Genetic Considerations in Pediatric Chronic Kidney Disease

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Abstract

Chronic kidney disease (CKD) in children is an irreversible process that, in some cases, may lead to end-stage renal disease. The majority of children with CKD have a congenital disorder of the kidney or urological tract arising from birth. There is strong evidence for both a genetic and epigenetic component to progression of CKD. Utilization of gene-mapping strategies, ranging from genome-wide association studies to single-nucleotide polymorphism analysis, serves to identify potential genetic variants that may lend to disease variation. Genome-wide association studies evaluating population-based data have identified different loci associated with CKD progression. Analysis of single-nucleotide polymorphisms on an individual level suggests that secondary systemic sequelae of CKD are closely related to dysfunction of the cardiovascular-inflammatory axis and may lead to advanced cardiovascular disease through abnormal vascular calcification and activation of the renin–angiotensin system. Similarly, genetic variants affecting cytokine control, fibrosis, and parenchymal development may modulate CKD through development and acceleration of renal interstitial fibrosis. Epigenetic studies evaluate modification of the genome through DNA methylation, histone modification, or RNA interference, which may be directly influenced by external or environmental factors directing genomic expression. Lastly, improved understanding of the genetic and epigenetic contribution to CKD progression may allow providers to identify a population at accelerated risk for disease progression and apply novel therapies targeted at the genetic mechanism of disease.

Keywords

- pediatric chronic kidney disease
- epigenetic modifications
- single-nucleotide polymorphisms

Introduction

Chronic kidney disease (CKD) is defined as a progressive loss of renal function, measured by a decline in glomerular filtration rate (GFR). Most clinical and genetic epidemiological studies define CKD as estimated GFR less than 60 mL/min/1.73 m^2.[1] The interplay of heritable genetic traits on progression of CKD toward end-stage renal disease (ESRD) remains an evolving field in adult and pediatric nephrology. CKD in adults occurs primarily in the developed world as a consequence of longstanding disease processes, such as diabetes or hypertension, but may result also from primary glomerulopathies, infections, physical obstruction, interstitial nephritides, and genetic cystic kidney diseases.[2] On the contrary, in pediatric patients the etiology of CKD is dominated by congenital structural disorders occurring in the first year of life, primarily due to dysplasia or obstructive causes and monogenetic renal diseases that comprise ~20% of progressive CKD/ESRD diagnoses.[3] For example, specific single-gene genetic mutations causing hereditary proteinuria/nephrotic syndrome (nephrin [*NPHS1*], podocin [*NPHS2*], *α-actinin-4*, CD-2 molecule [*CD-2*], Wilms tumor 1 [*WT1*], transient

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receptor potential cation channel, subfamily C, member 6 [*TRPC6*], phospholipase C, epsilon 1 [*PLCE1*], laminin β-2 [*LAMB2*], LIM homeobox transcription factor 1 β [*LMX1B*], myosin, heavy chain 9 [*MYH9*], fibronectin), Alport syndrome (type IV collagen), and hereditary tubulointerstitial diseases (polycystic kidney disease [*PKD1*, *PKD2*], juvenile nephronophthisis [*NPHP1*], *UMOD,* HNF1 homeobox B [*HNF1B*])[4] are associated with progressive renal disease, often leading to ESRD and need for renal transplantation. However, monogenic causes of CKD are beyond the scope of this review.

Regardless of the cause, chronically injured kidneys are characterized histologically by tubulointerstitial fibrosis and glomerulosclerosis and the extent of tubulointerstitial fibrosis is the best predictor of kidney survival irrespectively of the underlying disease.[5] Interestingly, even in the presence of identical underlying disease states with similar histopathology and known genetic loci, CKD progression can be very variable in nature.[6,7] This may further be explained by the complexity of CKD progression involving both an inherited predisposition (DNA) and susceptibility to environmental factors. To illustrate, in a 26,000 adult dialysis patient registry, nearly 23% of patients without Mendelian single-gene mutations were found to have another first- or second-degree relative on dialysis,[8] and risk for CKD progressing to ESRD is particularly marked with a strong family history (e.g., two or more first-degree relatives) of renal disease.[8,9]

Emerging evidence suggests that polymorphic genetic variations (i.e., single-nucleotide polymorphisms [SNPs]) may be key factors in CKD progression, in addition to more recently identified epigenetic modifications of the genome. The vast majority of genetic polymorphic research in the field of CKD progression has been performed with adult data and may confer inherent weakness in extrapolation of data directly to pediatric patients. Contrary to adult CKD, pediatric CKD characteristically occurs without comorbidities such as diabetes and cardiovascular disease. Pediatric patients may, conversely, develop early-onset cardiovascular disease, nutritional abnormalities, and growth disruption as sequelae of renal disease. In spite of the differences, it is likely that the information gleaned from adult genetic and epigenetic analyses can reasonably be applied to our understanding of pediatric CKD progression. The following text reviews our current understanding of genetic and epigenetic factors that could be applicable to pediatric CKD progression.

Gene Mapping Strategies in Chronic Kidney Disease

Complex traits, such as CKD, do not have recognizable Mendelian inheritance patterns or concordance between genetic variation and phenotype. Genetic analyses provide an integral role in identifying how progression of CKD differs between individuals, but they require thoughtful collaboration between laboratory, clinical, and epidemiological resources in their utilization to provide meaningful results (►**Fig. 1**).[10] Genetic mapping provides a link between the human genotype and phenotype of CKD progression. In understanding the genetics of CKD, an accurate disease phenotype must be established to reliably test an assumed genotype–phenotype relationship, which makes the comparison among studies challenging. Despite limitations, improvement in laboratory techniques and bioinformatics allows for increasingly cost-effective genotyping approaches, ranging from high-density microarrays that efficiently examine several million SNPs in a targeted manner to next-generation sequencing approaches that interrogate an individual's entire genome. Gene mapping strategies such as candidate gene approaches, linkage studies, and genome-wide association studies (GWASs) have been utilized in further delineating the genetic and epigenetic basis of CKD.

Candidate gene studies utilize analysis of previously identified polymorphisms or regulatory genes with known regulatory functions to search for novel genetic variants associated with common disease progression. Candidate gene studies currently provide much of the pediatric data available for understanding the genetic mechanisms of pediatric CKD progression in relation to cardiovascular disease and progression of tubulointerstitial fibrosis, as described below. This approach to genetic analysis is limited by variability in genotyping methods utilized, phenotypic differences in the population studied, and small sample sizes (particularly in pediatric studies) with subsequent poor power to detect significance.[11] Furthermore, study design in candidate gene studies may be prone to influence from investigator biases regarding underlying genetic mechanisms for CKD progression, in that the investigator chooses candidate genes a priori such that a study is hypothesis-driven rather than hypothesis-generating in nature.[12]

Linkage studies employ family-based collections of DNA to track transmission of genetic variants linked with a common disease and relate inheritance of sparsely distributed polymorphic genetic markers with disease phenotypes among families. Linkage studies have been primarily successful identifying rare genetic markers with disease phenotypes within families such as autosomal dominant polycystic kidney disease.[13] This methodology has also been used in understanding genetic factors associated with CKD progression. More than 20 larger scale linkage studies have been conducted to identify loci associated with CKD,[14] including genome-wide association linkage studies and genome scan meta-analysis, the latest being an exploratory technique used to quantitatively synthesize linkage results from individual studies to evaluate concordance.[15] A challenge in conducting linkage studies lies particularly in recruitment of family members to provide a sufficient population within a sample for tracking genetic risk across generations.[14] In an attempt to overcome this limitation, Rao et al[16] conducted a meta-analysis of genome-wide linkage scans for renal function traits with data from 14 linkage studies but failed to identify any significant genomic region for renal function traits of GFR, urinary albumin-to-creatinine ratio, serum creatinine, or creatinine clearance.

GWAS is a more powerful approach in diseases like CKD where the genetic risk factors have small or moderate effect sizes; it offers improved resolution for genotyping and makes easier the collection of unrelated renal phenotype cases and

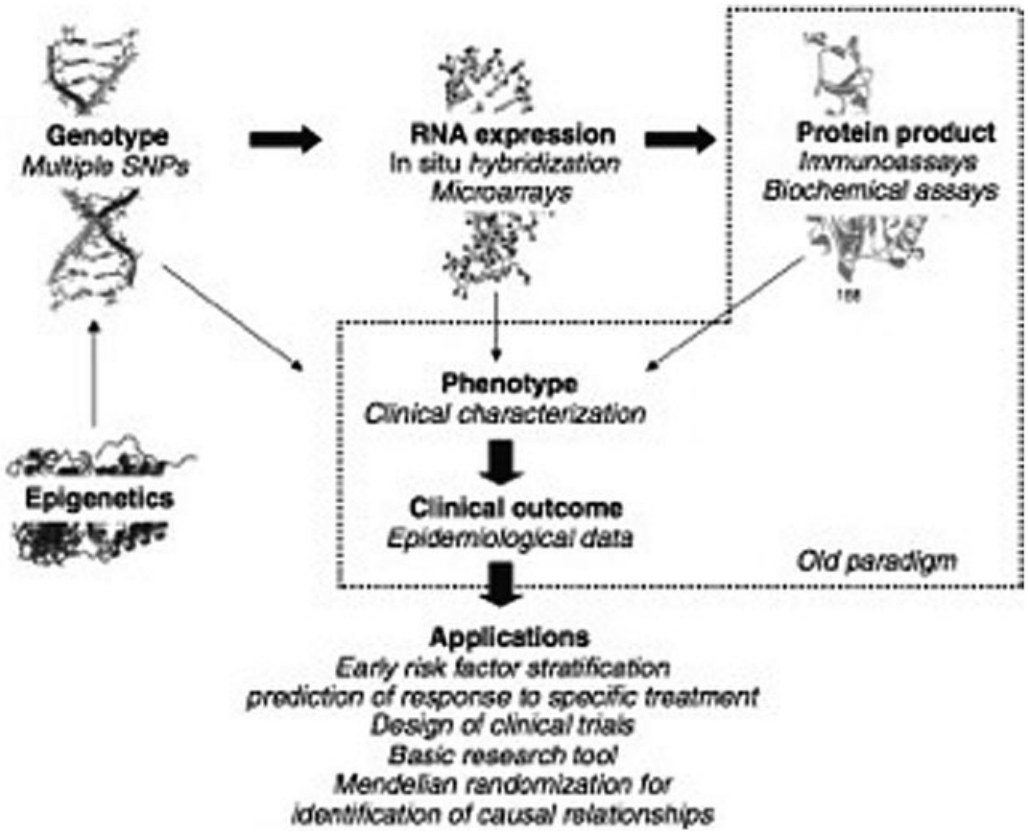

Fig. 1 Genetic analyses play a key role in understanding chronic kidney disease progression, but require close interaction with laboratory, clinical, and epidemiological resources to provide clinical application to both the individual patient and population as a whole. (Figure obtained with permission from Axelsson et al.[10])

controls. GWAS compares the frequency of naturally occurring genetic variants in populations with a disease to those without disease and drives the genetic study of CKD based on the "common disease, common variant" hypothesis.[7] This concept is based on the assumption that common diseases are caused by genetic variation occurring within the genome at a frequency greater than 1% within the general population[17] and that functional changes associated with specific mutations are mild. Therefore, many common variants are required to segregate in individuals with common diseases in order for phenotypic disease to become clinically apparent. In GWASs, a stringent phenotype definition allows for improved statistical power to more reliably associate phenotype with an otherwise discovered genetic etiology of CKD.[18]

More than 1,500 GWASs have been published since 2005 with the goal of identifying genetic polymorphisms predisposing to CKD progression,[19] and since that time, GWAS data in the field of CKD remain extremely adult-focused with no currently published primary pediatric CKD GWASs. The first GWAS of CKD was performed in 19,877 individuals of European ancestry from the Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium[20] to identify genetic risk loci for CKD. A significant risk locus was identified within the *UMOD* gene. A secondary GWAS further validated the initial association of CKD progression with *UMOD*, whereby polymorphisms conferring elevated *UMOD* concentrations increased the 10-year risk of CKD by over 70%.[21] Use of GWAS provided evidence that a common *UMOD* gene variant, which was previously known to cause autosomal dominant medullary cystic kidney disease type 2 and familial juvenile hyperuricemic nephropathy,[22,23] was present in up to 18% of a large study population and could contribute to progression of CKD in the general population.[20] More recently, data from over 67,000 participants within the CKDGen Consortium were evaluated in meta-analytic discovery genome-wide analysis to identify susceptibility loci for reduced renal function, with additional samples from over 20,000 individuals subsequently reviewed in replication follow-up.[24] The discovery analysis from GWAS identified 13 new loci associated with reduced renal function and CKD (longevity assurance homologue 2 of yeast [*LASS2*], glucokinase regulatory protein [*GCKR*], Alstrom syndrome protein 1 [*ALMS1*], transcription factor Dp-2 [*TFDP2*], disabled 2 mitogen-responsive phosphoprotein [*DAB2*], solute carrier family 24 member 1 [*SLC34A1*], vascular endothelial growth factor A [*VEGFA*], protein kinase AMP-activated, gamma 2 noncatalytic subunit [*PRKAG2*], phosphatidylinositol-4-phosphate-5-kinase, type 1 β [*PIP5K1B*], ataxin 2 [*ATXN2*], dachshund family transcription factor 1 [*DACH1*], ubiquitin-conjugating enzyme E2Q family member 2 [*UBE2Q2*], and solute carrier family 7 [*SLC7A9*]) and 7 loci suspected to affect creatinine production and secretion (carbamoyl-phosphate synthetase 1 [*CPS1*], solute carrier family 22 [*SLC22A2*], transmembrane protein 60 [*TMEM60*], WD repeat domain 37 [*WDR37*], solute carrier

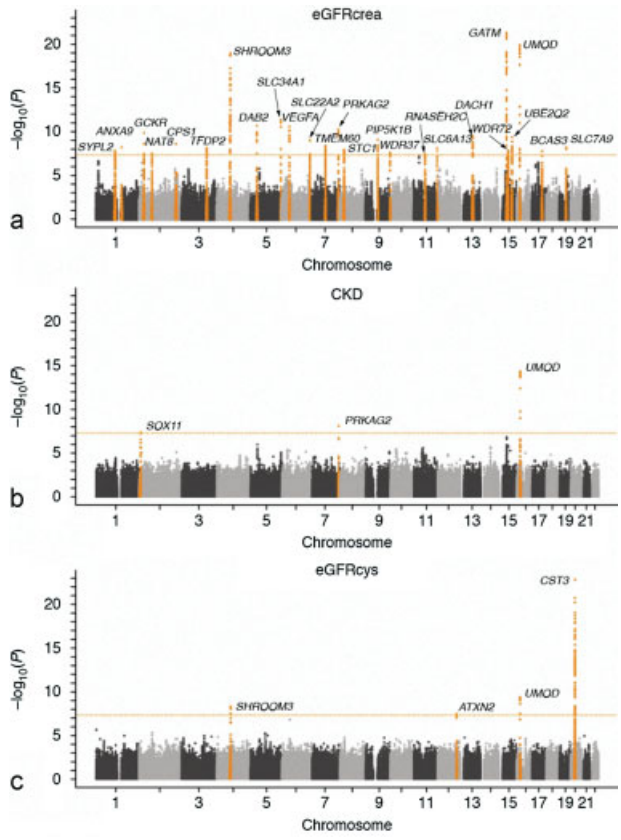

Fig. 2 Manhattan plot from Köttgen et al[24] illustrating the discovery analysis from a GWAS that identified 13 new genetic loci associated with reduced renal function and chronic kidney disease with an additional 7 loci suspected to affect creatinine production and secretion. Previously discovered susceptibility variants for renal function and chronic kidney disease at *UMOD*, *SHROOM2*, and *STC1* are also shown.[24] The dotted line indicates the genome-wide significance threshold at $p = 5 \times 10 - 8$.

family 6 (neurotransmitter transporter), member 13 [*SLC6A13*], WD repeat domain 72 [*WDR72*], and breast carcinoma amplified sequence 2 [*BCAS2*]), in addition to the previously discovered susceptibility variants for renal function and CKD at *UMOD*, shroom family member 2 (*SHROOM2*) and stanniocalcin 1 (*STC1*) loci (►**Fig. 2**). Of those, it is important to highlight some of the known to be affected in renal disease such as *ALMS1* (ciliopathies), *SLC7A9* (nephrolithiasis, cystinuria), *SLC34A1* (hypophosphatemic nephrolithiasis/osteoporosis), *DAB2* (nondiabetic kidney disease in African Americans), *VEGFA* (stimulation of ureteric bud branching during embryogenesis and affects final nephron number, it is secreted by podocytes), *GCKR* (involved in formation of primary cilia), *PRKAG2* (renal hypertrophy), and *DACH1* (branchio-oto-renal syndrome).[24] Another gene that was found to be associated with CKD from GWASs is the *MYH9-APOL1* (myosin heavy chain 9, apolipoprotein L, 1) gene on chromosome 22,[25,26] which is known to be associated with focal segmental glomerulosclerosis, diabetic kidney disease, and ESRD.[27,28] Interestingly, *APOL1* SNPs associated with kidney disease are common in African lineage but extremely rare in European populations.[26]

One of the most significant weaknesses in utilization of GWASs is the inability to generalize results for individuals who are not of the primary ethnicity represented in the sample analyzed. In an effort to understand the impact of ethnicity, cross-ethnic analyses have been performed with data from over 8,000 samples within the Candidate-gene Association Resource (CARe) Consortium, demonstrating that genomic risk regions are largely conserved and shared across ethnic groups.[29]

Genetic Polymorphism in Pediatric Chronic Kidney Disease

In pediatric CKD, it is reasonable to consider that polymorphic mutations linked with common diseases may further alter the amount or activity of progression of CKD. Numerous genetic polymorphisms have been identified that are associated with pediatric CKD progression. These polymorphic variations may account for some of the differences in both focal and systemic disease associated with renal impairment (e.g., cardiovascular disease and development of tubulointerstitial fibrosis) between individual patients with pediatric CKD. We review a selection of key functional polymorphisms in the following sections.

Cardiovascular Polymorphisms in Chronic Kidney Disease Progression

Cardiovascular disease is a well-recognized feature of CKD progression. Hypertension and subsequent prevention of end-organ damage (including left ventricular hypertrophy [LVH]) are primary therapeutic targets in disease progression. Ultimately, cardiovascular-related death remains the leading cause of mortality in children on maintenance dialysis and posttransplantation across the world.[30–32]

Vascular calcification and atherosclerotic cardiovascular disease are well-known complications in the transition from CKD to ESRD and are important risk factors for cardiovascular disease. Fetuin-A (also known as α 2-Heremans-Schmid glycoprotein) is a circulating negative acute-phase protein released in response to an inflammatory stimulus on endothelial surfaces that inhibits calcium phosphate product formation and precipitation on the vascular endothelial surface.[33–35] CKD patients appear to have significantly lower Fetuin-A levels, which is associated with increased risk for vascular disease and poorer hemodialysis survival in CKD.[33,36] The Fetuin-A Thr256Ser polymorphism is linked to increased atherosclerosis and heightened cardiovascular mortality in the ESRD population and may be a marker of accelerated vascular calcification risk.[36] Although the aforementioned studies provide insight into genetic cardiovascular risk in CKD, none included data from a pediatric population. Data available from one pediatric sample do demonstrate that lower Fetuin-A levels predict intima-media thickness changes of the carotid arteries in children with CKD.[37]

The Renin–Angiotensin System

The renin–angiotensin system (RAS) facilitates blood pressure regulation, with activation and upregulation in CKD

leading to end-organ damage, including LVH.[38] Polymorphic change in the angiotensinogen (*ANG*) gene is associated with progressive cardiovascular and renal disease. The *ANG* gene has a Met235Thr polymorphism with Thr/Thr haplotype associated with increased risk for hypertension and cardiac remodeling with LVH in both healthy and ESRD populations secondary to high ANG levels.[39–41] Insertion/deletion (I/D) polymorphisms in the angiotensin-converting enzyme (*ACE*) gene have been shown to affect the activity of the RAS.[42] The *ACE* has a known I/D polymorphism in intron 16, and deletion/deletion (D/D) individuals have higher levels of ACE. The *ACE* D/D polymorphism is linked with LVH,[43] hypertension,[44] and progression of renal disease in children with known CKD.[45–47] There is additional evidence that the *ACE* D/D genotype may confer increased risk for renal parenchymal damage in children with congenital abnormalities of the urologic tract and renal scarring following urinary tract infections.[45,48–50] The effect of these genes on renal scarring has been postulated due to gene roles in both local vasomotor and inflammatory control within renal parenchyma following injury. Patients with the *ACE* D/D genotype may have a more favorable response to ACE inhibition with decrease in proteinuria and reduction in rate of GFR decline in contrast to patients with I/D or insertion/insertion genotypes.[51,52]

ACE activity determines levels of the vasoactive peptide angiotensin-II (ANG II). ANG II has both systemic and intrarenal vasoconstrictor effects. The intrarenal effects of ANG II are driven by the angiotensin type 1 receptor (AT1R) and angiotensin type 2 receptor (AT2R). Receptor polymorphism analyses have yet to provide significant associations between known polymorphisms for the *AT1R* or *AT2R* and progression of CKD. The *AT1R* polymorphism at A1166C has minimal evidence for CKD progression.[44,53] Similarly, the *AT2R* A1332G polymorphism has been investigated with no significant effect on the pathogenesis or outcomes of CKD progression in patients with vesicoureteral reflux in individual studies[54–56] or meta-analytic review of existing data.[53]

Inflammatory Polymorphisms in Chronic Kidney Disease Progression

Progressive CKD can be considered a proinflammatory state. In CKD, perturbations in the inflammatory-axis occur secondary to multiple factors (e.g., oxidative stress, decreased clearance of inflammatory cytokines with falling GFR, poor antioxidant intake) and can lead to accelerated atherosclerosis, endothelial damage, and malnutrition via induced anorexia and protein-energy wasting.

Homocysteine is an inflammatory molecule implicated in risk for vascular disease. CKD patients are at risk for hyperhomocysteinemia secondary to nutritional and intradialytic losses of vitamin B12 and folate. The enzyme methylenetetrahydrofolate reductase (MTFHR) is key in homocysteine regulation via reduction of homocysteine to methionine.[57] Genetic variation in the *MTHFR* gene may lead to homocysteine accumulation in patients carrying a genetic polymorphism of the *MTHFR* gene, Ala677VaL (C/T), conferring reduction of enzyme function.[58] Data suggest that pediatric dialysis patients having a *MTHFR* (C/T) polymorphism are at increased risk for hyperhomocysteinemia, although it is unclear exactly what the implications are for long-term cardiovascular disease progression.[59]

Interleukin (IL)-10 is an anti-inflammatory cytokine that mediates the inflammatory response through regulation of the adaptive immune system interaction with antigen-presenting cells with subsequent ability to downregulate release of proinflammatory molecules, such as IL-1 β, tumor necrosis factor-α, and IL-6.[60] Several *IL-10* polymorphisms have been identified within the promoter region of the *IL-10* gene; however, data for the G/G-1082 polymorphism are the most robust. The G/G-1082 gene polymorphism results in quantitatively higher levels of IL-10 in comparison to A/A- or A/G-1082 variants.[61,62] Patients who are high or intermediate IL-10 producers (G/G and G/A alleles) are more likely to rate higher Karnofsky functional status scores than low producers (A/A alleles).[63] Conversely, animal models suggest that constitutively high levels of IL-10 could induce anorexia and weight loss.[64] Cumulatively, data demonstrate that under some conditions, IL-10 has a protective effect in counterbalancing the inflammatory response with decreased comorbidity[65] and cardiovascular events,[66] but unchecked, high levels of IL-10 may be associated with adverse patient outcomes.

Genetic Variants in Fibrosis and Parenchymal Development: Transforming Growth Factor-β

Fibrosis is one of the histological landmarks of progressive CKD. Transforming growth factor-β (TGF-β) is a cytokine that regulates cell growth and extracellular matrix production.[67] Prolonged expression of TGF-β has been associated with disruption of renal architecture at the cellular level, leading to progression of CKD, specifically tubulointerstitial fibrosis and extracellular matrix deposition.[68] TGF-β mediates progression of renal and cardiac fibrosis in association with activation of ANG II within renal parenchyma and systemic RAS activation, with subsequent development of hypertension[69] and secondary LVH.[70] ANG II blockade (e.g., with ACE inhibitors or angiotensin receptor blocking agents) has been shown to suppress TGF-β overexpression in kidney and heart.[71] TGF-β production may vary between patients, given the presence of several polymorphic variants identified that modulate levels of cytokine production.[72] Furthermore, risk for scarring following urinary tract infection is significantly increased in children with the TGF-β1 509T polymorphism, irrespective of presence or absence of vesicoureteral reflux.[73]

Role of Epigenetics in Chronic Kidney Disease

Epigenetic modifications of DNA occur through DNA methylation, histone modifications, and RNA interference. They serve as key regulators in gene expression and repression to allow for normal cellular functioning. The ability to identify and target epigenetic modifications, in contrast to polymorphic variation, represents an opportunity to pinpoint CKD-related processes that are reversible, developmentally and temporally variable, and susceptible to environmental cues.[74] There is some evidence suggesting that some extreme

environmental cues, for example, intrauterine growth restriction or starvation, induce long-term epigenetic genomic modifications.[75] Epigenetic modifications in the fetal environment are thought to play a key role in the link between low-birth-weight infants and congenital deficits in nephron number,[76] which ultimately lead to an increased lifetime risk of hypertension, glomerulosclerosis, and CKD/ESRD.[77] Moreover, CKD progression may be influenced by external factors acting on the patient epigenome, opening new options for novel therapeutic approaches in the future. For example, chronic inflammation (as evidenced by hyperhomocysteinemia) and oxidative stress have been hypothesized to act as negative epigenetic risk factors in CKD progression[74] and correction of hyperhomocysteinemia with exogenous folate therapy has been shown to correct significant DNA hypomethylation in an adult hemodialysis population.[78] Bechtel et al[79] noted that cytosine hypermethylation of the RAS protein activator-like 1 (*RASAL1*) gene was associated with activation of fibroblasts and fibrogenesis in mouse models and that fibrogenesis could be rescued in vitro using a demethylating agent, 5′-azacitidine. Similarly, Ko et al[80] describe cytosine methylation analysis of renal epithelial samples in both diseased and control patients with more than 4,000 differentially methylated enhancer regions found in CKD samples compared with controls.

Deregulation of histone modification has been widely implicated in renal disease leading to CKD, for example, congenital renal anomalies, fibrosis, and diabetic renal sequelae.[81,82] Angiotensin blockade with Losartan reverses histone H3 modification within the glomeruli[83] of diabetic mice, suggesting additional therapeutic benefit of adequacy in drug utilization. Similarly in CKD, TGF-β production increases histone H3 methylation with subsequent upregulation of profibrotic collagen-1α1 within the extracellular matrix and plasminogen activator inhibitor-1 in mesangial cells.[84] Inhibition of TGF-β and renal fibroblast activation is potentially possible through blockade of class I histone deacetylates with a selective class I histone deacetylase inhibitor MS-275.[85]

MicroRNAs (miRs) are small, noncoding RNAs that act as intrinsic regulators of gene expression and affect the expression of genes at the posttranslational level. MiRNAs have been implicated in a variety of biological processes affecting CKD.[86] Data specific to miR-21 demonstrate association within CKD through sustained expression contributing to pathways promoting renal fibrosis through the peroxisome proliferator-activated receptor-α.[87] miR-192 is associated with development of progressive renal fibrosis and known to be upregulated in ureteral obstruction mouse models as well as rat models with activation of TGF-β.[88] In humans, there was significant upregulation of miR-200a, miR-200b, miR-141, and miR-429 intrarenal expression in kidney biopsies of patients with hypertensive nephrosclerosis.[89]

Conclusion

Pediatric research in genetic and epigenetic factors that contribute to understanding of pediatric CKD progression is greatly lacking. Although the majority of pediatric CKD cases are due to congenital causes, there is still significant variability in rate of CKD progression that may reflect the complexity of CKD pathophysiology involving both inherited predisposition, such as genetic polymorphisms, and environmental factors causing epigenetic modifications. In contrast to adult samples where the onset of CKD may be ambiguous, the pediatric population largely has an identifiable onset of renal insult leading to CKD and genetic samples could readily be obtained at identifiable time points in a child's disease course. Certainly, pediatric CKD research must also take advantage of multicenter cooperative trials to garner adequate sample sizes given the small sample size otherwise found at individual centers.

Characterization of polymorphic variants is important and epigenetic modifications in pediatric CKD progression may prompt the pediatric nephrologist to be increasingly directed at improving modifiable risk factors for disease progression, including those related to cardiovascular status, even for those of mild/moderate CKD status. Increased understanding of the genetic and epigenetic impact on CKD progression may assist in development of genetic screening tools to identify those children comparatively at risk, and this may someday allow nephrologists to provide targeted therapies to prevent progression of CKD, improve health outcomes into adulthood, and enhance quality of life.

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