplementary materials, which we parsed to identify findings of importance to kidney disease. A related approach is to study special populations whose structure makes them more advantageous for gene discovery. For example, the Pakistani Genomic Resource aims to characterize common diseases in the Pakistani population, which has a higher rate of consanguinity (70). Because consanguineous unions are more likely to result in offspring carrying homozygous loss-of-function mutations, analysis of this population enables better assessment of the phenotypic consequence of null alleles in humans and facilitates new gene discovery. Finally, integrating multiple large data sets may enable the identification of protective signals. For example, analysis of large cohorts has enabled identification of loss-of-function mutations that confer protection for chronic liver disease and atherosclerotic cardiovascular disease suggesting opportunities for drug therapy (71–73).

Exome Sequencing in the UK Biobank

The UKB's exome-wide association study (ExWAS) was performed using 2,108,983 common and rare variants from ES data to assess 17,361 binary and 1,419 quantitative traits, including the kidney disease–related outcomes of acute kidney injury (AKI), CKD, and kidney transplantation, as well as the kidney-relevant biomarkers creatinine and cystatin C levels (69). Within the binary traits of AKI, CKD, kidney transplantation, and calculi of the kidney, 78 significant variant–phenotype pairs were identified, driven by 11 variants in three genes. Five of these variants are rare and account for 42 (53%) of the significant signals. The common variant results align with prior GWAS, where mainly synonymous variants with small protective and deleterious effects were identified. The rare variants are quite different, as they are all nonsynonymous with large deleterious effects. The effect size of the rare variants ranges from an odds ratio of 9 for AKI associated with 9–5073770-G-T in *JAK2* to 2,358 for CKD stage G5 associated with 16–20349020-CA-C in *UMOD*. Even though it has been hypothesized that common variants in genes associated with Mendelian kidney disease may be associated with common forms of CKD, there were no significant ExWAS signals. The use of ICD code-based phenotyping limits phenotypic granularity and may limit the ability to identify a uniform case cohort with shared genetic etiologies. This

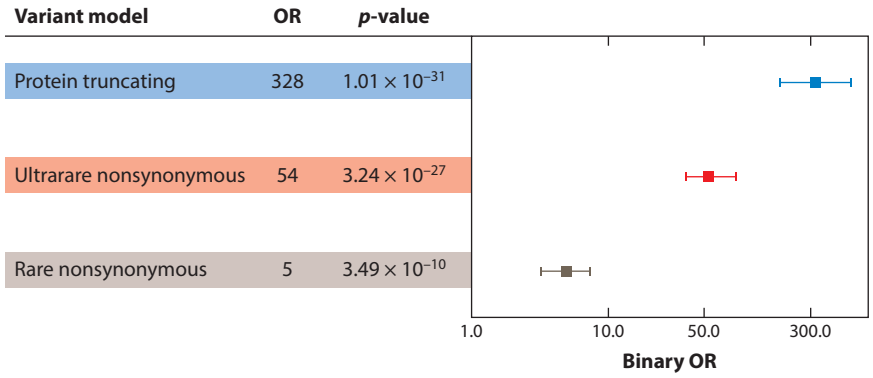

Figure 3

Forest plot showing the gene-based collapsing analysis binary odds ratio (OR) of *PKD1* for the trait of end-stage kidney disease from the major models using data from Wang et al. (69).

is supported by a recent GWAS that used a more specific case selection approach to evaluate for genetic associations with glomerular hematuria using imputed microarray data from the UKB and identified two significant rare variant signals in the known *COL4A3* and *COL4A4* genes (74–76).

The same data set was used to perform a gene-based collapsing analysis to assess variant enrichment across 18,762 genes and 18,780 phenotypes under 12 distinct variant selection models. This identified four genes with associations to kidney disease phenotypes, including two known genes, *PKD1* and *PKD2*. In addition, potential novel associations were identified between kidney disease and two other known genes, but under a different mode of inheritance: *IFT140* and *UMOD*. Despite the inclusion of 521 individuals with cystic kidney disease, 326 with polycystic kidney disease, and 1,695 individuals with glomerulonephritis, no novel genes associated with Mendelian kidney disease were uncovered.

The gene with the most significant associations and the strongest enrichment is *PKD1*, which demonstrated enrichment of rare and ultrarare protein truncating as well as nonsynonymous variants across phenotypes capturing polycystic kidney disease, CKD, kidney failure, and kidney transplantation. When looking at kidney failure as a phenotype, protein-truncating variants are associated with the largest effect size [odds ratio (OR) = 328, $p = 1.01 \times 10^{-31}$], while rare nonsynonymous variants are associated with the smallest effect sizes (OR = 3.2–5.8). Within the nonsynonymous variants, ultrarare variants have a larger effect size (OR = 32–54) than rare variants, in line with the paradigm of more common variants having smaller effect sizes (**Figure 3**).

In addition, rare protein-truncating somatic variants within the *TET2* gene and common protein-truncating somatic variants in *ASXL1* were found to be enriched in cases with CKD despite the inclusion of age as a covariate. Somatic variants in *TET2* and *ASXL1* are common driver variants in individuals with CHIP, and the associated effect size seen in this UKB cohort was similar to that seen in other cohorts with CKD, suggesting that this finding is likely driven by unrecognized individuals with CHIP (OR = 3–5) (17).

Phenome-wide Association Study and Electronic Phenotyping

Large biobank data sets can also be used in a genotype-to-phenotype approach to conduct a phenome-wide association study (PheWAS) across many phenotypes simultaneously, assessing individual variants or gene-based aggregated variant counts to identify associated phenotypes. PheWAS approaches can identify patients who may not carry a clinical diagnosis of a disease but

have evidence of manifestations within their clinical record, and it can be useful for genes that exhibit pleiotropy. PheWAS was applied to the Penn Medicine Biobank to evaluate the phenotypes associated with variants in *LMNA*, a gene chosen due to phenotypic heterogeneity (77). Of the 68 individuals with a rare qualifying variant in *LMNA*, only 10 (15%) had undergone genetic testing due to a concern about laminopathies, suggesting that most cases were not identified by standard clinical evaluation. As expected, a significant signal was identified associating *LMNA* variants with cardiomyopathy and other cardiac phenotypes such as atrial fibrillation, heart failure, and cardiac transplant. In addition, a significant association was observed between variants in *LMNA* and CKD stage G3, defined as an estimated glomerular filtration rate $\leq$60 mL/min/1.73 m^2 (OR = 4.91, $p = 1.13 \times 10^{-6}$), which was relatively robust ($p = 1.33 \times 10^{-3}$) to conditioning on the top phenotypic signal of cardiomyopathy, suggesting that it may not be due to underlying cardiac disease. While there have been reports of proteinuric kidney disease, notably FSGS, associated with acquired partial lipodystrophy due to *LMNA* variants in the literature, these PheWAS results support an underdiagnosed kidney phenotype and demonstrate the utility of PheWAS in evaluating novel gene–disease associations (78–80). In the future, PheWAS approaches may be used to identify phenotypic manifestations of known Mendelian kidney disease that went unrecognized due to reduced penetrance, clinical subtlety, or unstructured case evaluations.

The expected benefits of using large data sets to identify new gene–disease associations have not been realized in nephrology yet, as almost all of the identified associations have come from small, well-phenotyped familial studies or case-control analyses. Given the expected rarity of genetic conditions and the clinical heterogeneity of kidney disease, utilizing even larger sample sizes may fall short of leading to new discoveries. Improvements in phenotyping of existing large cohorts will be key to unlocking their potential. Identification of individuals with CKD using multiple data sources in electronic health records instead of relying solely on ICD codes has been highly successful but still lacks the granularity required to create homogeneous case cohorts of kidney disease subtypes (81). Nonetheless, the derivation of an electronic algorithm for CKD enabled derivation and validation of a genome-wide polygenic score (GPS) that identifies patients at high risk of progression (82). As disease-specific polygenic scores are developed, these can be combined with the CKD GPS and other clinical predictors to provide better risk stratification. In addition, improvement of large-scale phenotyping remains an active area of research, including machine learning, natural language processing and the integration of imaging and biopsy data (83). For example, phenotype risk scores have been shown to identify undiagnosed Mendelian disorders in biobanks (84, 85).

CONCLUSIONS AND FUTURE DIRECTIONS

Rare variants play a significant role in kidney disease, given the common and complex nature of CKD. Very rare and private variants have been prominent in diagnostic studies of individuals with kidney disease and are increasingly important in the identification of new gene and phenotype associations. Understanding the full predictive power of rare variants for patients with kidney disease requires further research to provide patients with personalized prognostic and treatment recommendations.

We have seen the limitations of working with rare variants, most notably the difficulties in identifying new associations driven both by the lack of adequate sample size and difficulties in phenotyping cases at scale. This challenge has led to the development of new approaches to gain insights into the role of genetics in kidney disease. In the future, the number of people who have undergone genetic testing will continue to grow, and we will be able to harness even larger sample sizes to improve the power of future association studies. We will also see improvements

in phenotyping techniques that provide more specific and deeper phenotypes at scale, allowing better classification of cases and construction of more homogeneous cohorts for evaluation. Extensive integration of multi-omics data will enable further insight into the interactions of genetics with the environment, transcription and translation, and epigenetics, as we are beginning to see take shape in studies such as the Kidney Precision Medicine Project (86). As these data become more refined, we hope they will allow us to provide patients with personalized care built on molecular diagnoses, accurate prognostication, and targeted therapy.

DISCLOSURE STATEMENT

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LITERATURE CITED

1. Levin A, Stevens PE, Bilous RW, et al. 2013. Kidney Disease: Improving Global Outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int. Suppl.* 3(1):1–150
2. Bikbov B, Purcell CA, Levey AS, et al. 2020. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 395(10225):709–33
3. Arpegård J, Viktorin A, Chang Z, et al. 2015. Comparison of heritability of cystatin C- and creatinine-based estimates of kidney function and their relation to heritability of cardiovascular disease. *J. Am. Heart Assoc.* 4(1):e001467
4. Wuttke M, Li Y, Li M, et al. 2019. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat. Genet.* 51(6):957–72
5. Zhang J, Thio CHL, Gansevoort RT, et al. 2021. Familial aggregation of CKD and heritability of kidney biomarkers in the general population: the Lifelines Cohort Study. *Am. J. Kidney Dis.* 77(6):869–78
6. Karczewski KJ, Francioli LC, Tiao G, et al. 2020. The mutational constraint spectrum quantified from variation in 141,456 humans. *Nature* 581(7809):434–43
7. Lek M, Karczewski KJ, Minikel EV, et al. 2016. Analysis of protein-coding genetic variation in 60,706 humans. *Nature* 536(7616):285–91
8. The 1000 Genomes Proj. Consort. 2015. A global reference for human genetic variation. *Nature* 526(7571):68–74
9. Ars E, Ballarin J, Ruiz P, et al. 2011. Clinical utility of genetic testing in children and adults with steroid-resistant nephrotic syndrome. *Clin. J. Am. Soc. Nephrol.* 6(5):1139–48
10. Wühl E, van Stralen KJ, Wanner C, et al. 2014. Renal replacement therapy for rare diseases affecting the kidney: an analysis of the ERA-EDTA Registry. *Nephrol. Dialysis Transplantation.* 29(Suppl. 4):iv1–8
11. Cocchi E, Nestor JG, Gharavi AG. 2020. Clinical genetic screening in adult patients with kidney disease. *Clin. J. Am. Soc. Nephrol.* 15(10):1497–510
12. Génin E. 2020. Missing heritability of complex diseases: case solved? *Hum Genet*. 139(1):103–13
13. Wainschtein P, Jain D, Zheng Z, et al. 2022. Assessing the contribution of rare variants to complex trait heritability from whole-genome sequence data. *Nat. Genet.* 54(3):263–73
14. Verbitsky M, Westland R, Perez A, et al. 2019. The copy number variation landscape of congenital anomalies of the kidney and urinary tract. *Nat. Genet.* 51(1):117–27
15. Groopman EE, Marasa M, Cameron-Christie S, et al. 2018. Diagnostic utility of exome sequencing for kidney disease. *N. Engl. J. Med.* 380(2):142–51

16. Tan AY, Zhang T, Michaeel A, et al. 2018. Somatic mutations in renal cyst epithelium in autosomal dominant polycystic kidney disease. *J. Am. Soc. Nephrol.* 29(8):2139–56
17. Vlasschaert C, McNaughton AJM, Chong M, et al. 2022. Association of clonal hematopoiesis of indeterminate potential with worse kidney function and anemia in two cohorts of patients with advanced chronic kidney disease. *J. Am. Soc. Nephrol.* 33(5):985–95
18. Fu XJ, Nozu K, Kaito H, et al. 2016. Somatic mosaicism and variant frequency detected by next-generation sequencing in X-linked Alport syndrome. *Eur. J. Hum. Genet.* 24(3):387–91
19. Rasouly HM, Groopman EE, Heyman-Kantor R, et al. 2019. The burden of candidate pathogenic variants for kidney and genitourinary disorders emerging from exome sequencing. *Ann. Intern. Med.* 170(1):11–21
20. Devuyst O, Knoers NVAM, Remuzzi G, et al. 2014. Rare inherited kidney diseases: challenges, opportunities, and perspectives. *Lancet* 383(9931):1844–59
21. Ingelfinger JR, Kalantar-Zadeh K, Schaefer F, et al. 2016. Averting the legacy of kidney disease—focus on childhood. *Kidney Dis.* 2(1):46–52
22. Bierzynska A, McCarthy HJ, Soderquest K, et al. 2017. Genomic and clinical profiling of a national nephrotic syndrome cohort advocates a precision medicine approach to disease management. *Kidney Int.* 91(4):937–47
23. Mikó Á, Menyhárd DK, Kaposi A, et al. 2018. The mutation-dependent pathogenicity of NPHS2 p.R229Q: a guide for clinical assessment. *Hum. Mutat.* 39(12):1854–60
24. van der Ven AT, Connaughton DM, Ityel H, et al. 2018. Whole-exome sequencing identifies causative mutations in families with congenital anomalies of the kidney and urinary tract. *J. Am. Soc. Nephrol.* 29(9):2348–61
25. Jayasinghe K, Stark Z, Kerr PG, et al. 2021. Clinical impact of genomic testing in patients with suspected monogenic kidney disease. *Genet. Med.* 23:183–91
26. Cornec-Le Gall E, Audrézet M-P, Rousseau A, et al. 2016. The PROPKD score: a new algorithm to predict renal survival in autosomal dominant polycystic kidney disease. *J. Am. Soc. Nephrol.* 27(3):942–51
27. Hwang Y-H, Conklin J, Chan W, et al. 2016. Refining genotype-phenotype correlation in autosomal dominant polycystic kidney disease. *J. Am. Soc. Nephrol.* 27(6):1861–68
28. Gibson JT, Huang M, Shenelli Croos Dabrera M, et al. 2022. Genotype-phenotype correlations for *COL4A3–COL4A5* variants resulting in Gly substitutions in Alport syndrome. *Sci. Rep.* 12:2722
29. Yamamura T, Horinouchi T, Nagano C, et al. 2020. Genotype-phenotype correlations influence the response to angiotensin-targeting drugs in Japanese patients with male X-linked Alport syndrome. *Kidney Int.* 98(6):1605–14
30. Bekheirnia MR, Reed B, Gregory MC, et al. 2010. Genotype-phenotype correlation in X-linked Alport syndrome. *J. Am. Soc. Nephrol.* 21(5):876–83
31. Fahed AC, Wang M, Homburger JR, et al. 2020. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. *Nat. Commun.* 11(1):3635
32. Wang N, Zheng Y, Zhang L, et al. 2022. A family segregating lethal primary coenzyme Q10 deficiency due to two novel COQ6 variants. *Front. Genet.* 12:811833
33. Bollée G, Harambat J, Bensman A, et al. 2012. Adenine phosphoribosyltransferase deficiency. *Clin. J. Am. Soc. Nephrol.* 7(9):1521–27
34. Kemper MJ, Lemke A. 2018. Treatment of genetic forms of nephrotic syndrome. *Front. Pediatr.* 6:72
35. Khan A, Barber DL, Huang J, et al. 2021. Lentivirus-mediated gene therapy for Fabry disease. *Nat. Commun.* 12(1):1178
36. McCafferty EH, Scott LJ. 2019. Migalastat: a review in Fabry disease. *Drugs* 79(5):543–54
37. Hughes DA, Nicholls K, Shankar SP, et al. 2017. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. *J. Med. Genet.* 54(4):288–96
38. Germain DP, Hughes DA, Nicholls K, et al. 2016. Treatment of Fabry's disease with the pharmacologic chaperone migalastat. *N. Engl. J. Med.* 375(6):545–55
39. Germain DP, Arad M, Burlina A, et al. 2019. The effect of enzyme replacement therapy on clinical outcomes in female patients with Fabry disease—a systematic literature review by a European panel of experts. *Mol. Genet. Metab.* 126(3):224–35

40. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. 2018. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N. Engl. J. Med.* 379(1):11–21
41. Garrelfs SF, Frishberg Y, Hulton SA, et al. 2021. Lumasiran, an RNAi therapeutic for primary hyperoxaluria type 1. *N. Engl. J. Med.* 384(13):1216–26
42. Gillmore JD, Gane E, Taubel J, et al. 2021. CRISPR-Cas9 in vivo gene editing for transthyretin amyloidosis. *N. Engl. J. Med.* 385(6):493–502
43. Yamamura T, Horinouchi T, Adachi T, et al. 2020. Development of an exon skipping therapy for X-linked Alport syndrome with truncating variants in *COL4A5*. *Nat. Commun.* 11(1):2777
44. Daneshpajouhnejad P, Kopp JB, Winkler CA, et al. 2022. The evolving story of apolipoprotein L1 nephropathy: the end of the beginning. *Nat. Rev. Nephrol.* 18(5):307–20
45. Lander ES, Botstein D. 1989. Mapping mendelian factors underlying quantitative traits using RFLP linkage maps. *Genetics* 121(1):185–99
46. Claussnitzer M, Cho JH, Collins R, et al. 2020. A brief history of human disease genetics. *Nature* 577(7789):179–89
47. Barker DF, Hostikka SL, Zhou J, et al. 1990. Identification of mutations in the COL4A5 collagen gene in Alport syndrome. *Science* 248(4960):1224–27
48. Mochizuki T, Lemmink HH, Mariyama M, et al. 1994. Identification of mutations in the alpha 3(IV) and alpha 4(IV) collagen genes in autosomal recessive Alport syndrome. *Nat. Genet.* 8(1):77–81
49. Eur. Polycystic Kidney Dis. Consort. 1994. The polycystic kidney disease 1 gene encodes a 14 kb transcript and lies within a duplicated region on chromosome 16. *Cell* 77(6):881–94
50. Mochizuki T, Wu G, Hayashi T, et al. 1996. *PKD2*, a gene for polycystic kidney disease that encodes an integral membrane protein. *Science* 272(5266):1339–42
51. Cornec-Le Gall E, Alam A, Perrone RD. 2019. Autosomal dominant polycystic kidney disease. *Lancet* 393(10174):919–35
52. Winn MP, Conlon PJ, Lynn KL, et al. 2005. A mutation in the TRPC6 cation channel causes familial focal segmental glomerulosclerosis. *Science* 308(5729):1801–4
53. Li AS, Ingham JF, Lennon R. 2020. Genetic disorders of the glomerular filtration barrier. *Clin. J. Am. Soc. Nephrol.* 15(12):1818–28
54. Braun DA, Hildebrandt F. 2017. Ciliopathies. *Cold Spring Harb. Perspect. Biol.* 9(3):a028191
55. Hildebrandt F, Benzing T, Katsanis N. 2011. Ciliopathies. *N. Engl. J. Med.* 364(16):1533–43
56. Roach JC, Glusman G, Smit AFA, et al. 2010. Analysis of genetic inheritance in a family quartet by whole-genome sequencing. *Science* 328(5978):636–39
57. Sebat J, Lakshmi B, Malhotra D, et al. 2007. Strong association of de novo copy number mutations with autism. *Science* 316(5823):445–49
58. Iossifov I, O'Roak BJ, Sanders SJ, et al. 2014. The contribution of de novo coding mutations to autism spectrum disorder. *Nature* 515(7526):216–21
59. Xu B, Roos JL, Dexheimer P, et al. 2011. Exome sequencing supports a de novo mutational paradigm for schizophrenia. *Nat. Genet.* 43(9):864–68
60. Vissers LELM, de Ligt J, Gilissen C, et al. 2010. A de novo paradigm for mental retardation. *Nat. Genet.* 42(12):1109–12
61. Zaidi S, Choi M, Wakimoto H, et al. 2013. De novo mutations in histone-modifying genes in congenital heart disease. *Nature* 498(7453):220–23
62. Azzariti DR, Hamosh A. 2020. Genomic data sharing for novel Mendelian disease gene discovery: the matchmaker exchange. *Annu. Rev. Genom. Hum. Genet.* 21:305–26
63. Martin EMMA, Enriquez A, Sparrow DB, et al. 2020. Heterozygous loss of WBP11 function causes multiple congenital defects in humans and mice. *Hum. Mol. Genet.* 29(22):3662–78
64. Connaughton DM, Dai R, Owen DJ, et al. 2020. Mutations of the transcriptional corepressor ZMYM2 cause syndromic urinary tract malformations. *Am. J. Hum. Genet.* 107(4):727–42
65. Povysil G, Petrovski S, Hostyk J, et al. 2019. Rare-variant collapsing analyses for complex traits: guidelines and applications. *Nat. Rev. Genet.* 20(12):747–59
66. Sanna-Cherchi S, Khan K, Westland R, et al. 2017. Exome-wide association study identifies *GREB1L* mutations in congenital kidney malformations. *Am. J. Hum. Genet.* 101(5):789–802

67. Cameron-Christie S, Wolock CJ, Groopman E, et al. 2019. Exome-based rare-variant analyses in CKD. *J. Am. Soc. Nephrol.* 30(6):1109–22
68. Wang M, Chun J, Genovese G, et al. 2019. Contributions of rare gene variants to familial and sporadic FSGS. *J. Am. Soc. Nephrol.* 30(9):1625–40
69. Wang Q, Dhindsa RS, Carss K, et al. 2021. Rare variant contribution to human disease in 281,104 UK Biobank exomes. *Nature* 597(7877):527–32
70. Saleheen D, Natarajan P, Armean IM, et al. 2017. Human knockouts and phenotypic analysis in a cohort with a high rate of consanguinity. *Nature* 544(7649):235–39
71. Verweij N, Haas ME, Nielsen JB, et al. 2022. Germline mutations in CIDEB and protection against liver disease. *N. Engl. J. Med.* 387(4):332–44
72. Abul-Husn NS, Cheng X, Li AH, et al. 2018. A protein-truncating HSD17B13 variant and protection from chronic liver disease. *N. Engl. J. Med.* 378(12):1096–106
73. Cohen JC, Boerwinkle E, Mosley TH, et al. 2006. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N. Engl. J. Med.* 354(12):1264–72
74. Bycroft C, Freeman C, Petkova D, et al. 2018. The UK Biobank resource with deep phenotyping and genomic data. *Nature* 562(7726):203–9
75. Das S, Forer L, Schönherr S, et al. 2016. Next-generation genotype imputation service and methods. *Nat. Genet.* 48(10):1284–87
76. Taliun SAG, Sulem P, Sveinbjornsson G, et al. 2022. GWAS of hematuria. *Clin. J. Am. Soc. Nephrol.* 17(5):672–83
77. Pais LS, Snow H, Weisburd B, et al. 2022. seqr: A web-based analysis and collaboration tool for rare disease genomics. *Hum. Mutat.* 43(6):698–707
78. Thong KM, Xu Y, Cook J, et al. 2013. Cosegregation of focal segmental glomerulosclerosis in a family with familial partial lipodystrophy due to a mutation in *LMNA*. *Nephron Clin. Pract.* 124(1–2):31–37
79. Fountas A, Giotaki Z, Dounousi E, et al. 2017. Familial partial lipodystrophy and proteinuric renal disease due to a missense c.1045C > T LMNA mutation. *Endocrinol. Diabetes Metab. Case Rep.* 2017:17-0049
80. Hussain I, Jin RR, Baum HBA, et al. 2020. Multisystem progeroid syndrome with lipodystrophy, cardiomyopathy, and nephropathy due to an *LMNA* p.R349W variant. *J. Endocr. Soc.* 4(10):bvaa104
81. Shang N, Khan A, Polubriaginof F, et al. 2021. Medical records-based chronic kidney disease phenotype for clinical care and "big data" observational and genetic studies. *NPJ Digit. Med.* 4(1):70
82. Khan A, Turchin MC, Patki A, et al. 2022. Genome-wide polygenic score to predict chronic kidney disease across ancestries. *Nat. Med.* 28(7):1412–20
83. Garcelon N, Burgun A, Salomon R, et al. 2020. Electronic health records for the diagnosis of rare diseases. *Kidney Int.* 97(4):676–86
84. Bastarache L, Hughey JJ, Hebbring S, et al. 2018. Phenotype risk scores identify patients with unrecognized Mendelian disease patterns. *Science* 359(6381):1233–39
85. Son JH, Xie G, Yuan C, et al. 2018. Deep phenotyping on electronic health records facilitates genetic diagnosis by clinical exomes. *Am. J. Hum. Genet.* 103(1):58–73
86. de Boer IH, Alpers CE, Azeloglu EU, et al. 2021. Rationale and design of the Kidney Precision Medicine Project. *Kidney Int.* 99(3):498–510

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