REVIEW ARTICLE

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Genetics of Chronic Kidney Disease

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Chronic kidney disease (CKD) is a public health challenge that affects more than 800 million people worldwide.[1] CKD can be caused by a variety of disease processes. Many causes are difficult to identify with the use of traditional clinical diagnostics, and precise causes often remain unknown. Globally, most cases of CKD have been attributed to diabetes mellitus or hypertension, which are not discussed here. However, genetic causes of CKD are increasingly recognized. The Kidney Disease: Improving Global Outcomes (KDIGO) organization recently highlighted the importance of genetics in the classification and management of CKD and advised clinicians to consider genetic testing in order to improve diagnostic accuracy and facilitate personalized medical management in nephrology.[2]

Our understanding of the genetic basis of kidney diseases has evolved considerably since the identification of the autosomal dominant polycystic kidney disease (ADPKD) locus in 1985.[3] Since then, hundreds of different genes involved in kidney disease have been identified, many through massively parallel sequencing. Lists of genes related to CKD have been published elsewhere[4-6] and are continually updated.[7]

Genetic diseases have been identified much more frequently among children with CKD and have only recently emerged as important causes of CKD in adults.[8-11] This review discusses the diagnosis and management of CKD of genetic origin, with a focus on monogenic forms of CKD and on variants that confer a substantial risk of progressive CKD. Genetic variants that are important only in the context of polygenic risk scores[12] or risk alleles that modulate certain measures of kidney function (e.g., the estimated or measured glomerular filtration rate [eGFR or GFR][13] or urinary protein concentration) are beyond the scope of this review.

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EPIDEMIOLOGY

It has long been known that many common and diverse causes of CKD cluster in families, indicating genetic contributions.[14] Furthermore, disparities among racial and ethnic groups have suggested genetic contributions. Most genetic kidney diseases are rare. Collectively, however, they contribute substantially to the global prevalence of CKD. Multiple worldwide reports indicate that a diverse array of distinct monogenic disorders may explain approximately 30 to 50% of CKD cases among children[6,15-17] and approximately 10 to 20% of adult cases.[8-11,18] Genetic kidney diseases in childhood and adulthood constitute an age-dependent continuum[11] without an upper diagnostic age limit.[2]

PATHOPHYSIOLOGICAL MECHANISMS AND CLASSIFICATION

The genetic risk of CKD can also be viewed on a spectrum of low-penetrance to high-penetrance genetic variants. At one end of the spectrum are high-penetrance,

KEY POINTS

GENETICS OF CHRONIC KIDNEY DISEASE

- Genetic causes of chronic kidney disease (CKD) are not uncommon. Patients with CKD should be referred for genetic consultation and testing when indicated.
- Obtaining a variant-level molecular diagnosis is important, even when the clinical phenotype–based diagnosis supports a specific genetic cause. Genetic–molecular diagnoses establish precise causes, with clinical implications for personalized monitoring and treatment and for effective genetic family counseling.
- The most common monogenic CKD diagnoses worldwide include pathogenic variants in *PKD* and *COL4A*. Pathogenic variants in many other genes account for the remaining genetic diagnoses.
- Some types of CKD have complex genetic determinants, with the risk of disease dependent on genotype (e.g., the *APOL1* genotype) and environment. Persons of African ancestry are more likely than persons of other ancestries to harbor *APOL1* risk variants.
- Genetic research on CKD is rapidly growing. Even patients with negative results of genetic testing should be periodically reassessed as novel risk genes and variants are identified and as genetic tests become more available and informative. Genetic diagnoses of CKD may render patients eligible for existing and, possibly, emerging gene-related therapies.

mendelian diseases. The disease phenotype of such entities is caused by a pathogenic variant — or, in recessive disease, two pathogenic variants (or one in the homozygous state) — in a single gene. These conditions often have tight genotype–phenotype correlations. In contrast, low-penetrance variants or risk alleles often act in concert with environmental factors to cause disease (Fig. 1).

The causes of CKD can be classified on the basis of clinical manifestations, renal histologic characteristics, or genetic features. Given the extent of the genetic and phenotypic heterogeneity of CKD, gene-related definitions are the most specific and accurate. A genetic diagnosis points to the root cause of a given disease and can potentially provide insights into molecular mechanisms and often into prognosis and management that go beyond the insights provided by traditional CKD phenotypes.

Genetic kidney diseases can be grouped into multiple subcategories that encompass various malformations or syndromes attributable to specific single-gene conditions (Fig. 2). Gene-related definitions do not necessarily correspond to specific clinical manifestations or renal histologic features. Moreover, a genetic diagnosis leads to reclassification of the original clinical or histologic diagnosis in 10 to 50% of cases.[11,18,20] Such reclassification may prompt a change in management to an approach focused on genetic–molecular mechanisms. Thus, genetic testing may complement or even supersede kidney biopsy as the standard for the diagnosis and management of some forms of CKD. These insights have resulted in a CKD molecular taxonomy that may facilitate the use of precision medicine as standard clinical practice (Fig. 2).

GENOTYPE AND PHENOTYPE IN GENETIC FORMS OF CKD

To date, hundreds of genes have been associated with genetic forms of CKD. It is therefore helpful to focus on practice-relevant insights concerning the most common genetic causes of CKD in adults.

CYSTIC KIDNEY DISEASES

Cystic kidney diseases are most commonly due to renal ciliopathies, a diverse group of genetic disorders caused by alterations in proteins localized within the cilium–centrosome complex.[21] Clinical phenotypes include multiple renal cysts, as seen in ADPKD, and normal-size or small echogenic kidneys, as often seen in nephronophthisis.

ADPKD

ADPKD is the most common genetic kidney disease worldwide, affecting 4 to 8% of all patients with kidney failure.[22] A systemic disorder with variable clinical expression, ADPKD may include extrarenal manifestations such as liver cysts, cerebral aneurysms, and cardiac valvular disease.[22] The main causes of ADPKD are patho-

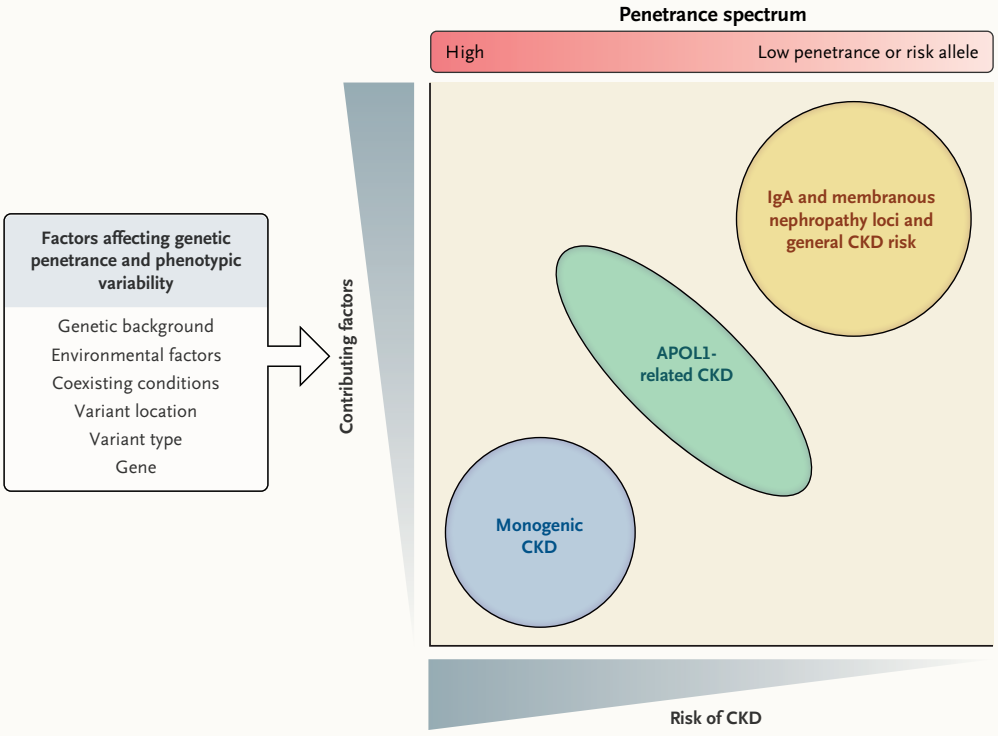

Figure 1. Risk of Genetic Chronic Kidney Disease (CKD) According to Genetic Penetrance and Contributing Factors.

Genetic penetrance refers to the proportion of people with a particular genetic variant who have a disease phenotype attributed to the genetic variant. Consensus genetic terminology has recently been defined by the National Institutes of Health Clinical Genome Resource (ClinGen).[19] "Low penetrance" describes variants for which there may be evidence of segregation in a mendelian inheritance pattern but without the development of disease features in the majority of carriers. However, carriers of these variants have a higher rate of disease than the background prevalence for the associated condition, which makes the presence of a low-penetrance variant alone clinically significant, as evident in the case of APOL1-related CKD. "Risk allele" describes variants that are not themselves causative and are not manifested in a mendelian pattern of inheritance but that may combine with other genomic variants to increase the CKD risk. Furthermore, such an allele, instead of causing disease, may be genetically linked to another variant that directly contributes to disease causation or may be part of a set of variants for which a single major variant contributing to disease risk cannot be distinguished. Examples are risk alleles linked to IgA nephropathy or idiopathic membranous nephropathy.

genic variants in two genes, *PKD1* (in approximately 78% of cases) or *PKD2* (in approximately 15% of cases), which encode the polycystin 1 and polycystin 2 proteins, respectively. Genotype–phenotype correlation studies show that truncated *PKD1* variants are associated with more severe kidney disease, as compared with *PKD1* missense and *PKD2* variants.[23] Several additional genes have recently been implicated in rare cases of ADPKD (e.g., *IFT140*, *GANAB*, *NEK8*, and *DNAJB11* [Table S1]). The polygenic background accompanying the mutant protein may explain, in part, the observed interfamilial variation in the severity of ADPKD.[24] Although the pathogenetic mechanisms of ADPKD are unclear, data from mouse models point to dose-dependent cystogenesis through the encoded mutant protein.[25,26]

In children, ADPKD may be diagnosed after asymptomatic solitary or multiple renal cysts are detected incidentally on renal ultrasonography. Valvular heart disease[27] and severe early cystic kidney disease due to biallelic *PKD1* or *PKD2* variants have also been reported.[28,29] Autosomal recessive polycystic kidney disease due to variants in the gene encoding fibrocystin (*PKHD1*) is

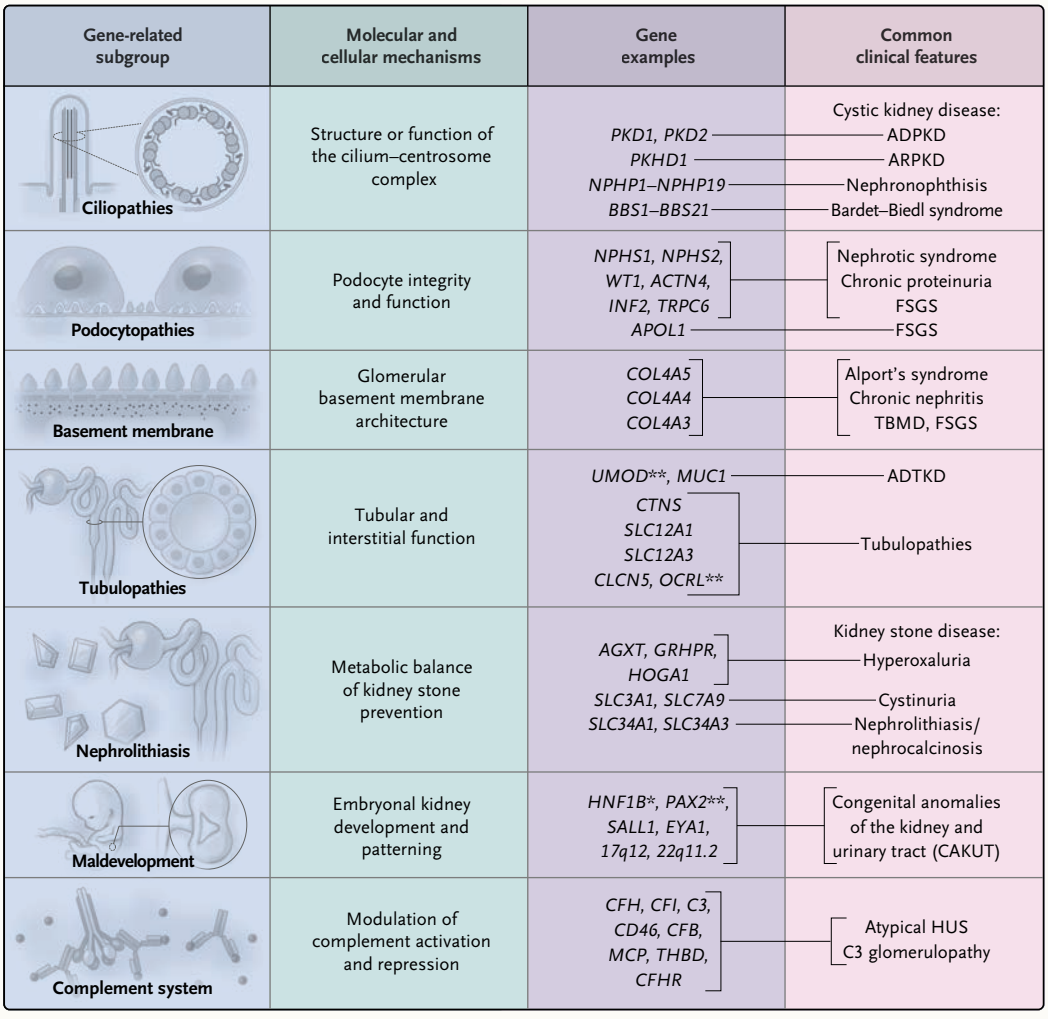

Figure 2. Major Cellular and Molecular Categories of CKD of Genetic Origin.

The most common genes and their various clinical features are shown as examples of syndromes related to CKD of genetic origin in each subgroup shown. Given the extent of genetic and phenotypic heterogeneity, combined with the importance of precise delineation of causal variants for disease management, gene-based use of CKD categorization is becoming a standard of clinical practice. Disorders related to CKD of genetic origin can be defined by specific gene variants that provide molecular and mechanistic information about pathophysiological features and about potential treatment options. Thus, similar CKD conditions may be managed with treatments that differ according to the specific molecular pathogenesis. Genetic forms of CKD are characterized by high degrees of genetic and phenotypic heterogeneity. For example, a histologically based diagnosis of focal segmental glomerulosclerosis (FSGS) is nonspecific and reflects a shared pathophysiological process and histopathological outcome downstream of many different single-gene variants, such as those in *APOL1*, *COL4A5*, *UMOD*, and *INF2*. Each variant initiates a distinct causal process, eventually leading to CKD with kidney biopsy findings of FSGS. This phenomenon is known as genetic or locus heterogeneity. Conversely, variants in the same gene can sometimes lead to different clinical and histopathological CKD phenotypes among individual patients. For example, variants in *HNF1B* can lead to developmental renal anomalies, as well as tubular dysfunction leading to hypomagnesemia and hyperuricemia, or cause cystic kidney disease, which can be phenotypically similar to autosomal dominant polycystic kidney disease (ADPKD). This phenomenon is known as allelic or phenotypic heterogeneity. The horizontal lines represent classical phenotypes. The gene *HNF1B* (single asterisk) has been rarely reported to cause an autosomal dominant tubulointerstitial kidney disease (ADTKD) phenotype. The genes *CLCN5, OCRL* and *PAX2* (double asterisk) have also been reported to cause FSGS. ARPKD denotes autosomal recessive polycystic kidney disease, HUS hemolytic–uremic syndrome, and TBMD thin basement membrane disease.

primarily a childhood cystic kidney disease, but rare cases have developed in adulthood.[30] Such late presentations often depend on the severity of the *PKHD1* variants,[31] and extrarenal signs of hepatic involvement are frequently detected.[30]

Until recently, routine clinical genetic testing in persons with ADPKD was seldom performed.[32] Nonetheless, a diagnosis at the genetic level is important, since variants in more than 15 different genes can mimic an ADPKD phenotype (Table S1). Using exome sequencing, Chang et al.[33] reported that 19 of 235 patients (8.1%) with a clinical diagnosis of ADPKD had variants in genes other than *PKD1* or *PKD2*. Thus, genetic testing in patients with cystic kidney disease can inform clinical management and family planning and reclassify patients on the ADPKD spectrum. Genetic testing using Sanger or short-read exome sequencing of *PKD1* may have major limitations because of duplications and homology with similar pseudogenes.[34] Therefore, validation through a long-range polymerase-chain-reaction (PCR) assay is necessary for complete detection of *PKD1* variations.

Nephronophthisis

Nephronophthisis is a group of genetically heterogeneous autosomal recessive diseases characterized by nonspecific, progressive deterioration in kidney function. The disorder may occur at any age — childhood, adolescence, or adulthood — and is characterized by polyuria, growth retardation (in children), and anemia but with a generally bland urinary sediment. Extrarenal manifestations, with eye, brain, liver, or skeletal abnormalities, are present in 15 to 50% of cases, depending on the involved gene.[35,36]

Nephronophthisis is most accurately diagnosed by genetic testing (with a yield of approximately 70% in suspected cases).[37] Homozygous variants (most commonly deletions) in *NPHP1* account for 20 to 50% of all cases.[35,38] The remaining cases are caused by variants in any one of approximately 90 different genes related to multiple molecular pathways regulating planar cell polarity, sonic hedgehog signaling, the DNA damage response, or cyclic AMP signaling.[36,37] Genotype–phenotype correlation studies show that null variants in nephronophthisis genes are associated with a younger age at presentation and more severe disease phenotypes.[35,39] Data from a recent cohort of 600 patients with nephronophthisis suggest that adult-onset disease with underdiagnosis is the rule.[35]

GENETIC GLOMERULAR DISEASES

Genetic glomerular diseases often involve mutant gene products that normally maintain podocyte function or pathogenic variants of proteins that make up the glomerular basement membrane (e.g., collagen type IV). Clinical presentations include the steroid-resistant nephrotic syndrome (SRNS) with focal segmental glomerulosclerosis (FSGS) on kidney biopsy or chronic proteinuria with or without hematuria. FSGS is a nonspecific lesion that represents a pattern of podocyte injury rather than a defined disease entity. Genetic forms of FSGS may be familial or sporadic. Extrarenal features may be present, depending on the involved gene.[40]

CKD Related to Type IV Collagen

Variants in the genes encoding the α3, α4, and α5 chains of type IV collagen (*COL4A3*, *COL4A4*, and *COL4A5*, respectively) are the second most common genetic cause of CKD after ADPKD, accounting for approximately 2 to 3% of cases in adults with advanced CKD.[8] More than 30 years ago, alterations in type IV collagen, a major component of the glomerular basement membrane, were identified in patients with Alport's syndrome (so-called familial nephritis). Subsequent studies have shown wide phenotypic variation among patients with collagen variants, often associated with modes of inheritance and the location and types of variant within the genes encoding type IV collagen. Clinical features range from classic Alport's syndrome (glomerular hematuria, hearing loss, and eye abnormalities) to disease confined solely to the kidneys, with a thin basement membrane seen on electron microscopy, or FSGS. Multiple studies show that previously underappreciated variants in genes encoding type IV collagen are responsible for many cases of CKD in adults who do not have the classic extrarenal features of Alport's syndrome.[8-11] Such patients may initially have persistent, isolated hematuria or proteinuria, with subsequent development of progressive CKD.

Genotype–phenotype correlations for the genes encoding type IV collagen have been described extensively.[41-43] X-linked disease is caused by pathogenic variants in *COL4A5* and autosomal reces-

sive or autosomal dominant inheritance of pathogenic variants in *COL4A3* or *COL4A4.* X-linked and autosomal recessive disease are associated with the highest risk of kidney failure. Kidney failure develops in most men and 15 to 30% of women with X-linked disease, as well as in most persons with autosomal recessive disease.[41,42] Alport's syndrome resulting from pathogenic variants in two different genes encoding type IV collagen (digenic inheritance) may have worse clinical outcomes than disease due to a single-gene heterozygous variant.[44] Furthermore, truncating variants are associated with worse renal outcomes, as compared with missense variants, with a younger age at the onset of kidney failure.[41,43] Missense variants often affect glycine residues that are required for assembling the collagen heterotrimer structure. Establishing the precise molecular diagnosis of variants of genes encoding type IV collagen is critical for selection of appropriate treatment and a possible kidney donor.[45]

Monogenic Forms of SRNS and FSGS

Two decades ago, the identification of variants in the podocyte-associated genes encoding nephrin (*NPHS1*)[46] and podocin (*NPHS2*)[47] in children with congenital forms of autosomal recessive nephrotic syndrome established podocyte disease as a cause of chronic proteinuria and progressive kidney failure.[48] Autosomal dominant and recessive inherited alterations in more than 50 different gene products that maintain podocyte ultrastructure, mediate signal transduction, or control podocyte cytoskeletal rearrangements have been reported as genetic causes of nephrotic syndrome or chronic proteinuria.[40] Persons with these variants most often present during childhood but occasionally present during adulthood. For example, variants in podocin, the most commonly mutated protein in children with infantile nephrotic syndrome, have also been reported in adult-onset cases of proteinuria or FSGS. In addition, the podocin variant R229Q, found in approximately 4% of the European population, has been associated with an increased risk of adult-onset FSGS, a risk modulated by the podocin variant of the second allele.[49,50] Additional single-gene causes of adult-onset proteinuria and FSGS include autosomal dominant variants in the cytoskeletal genes *ACTN4*[51] and *INF2*[52] and the cation channel protein encoded by *TRPC6*.[53,54] Identification of the associated monogenic syndromes can inform clinical management.

TUBULOINTERSTITIAL DISEASES

Genetic conditions affecting renal tubular function (tubulopathies) encompass more than 50 syndromes, which usually involve ion channels or transporters.[55] Clinical features can include fluid-shift imbalances. Laboratory abnormalities include electrolyte or acid–base disturbances and tubular proteinuria. Imaging can show nephrolithiasis or nephrocalcinosis, and nonspecific tubulointerstitial damage is often seen in kidney biopsy specimens.

Uromodulin (also known as Tamm–Horsfall protein) is a kidney-specific protein that is synthesized by the thick ascending limb of the loop of Henle and secreted into the urine. It is the most abundant protein in normal urine and is involved in regulation of salt transport, defense against urinary tract infections, and stone formation.[56] Studies suggest that autosomal dominant disease due to gain-of-function variants in *UMOD* is one of the most prevalent monogenic causes of adult CKD worldwide, accounting for approximately 0.3 to 1% of all cases of advanced CKD.[8,57,58]

UMOD variants[59] cause a spectrum of disorders that have been termed UMOD-related autosomal dominant tubulointerstitial kidney disease (ADTKD).[56] ADTKD is characterized by insidious kidney failure between the third and sixth decades of life. Patients may also have hyperuricemia and gout related to reduced fractional excretion of urate, despite a normal GFR.[58] In addition to tubulointerstitial disease that is evident on kidney biopsy, features of FSGS have been reported.[60] ADTKD often remains unrecognized because it lacks distinctive clinical or histologic features; indeed, few physicians are aware of the disease entity, and genetic testing is often unavailable. Most disease-causing genetic variants are missense variants, often located in exons 3 and 4; 60% involve a cysteine residue.[58] Pathogenic *UMOD* variants cause protein misfolding, with subsequent retention of protein in the endoplasmic reticulum and mistargeting of uromodulin in the thick ascending limb of the loop of Henle. The resulting tubulointerstitial damage leads to CKD.[61]

Variants in other genes can also cause ADTKD. Variants in *MUC1* are the second most common genetic cause of ADTKD and should always be

considered in UMOD-negative cases. Specialized testing is required to identify *MUC1* variants,[62] which are undetectable with Sanger or short-read exome sequencing. In addition, rare heterozygous variants in *REN*[63,64] or *SEC61A1*[65] can result in the ADTKD phenotype.

KIDNEY STONE DISEASE

Kidney stone disease is a multifactorial condition that often includes a genetic component. In many cases, the disease is driven by metabolic imbalances that lead to urinary crystallization. Therefore, pathogenic variants in genes that encode products that normally maintain metabolic balance are expected to cause heritable forms of nephrolithiasis, sometimes leading to CKD. More than 30 different genes have been implicated in stone formation and have been estimated to affect 16 to 29% of children and 11% of adults with nephrolithiasis.[66-68] Although the overall percentage of patients with kidney failure who have nephrolithiasis is only 3%, genetic forms of kidney stone disease, such as adenine phosphoribosyltransferase deficiency, Dent's disease, familial hypomagnesemia with hypercalciuria and nephrocalcinosis, and primary hyperoxaluria, frequently lead to CKD and progress to kidney failure. Moreover, patients with adenine phosphoribosyltransferase deficiency or primary hyperoxaluria are at risk for recurrent disease after kidney transplantation, since transplantation does not address the underlying metabolic defect. Additional information about the genetic basis of nephrolithiasis, congenital anomalies of the kidneys and urinary tract, and complement-related nephropathies is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

CKD OF UNKNOWN CAUSE

In approximately 10 to 20% of cases of kidney failure among adults in the United States and Europe, the cause of CKD remains unknown after an extensive workup, including imaging and kidney biopsies.[69] Reports suggest that up to 20% of these cases may be attributable to genetic conditions.[8,9,70] Although variants in genes encoding type IV collagen are often detected (in up to 30% of cases), comprehensive kidney gene panel or exome sequencing may be the preferred first diagnostic test, given that many cases are not related to collagen gene variants.

OTHER ASPECTS OF MONOGENIC CKD

Rare monogenic syndromes that can cause secondary kidney damage should also be considered in an investigation of the underlying genetic causes of CKD. These syndromes include monogenic diabetes, monogenic hyperlipidemia or hypertension, and monogenic systemic lupus erythematosus.[71]

NEPHROPATHIES WITH A COMPLEX GENETIC BASIS

APOL1-Related CKD

APOL1 belongs to a family of proteins that confer protection against infections with trypanosoma-mediated African sleeping sickness. In 2010, two groups of investigators independently identified two sets of *APOL1* variants (a linked pair of missense variants, S342G and I384M, and two consecutive amino acid deletions, N388 and Y389) within a previously suspected genomic region[72-74] as genetic drivers of several subtypes of progressive CKD.[75,76] These sets of mutually exclusive variants, designated G1 and G2, respectively, confer protection against an extended spectrum of trypanosoma species as compared with the ancestral G0 allele. The heterozygote advantage hypothesis states that both variants rose to high allele frequency in sub-Saharan populations to provide protection against trypanosoma infection, but these variants contribute to the long-noted increased frequency of CKD among persons with recent sub-Saharan African ancestry.[77]

APOL1 is associated with a broad spectrum of nephropathies, including FSGS, hypertensive nephropathy, and human immunodeficiency virus (HIV)–associated nephropathy, as well as lupus-associated nephritis[78]; these associations define a new spectrum of APOL1-related CKD. For example, two *APOL1* variants confer an increase in the risk of FSGS by a factor of 10 to 17 and an increase in the risk of HIV-associated nephropathy by a factor of 29 to 89.[79,80] Although some reports have indicated the possibility of a mild risk of kidney disease even with a single G1 or G2 risk allele,[81] this has not been established.

In vitro and in vivo[82] studies support a toxic gain-of-function mechanism in patients with two *APOL1* variants. Although the exact mechanisms of cellular injury are incompletely elucidated, the success of new therapies such as inaxaplin in FSGS points to glomerular podocytes as the target of cell injury. Luminal endoplasmic reticulum trafficking of the aberrant

gene product is thought to result in abnormal cell-membrane cation channel activity. This proximate step of cell injury is followed by a downstream cascade of inflammation and further cell injury.[83,84]

The genotype–phenotype correlation in *APOL1* appears to be unique. Although a recessive causal (biallelic) mode of inheritance is evident (the disease is strongly and causally associated with the genotypes G1/G1, G2/G2, and G1/G2, not with G0/G0, G1/G0, or G2/G0), the classic mendelian high penetrance often seen with autosomal recessive conditions is absent in *APOL1*-associated CKD. The G1 and G2 variants are relatively common, with approximately 13% of African Americans and more than 70 million people worldwide having high-risk *APOL1* genotypes.[85,86] However, CKD develops in only a subgroup of these persons (incomplete penetrance), depending on some known contributing factors (e.g., HIV infection or high interferon states[87]) and other, unknown factors. A further important refinement has been the recent observation that another DNA sequence variant, encoding an amino acid change from asparagine to lysine (N264K), renders the G2 risk variant innocuous in the small percentage of persons with the otherwise high-risk G2/G2 or G1/G2 genotype.[88,89] Thus, genetic testing for purposes of clinical management and research should include the N264K alteration. A strong rationale for APOL1 testing in glomerular disease gene panels and particularly for patients of African ancestry who have proteinuric CKD is the ability to enroll patients in ongoing clinical trials of APOL1-targeting therapies (as noted in the section below on emerging therapies).

Idiopathic Membranous Nephropathy and IgA Nephropathy

Seminal genomewide association studies over the past decade have investigated the genetic basis of biopsy-proven cases of idiopathic membranous nephropathy[90,91] and IgA nephropathy.[92,93] The results show that each of these immune-mediated glomerulopathies can have a telltale genetic landscape with disease-specific risk loci that may shed light on pathophysiological mechanisms (see the Supplementary Appendix). Further studies are required to determine whether these findings would be useful in the clinical setting.

Table 1. Indications for Considering Genetic Testing in Patients with Chronic Kidney Disease (CKD).

Indication
Family history of kidney disease, dialysis, or kidney transplantation
Consanguinity
Extrarenal manifestations*
Dysmorphic or syndromic features
Kidney failure at young age (<50 yr)
Cystic kidney disease
CKD of unknown origin
Steroid-resistant nephrotic syndrome
Chronic glomerular hematuria or proteinuria or FSGS of unclear cause†
Childhood-onset CKD
Clinical suspicion or actual clinical diagnosis of a specific genetic disorder

* Extrarenal manifestations include cardiac, central nervous system, or skeletal malformations; neurodevelopmental delay; eye abnormalities; hearing loss; gout; and maturity-onset diabetes of the young. FSGS denotes focal segmental glomerulosclerosis.

† Chronic glomerular hematuria refers to hematuria with dysmorphic red cells of at least 6 months' duration. Chronic proteinuria refers to daily protein excretion of at least 0.5 g, usually for more than 3 months' duration.[45]

CLINICAL AND DIAGNOSTIC EVALUATION

The first step in establishing a genetic diagnosis is comprehensive phenotyping. Obtaining a detailed family history and a three-generation pedigree are also important steps. Nonetheless, a negative family history of kidney disease does not preclude CKD of genetic origin.

The diagnostic yield of genetic testing in CKD is variable and depends on the disease phenotype, associated coexisting conditions, ethnicity, consanguinity, family history, and age at onset. Multiple studies support a list of major indications that should prompt clinicians to consider genetic analysis for their patients with CKD (Table 1). Moreover, several reports have indicated that using established criteria can result in an overall high diagnostic yield of genetic testing in CKD (40 to 57%), generally in nephrology clinics focused on genetic diagnoses and in genetic clinics.[94-96] Uncovering the underlying genetic cause of CKD can improve diagnostic accuracy and contribute to targeted monitoring and treat-

Table 2. Clinical Implications of a Genetic Diagnosis in Persons with CKD.*

Implications	Comments and Examples
Direct diagnostic implications	
Provide a definitive causal diagnosis	Identifying a definitive cause for kidney disease allows accurate and personalized clinical management and candidacy for enrollment in genetic studies.
Obviate the need for kidney biopsy	Early genetic testing ("genetic-first approach") for several nephropathies, such as CKD of unknown cause, steroid-resistant nephrotic syndrome, chronic unexplained proteinuria or hematuria, and nephronophthisis, can preclude the need for a kidney biopsy if a diagnosis is made.
Detect asymptomatic or subtle extrarenal manifestations	Many CKD disease genes affect extrarenal organs; genetic diagnoses can guide clinicians in identifying asymptomatic or mild extrarenal features ascribed to a specific gene.
Provide prognostic information	The type of variant can provide information about the natural history of the disease in certain cases; for instance, null variants, as compared with missense variants, often portend worse renal outcomes in patients with Alport's syndrome or ADPKD.
Implications for ongoing treatment	
Prevent inappropriate treatments or procedures	Patients with monogenic causes of FSGS or nephrotic syndrome typically do not have complete remission with immunosuppressive therapies; diagnostic procedures can be avoided for typical findings of syndromic CKD (e.g., aminotransferase levels may be elevated in patients with *HNF1B* variants but do not necessitate liver biopsy).
Guide early targeted monitoring	Several genes leading to cystic kidney disease may be phenotypically similar; however, each gene may have distinct extrarenal features that can be clinically silent and for which specific clinical monitoring should be sought (see Table S1); examples include screening for brain aneurysm development in patients with *PKD1* variants, screening for hyperuricemia in patients with *UMOD* or *HNF1B* variants, and screening for brain tumors in patients with *TSC1* variants.
Guide choice of renoprotective therapy	Some genetic conditions should be treated with specific renoprotective strategies; for example, all persons with hemizygous, recessive, or digenic type IV collagen variants should receive treatment with an inhibitor of the renin–angiotensin–aldosterone system[45]; another example is a low-oxalate diet in cases of hyperoxaluria.
Identify genetic conditions for which gene-specific therapies are available	Gene-specific treatments can be offered to persons with some genetic kidney diseases; for example, CoQ10 supplements should be considered for patients with the nephrotic syndrome who have variants in CoQ10 biosynthesis pathway genes; other examples are eculizumab for patients with atypical HUS due to complement-related variants and enzyme-replacement therapy for patients with Fabry's disease due to *GLA* variants.
Allow patients to become candidates for new treatments	Currently, there are multiple drugs in clinical trials for different genetic kidney diseases such as *APOL1*-related CKD and Alport's syndrome; preclinical studies have shown promising results for additional forms of CKD of genetic origin such as ADTKD-MUC1[97]; only with a molecular-genetic diagnosis can patients become candidates for these and future new therapies.
Implications for kidney transplantation	
Predict risk of disease recurrence after kidney transplantation	For nephronophthisis, UMOD-related CKD, and most monogenic nephrotic syndromes, there is no risk of disease recurrence after kidney transplantation; conversely, complement-related CKD, hyperoxaluria (e.g., due to *AGXT*, *GRHPR*, or *HOGA1* variants), and CKD due to *APRT* variants can recur in the transplanted kidney.
Help facilitate kidney donor selection	Genetic kidney diseases may be clinically unrecognized, and the presentation may be age-dependent; genetic testing can help with donor selection, particularly when potential donors are family members of the recipient; for instance, genetic testing may help assess the risk for potential donors with subclinical disease who have *APOL1* or *Col4A* variants.
Implications for family members	
Allow precise genetic counseling for family planning	The mode of inheritance can help predict disease recurrence in future offspring; in addition, variant-level genetic diagnoses can facilitate preimplantation genetic diagnoses for reproductive planning and prenatal or preimplantation testing.
Enable early diagnosis in affected family members	Patients with genetic forms of CAKUT, proteinuria, or cystic kidney disease may have a parent, child, or sibling with undiagnosed asymptomatic disease; genetic diagnoses often trigger urinalysis and renal ultrasonographic screening, as well as genetic testing for other family members.

* ADPKD denotes autosomal dominant polycystic kidney disease, ADTKD autosomal dominant tubulointerstitial kidney disease, CAKUT congenital anomalies of the kidneys and urinary tract, CoQ10 coenzyme Q10, HUS hemolytic–uremic syndrome, and UMOD uromodulin.

ment. It may also obviate the need for more invasive diagnostic procedures and allow precise genetic counseling for family planning. Table 2 summarizes the clinical implications of obtaining a genetic–molecular diagnosis in patients with CKD.

If genetic analysis is indicated, patients and their families should receive genetic counseling before as well as after testing to receive accurate information about the suspected condition, the recommended genetic testing technique, the estimated diagnostic yield, and possible implications, including the possibility of incidental genetic findings. The most appropriate specific genetic test depends on the particular patient's clinical presentation, the local availability of molecular diagnostics, and the patient's preference. Analyses of single kidney disease genes are currently being supplanted by large gene panels, exome sequencing, and whole-genome sequencing. The characteristics of common genetic tests and challenges specific to kidney diseases are outlined in Tables S2 and S3 in the Supplementary Appendix.

Once genetic test results are received, even if they are negative, genetic consultation is important for clinical reassessment and consideration of broader or complementary genetic testing. Further diagnostic steps are often required, and correct interpretation of the results is important. The interpretation of genetic variants should be based on the internationally accepted American College of Medical Genetics and Genomics–Association for Molecular Pathology guidelines.[98] Patients with negative genetic test results should undergo periodic reassessment.

Interpretation of genetic variants should be conducted with the use of ancestry-matched controls if they are available.[99] However, many populations in which CKD occurs are underrepresented in genetic databases, and population-specific exomes have frequently been interpreted in the context of European or Asian reference data. This may lead to ancestry bias, which can result in incorrect attribution of the pathogenicity of a variant and consequent clinical misinterpretation.[9]

EMERGING THERAPIES

Primary, secondary, and tertiary prevention of CKD is increasingly possible because of genetic diagnoses. A genetic diagnosis establishes eligibility for effective gene-related therapies and allows patients to become candidates for emerging treatments.

One recent example involved a short-term phase 2a study of the use of a small molecule (inaxaplin) to treat APOL1-related CKD.[100] The molecule reverses the toxic gain-of-function effect of *APOL1* high-risk variants. This early clinical study involved participants with two *APOL1* variants and biopsy-proven FSGS. Most of the participants had a clinically significant reduction in proteinuria after 13 weeks of treatment.[100] The study provided initial evidence that the targeted inhibition of APOL1 function is effective and may halt the progression of APOL1-related CKD. A phase 2–3 trial is in progress (ClinicalTrials.gov number NCT05312879).

Identifying CKD monogenic conditions may facilitate targeted molecular therapeutic strategies. For example, a recent study in a mouse model showed that reexpression of the polycystin 1 protein through Pkd1 transgene transfer markedly delayed cyst development, retarded cyst progression, and postponed kidney failure in Pkd1-null mice.[101] Another promising approach uses RNA-based technologies, including chemically modified antisense oligonucleotides or small interfering RNAs, which modulate the abundance, processing, and translational output of cellular RNA without the need for transgene delivery into the kidney, which is more complex.

Such RNA-based agents can change the expression of any protein, even proteins that are not amenable to traditional approaches involving small molecules, and can be used for previously "undruggable" targets. For example, a mouse model of Alport's syndrome suggests that exon-skipping therapy with the use of antisense oligonucleotides targeting truncating variants in exon 21 of *COL4A5* is beneficial in slowing the progression of kidney damage.[102] Such a strategy has resulted in milder phenotypic expression by avoiding an early stop codon. Similarly, antisense oligonucleotide treatment ameliorated interferon-γ–induced proteinuria in *APOL1*-related nephropathy with the use of a transgenic mouse model.[103] A recent, successful application of this technology in humans involved the use of small interfering RNA treatment (lumasiran and nedosiran) for hepatic overproduction of oxalate in patients with hyperoxaluria type 1 due to *AGXT*

variants.[104,105] Lumasiran reduced urinary oxalate excretion, which usually causes kidney failure in these patients.

On the basis of these concepts, additional gene-based treatments for kidney diseases are being studied. Drug delivery to the specific kidney cells of interest remains challenging.

CONCLUSIONS AND FUTURE DIRECTIONS

The use of genetic testing in CKD management and clinical treatment trials is rapidly increasing and may ultimately transform nephrology practice through the development of gene-specific therapies. Additional work is needed to define the role of genetics in kidney donors and to develop additional gene-specific treatments. Many genetic kidney diseases are rare. International study cohorts will increase the genetic information of underrepresented and diverse populations with kidney diseases and should help to alleviate the large global burden of CKD.

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