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Risk Factors for Progression of Chronic Kidney Disease

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Abstract

Purpose of Review—Provides an overview of the identified risk factors for chronic kidney disease (CKD) progression emphasizing the pediatric population.

Recent findings—Over the past ten years, there have been significant changes to our understanding and study of pre-terminal kidney failure. Recent refinements in the measurement of glomerular filtration rate (GFR) and GFR estimating equations are important tools for identification and association of risk factors for CKD progression in children. In pediatric CKD, lower level of kidney function at presentation, higher levels of proteinuria, and hypertension are known markers for a more rapid decline in GFR. Anemia and other reported risk factors from the pre-genomic era have need for further study and validation. Genome-wide association studies have identified genetic loci which have provided novel genetic risk factors for CKD progression.

Summary—With cohort studies of children with CKD becoming mature, they have started to yield important refinements to the assessment of CKD progression. While many of the traditional risk factors for renal progression will certainly be assessed, such cohorts will be important for evaluating novel risk factors identified by genome-wide studies.

Keywords

Chronic kidney disease; risk factors; blood pressure; proteinuria; anemia; genome wide association studies

Introduction

The state of kidney damage or reduced kidney function lasting three months or longer, known as chronic kidney disease (CKD), is both progressive and irreversible.[1] In the United States, 16 percent of general population is estimated to have CKD with the rate projected to increase.[2] The worldwide impact of CKD is significant, yet underestimated. According to the World Health Report 2002 and the global burden of disease project, kidney and urinary tract diseases contribute to 850,000 deaths per year and 15,010,167 in disability-adjusted life years.[3] The consequences of CKD in children are devastating, condemning patients to varying levels of chronic, lifelong medical disability.[4] We are clearly facing an urgent public health problem in this country and worldwide.

Operationally, CKD is defined as kidney damage or glomerular filtration rate (GFR) < 60mL/min/1.73m^2 for ≥ 3 months or more regardless of diagnosis. Kidney damage is usually identified by abnormalities in the blood, urine, imaging tests; and if needed, by kidney biopsy. Health care providers screen for CKD by either blood testing to estimate glomerular filtration rate (GFR) or urinary screening for the detection of proteinuria. Tests for total urine protein are preferred in children; for children with diabetes, screening for albuminuria should also be performed.[5].

Progression to Kidney Failure

While the dominant causes of CKD in adults are diabetic nephropathy and hypertension, nearly 60%-70% of children affected with CKD have congenital or inherited kidney disorders.[6] Patients with congenital anomalies of the kidney and urinary tract, including those with congenital solitary kidneys, carry an increased risk for end-stage renal disease by young adulthood.[7] Irrespective of the original cause of kidney damage, the onset of CKD initiates a chain of events that describe a common final pathway where pre-terminal kidney damage progresses to kidney failure. The term “renal progression” refers to this progressive decline in kidney function. Although some CKD patients have stable kidney function for years, others decline rapidly. The variability of CKD progression among patients suggests that biologically relevant factors may influence the course of CKD. This review will summarize the historical trends in the study of pre-terminal kidney disease, the recent updates to the determination GFR in children, the identification of clinical risk factors for renal progression, and the genetic risk factors associated with CKD progression. Although findings from the adult CKD population are discussed, there will be an emphasis on pediatric studies.

A Historical Perspective on CKD and Progression

Prior to the 21st century, children with kidney disease were considered to have significant kidney impairment below a GFR of 75ml/min/1.73m^2, termed chronic renal insufficiency (CRI). There were active efforts to treat and study pre-terminal kidney disease, yet different kidney diseases were studied as separate entities without enough cases to provide significant statistical power to derive firm conclusions. Although it was understood that patients with CRI progressed to kidney failure, there was little systematic data to define the patterns of decline and clinical measurements of this decline were not standardized. During this era, a significant focus of clinical care and research in children with kidney disease were toward the fundamental challenges of performing dialysis and transplantation in children, growth problems associated with chronic renal failure, treatment of nephrotic syndrome, and detection and treatment of hypertension.[8] By the beginning of the 21st century many of these fundamental challenges were overcome and the concept of CRI had been revised to our current model of CKD.

In 2002, the National Kidney Foundation (NKF) published the first Kidney Dialysis Outcome Quality Initiative (K/DOQI) clinical practice guidelines for CKD: evaluation, classification, and stratification. [9] The NKF committee members who generated the guidelines provided a broad conceptual framework in the identification, management, and the care of all patients with CKD.[9] This work acknowledged that despite multiple causes for kidney damage, all kidney diseases had a characteristic in common—a decline in kidney function overtime. This paradigm shift for the study of pre-terminal kidney failure facilitated epidemiologic study of CKD risk factors and a common nomenclature to define CKD progression. The committee developed the CKD staging system (Table 1) which relies on the level glomerular filtration rate (GFR) as an index of kidney function to categorize patients in a particular stage. Use of this system allows for consistency when describing CKD, accurate assessment of progression risk factors, and ultimately should improve outcomes.

Pediatric Nephrology Collaborative Studies

Multi-center consortia are necessary for clinical research in pediatric CKD due to the relatively small numbers of patients. Compared to the adult CKD population, the incidence of CKD is relatively low among children and is estimated to be 12.1 cases per year per million age-related population (MARP) compared to 74.7 cases per MARP for adults.[10] Several large consortia of multiple pediatric nephrology centers have provided recent data to further our understanding of risk factors and treatment for CKD progression in children, notably groups across Europe and North America. The recently published Effect of Strict Blood Pressure Control and ACE

Inhibition on the Progression of CRF in Pediatric Patients (ESCAPE) trial was performed by 33 pediatric nephrology units across Europe. The ESCAPE trial was a randomized intervention evaluating intensified blood pressure control in children 3-18 years of age (GFR between 15-80 ml/min/1.73m^2) on a fixed dose of angiotensin-converting-enzyme (ACE) inhibitor and its impact on disease progression.[11] The ongoing Chronic Kidney Disease in Children (CKiD) study is being performed by 43 pediatric nephrology centers across North America.[12] CKiD is gathering detailed epidemiologic information on 567 children with mild to moderate CKD and has provided recent data pertaining to our understanding of GFR assessment and risk factors associated with CKD progression in children.

GFR and renal progression

A reduction in GFR is a marker for CKD[5] and also a risk factor for renal progression. Recent studies in children demonstrate that a higher CKD stage at time of study entry has been shown to be independently associated with an increase rate of progression to renal failure.[4,13] Staples et al., in a retrospective cohort of approximately 4,000 children with CKD demonstrated that moderate (GFR 30-59ml/min/1.73m^2) to severe CKD (GFR 15-29ml/min/1.73m^2) at study entry had an associated higher risk of disease progression when compared to those with mild (GFR 60-75ml/min/1.73m^2) CKD. For moderate CKD the hazard ratio (HR) was 2.02 with a 95% confidence interval (95% CI) 1.67 – 2.46; and for severe CKD the HR was 6.84 with a 95% CI 5.59 – 8.37.[4]

Given the importance of CKD staging and accurate determination of GFR in children, there have been several recent contributions regarding the measurement and estimation of GFR in this population. There is general consensus that measurement of GFR by a timed urine collection for creatinine clearance can be variable and inaccurate.[14] This is accentuated by the high prevalence of urologic problems in the pediatric CKD which may cause inadequate bladder emptying leading to inaccurate measured GFR values. While GFR measurement by inulin clearance is accepted as the gold standard, it is labor intensive; it utilizes a difficult assay to perform; inulin is not readily available; and without bladder catheterization, accurate urine collection in children can be difficult.[15]

Having close agreement to the GFR measured by inulin clearance [16]. GFR measurement by iohexol plasma disappearance method has been validated by the CKiD study as an accurate, reproducible, non-radioactive and safe method for the measurement of GFR in children.[15] It is used as the gold standard to measure GFR in the CKiD study. Since the initial pilot study, the CKiD study has performed over 1000 measurements of GFR by iohexol plasma disappearance in children across 43 pediatric nephrology centers with no adverse events.[17] With the four-point plasma disappearance curve as described in the original pilot study, the rate of unattainable iohexol GFR (iGFR) measurements is approximately six to seven percent due to errors in timing, inadequate documentation, or infiltration of the intravenous line[17], proving that iohexol GFR measurements are relatively successful.

Since the 1970s, the GFR estimating equation by Schwartz (Table 2, formula 1) has been widely accepted as an accurate estimation of GFR in children. It was used in the CKiD study to determine study eligibility. Although convenient and practical, the Schwartz formula has been found to overestimate the true GFR particularly at lower levels of GFR.[9] The overestimation of the GFR by the original Schwartz formula has been attributed to the change in methodology for laboratory creatinine determination.[18] The newer enzymatic determination of creatinine results in a lower value of creatinine compared to the older Jaffe method, on which the original Schwartz formula was based.

CKiD has developed an improved GFR estimating formula. Due to the structure of the visits for CKiD, newer GFR estimating equations were needed to accurately determine the GFR

when iGFR was not measured (Table 2, formulae 2 and 3). Since the formulae were developed in children with moderate to severe CKD, the formulae have been validated for a range of GFR between 15 to 75ml/min/1.73m^2, but need to be evaluated in children with higher levels of GFR for accuracy. Additionally, the CKiD study investigators have assessed longitudinal formulas to determine current or future changes in GFR based on prior measurements of GFR and changes in other clinical parameters (Table 2, formula 4).[19] The limitations for use of the longitudinal equation include the select population of subjects with moderate to severe CKD as well as the minimal decline in GFR over one year within the cohort. With more follow-up time and further progression of the cohort, the longitudinal equation can be refined.

Proteinuria and renal progression

In human studies (both adult and pediatric), elevated urine total protein is shown to be an independent risk factor for more rapid decline in kidney function.[20-22] The increase in urinary protein causes injury to tubular cells, leading to interstitial inflammation and fibrosis.[1] In patients with CKD, blockade of the renin-angiotensin system (RAS) reduces proteinuria: in adults, 1g/day reduction in proteinuria is associated with an abatement of GFR decline by 1-2mL/min per year. The antiproteinuric efficacy of RAS blockade has also been validated in children with CKD.[23-25]

Given the importance of proteinuria as a risk factor for CKD progression, understanding the determinants of proteinuria severity has become an important focus of research. The CKiD study evaluated the patterns of proteinuria severity among children with CKD. From 419 subjects with first morning urine protein-to-creatinine ratios (Upcr) and iGFR, the median Upcr was 0.53 and interquartile range was 0.2 to 1.27; median iGFR was 42 ml/min/1.73m^2; and the median duration of CKD was six years. Log-linear regression demonstrated that proteinuria was associated with iGFR, age, race, and glomerular cause of CKD.[26] As seen in Figure 1, it is estimated that for every 10% decrease in iGFR, Upcr increased on average by 14% regardless of cause for CKD.

In the multivariate analysis, proteinuria continued to be associated with GFR, age, and cause of CKD. Additionally, independent of these factors, non-Caucasian race was associated with 40% higher level of proteinuria compared to Caucasian race.[26] In summary, while higher levels of proteinuria were associated with lower levels of GFR, the factors accounting for intra-individual variation of proteinuria among children with CKD might be associated with variation in genetic or environmental factors.

Hypertension and renal progression

Systemic hypertension causes intraglomerular hypertension that leads to glomerular hypertrophy and injury. Compared to normotensive CKD patients, hypertension is associated with a more rapid decline in kidney function among adult and pediatric CKD patients.[27-30] Yet, hypertension in pediatric nephropathies, though common, is typically less severe than in adult disorders.[31] Regardless, analysis of CKD registry data in children shows that renal function in children who are hypertensive declines more rapidly than in normotensive children.[29] As discussed by Dr. Wuhl in this issue of Current Opinion in Pediatrics(editor to insert page), CKD decline can be slowed with effective control of hypertension. Studies show that intensified blood pressure control slows renal progression in both adult and pediatric patients with CKD.[11,22,32,33] The results of the ESCAPE trial emphasize the importance of high blood pressure as both a risk factor and a treatment target for pediatric CKD progression.

Despite the known benefits of adequate hypertension control, baseline blood pressure (BP) data from 432 participants in CKiD indicate that hypertension is highly prevalent (54%).[34] In the cohort, risk factors for either elevated systolic BP or elevated diastolic BP included black

race, reported antihypertensive use, elevated serum potassium, glomerular cause of CKD, shorter duration of CKD, obesity, younger age, and nephrotic range proteinuria. In the multivariable analysis (adjusting for age, race, GFR, CKD diagnosis, duration of CKD, Upcr, antihypertensive use, obesity, and serum potassium), African American race, elevated serum potassium, longer duration of CKD, and antihypertensive use were independent risk factors for BP elevation.[34]

Among a sub-cohort of 202 CKiD subjects reporting use of antihypertensive medication for BP control, 36% had uncontrolled systolic or diastolic BP. The multivariable analysis demonstrated that male gender and shorter duration of CKD were associated with uncontrolled BP. Furthermore, use of ACE inhibitors or angiotensin receptor blockers was independently associated with BP control compared to other BP medications.[34] Although effective BP control is associated with improved outcomes in patients with CKD, the above data indicate that persistent barriers to achieving these goals exist in clinical practice.

Anemia and renal progression

Anemia is a universal complication of CKD caused by a decrease in renal production of erythropoietin.[35] The prevalence of anemia in the pediatric CKD population depends on CKD stage with a higher prevalence of anemia at higher stages of CKD. Wong et al found 36.6% of the pediatric CKD patients at their single center in Canada were anemic.[36] Compared to an anemia prevalence rate of approximately 30% in the earlier stages of CKD (stages 1 and 2), the rate of anemia was 66% at moderate CKD (stage 3), and 93% with severe CKD and end stage renal disease (ESRD) (stages 4 and 5) at their center. Estimates using the North American Pediatric Renal Trials and Collaborative Studies database indicate that the prevalence of anemia are 19% in CKD stage 2, 31% CKD stage 3, 55% CKD stage 4, and 68% in CKD stage 5.[37] Data from CKiD indicate that below a threshold iGFR of 43 ml/min/ $1.73m^2$ there is a statistically significant decrease in hemoglobin by -0.3 grams/dL for each 5ml/min/$1.73m^2$ decrease in iGFR, whereas above the threshold the decline is less: -0.1gram/dL for each 5ml/min/$1.73m^2$ decrease.[38]

Multiple studies have found anemia to be associated with an increased risk of morbidity and mortality in both pediatric ESRD and non-dialysis CKD patients.[37,39,40] More specifically, several studies have found an association between anemia and CKD progression. [41-43] Although there are wide variations in the study methods and definitions of anemia, the associated findings are consistent; anemic patients have a higher risk of CKD progression than patients without anemia.

In children with CKD, there is high interest in determining if anemia correction may slow CKD progression. Development of such trials have been complicated due to recent concerns regarding the increase in risk for morbidity and even mortality associated with normalization of hematocrit levels in adult CKD populations.[44-46] In pediatric CKD patients, increased risk for hospitalization or death were not associated with hematocrit levels above 36% or 39%. [37] Furthermore, correction of anemia with erythropoietin has been associated with a variety of beneficial effects in children, including improvement in quality of life, appetite, exercise tolerance, and Wechsler intelligence score, [47,48] highlighting the importance of attentive anemia management and the need for well-designed clinical trials in the pediatric CKD population.

Other risk factors for renal progression

While level of GFR, proteinuria, and hypertension are strongly associated risk factors for CKD progression, other reported risk factors associated with CKD progression include: low birth weight or prematurity[49,50], uric acid[51-53], lead or heavy metals[54,55], hyperlipidemia

[56], metabolic acidosis[57], oxidative stress[58], and disorders of bone and mineral metabolism [4,59-61]. While there is ongoing research to clarify the role of these risk factors on renal progression, the search for genetic susceptibility to CKD and its progression in humans have offered not only new directions for research but also potential targets for intervention.

Genome-Wide Scans and CKD

Recent findings regarding the genetic contribution to renal traits have provided new insights toward the pathogenesis and treatment for CKD. Significant advances in the field of genetics and genomic technology have made scanning the human genome for associations with complex diseases economically feasible. The success of genome-wide association studies (GWAS) is highlighted by the identification of candidate genes and loci for diabetic nephropathy susceptibility.[62-65] Recently, whole genome association studies have identified associations between renal traits and the non-muscle myosin heavy chain type 2 isoform A (MYH9) gene localized to chromosome 22q13[66,67]. This gene is associated with serum creatinine levels in non-CKD healthy Europeans. [67] In African Americans, MYH9 is associated with focal segmental glomerulosclerosis, nondiabetic ESRD, hypertensive ESRD, and among hypertensive patients urinary microalbumin-to-creatinine ratios. [66,68-70] Although the mechanism by which MYH9 participates in CKD susceptibility and progression is unknown, MYH9 is expressed by podocytes and suggested to be a major part of the actin-myosin contractile apparatus of the podocyte foot process.[71] Other genes associated with CKD include uromodulin (UMOD),[72] methenyltetrahydrofolate synthetase (MTHFS),[73,74] eyes absent homolog 1 (EYA1),[74] transcription factor-7-like 2 (TCF7L2),[75] and others [72-74] (Table 3).

While GFR and proteinuria are closely associated and are markers for CKD, they are distinct phenotypes.[79] Furthermore, available GWAS evidence from adults with diabetic CKD indicates the genetic loci associated with albuminuria is distinct from the loci associated with GFR.[62,63,80] The gene-disease associations for proteinuria from adult studies thus far do not generalize to children with CKD. This may be due to the fact that the types of diseases causing CKD are different in children versus adults. In fact, the NKF recommendations for proteinuria testing differ between children and adults. Tests for albuminuria are recommended when for screening for and monitoring adults with CKD; while albuminuria screening is recommended for diabetic children, urine total protein is recommended for children with kidney disease.[5] The genetics for proteinuria have yet to be elucidated in children with CKD, and are the focus of ongoing research.

Conclusions

With cohort studies of children with CKD becoming mature, they have started to yield important refinements to the assessment of CKD progression. The measurement of GFR by iohexol disappearance and refinement of GFR estimating equations represent recent improvements for measuring CKD progression in children. These are necessary to define the role of traditional and non-traditional risk factors for CKD progression in children. Traditional risk factors of proteinuria and hypertension are validated targets to slow CKD progression in children while other reported risk factors are still need of confirmation and validation in human studies. Adding to the growing list of putative CKD risk factors, genome-wide investigations in the adult CKD population have provided new genetic markers and pathways associated with CKD. Undoubtedly the ongoing cohort studies will assess the role traditional and novel risk factors for GFR decline. Furthermore, they will be ideal platforms for assessing genetic risk factors for CKD progression in the pediatric population.

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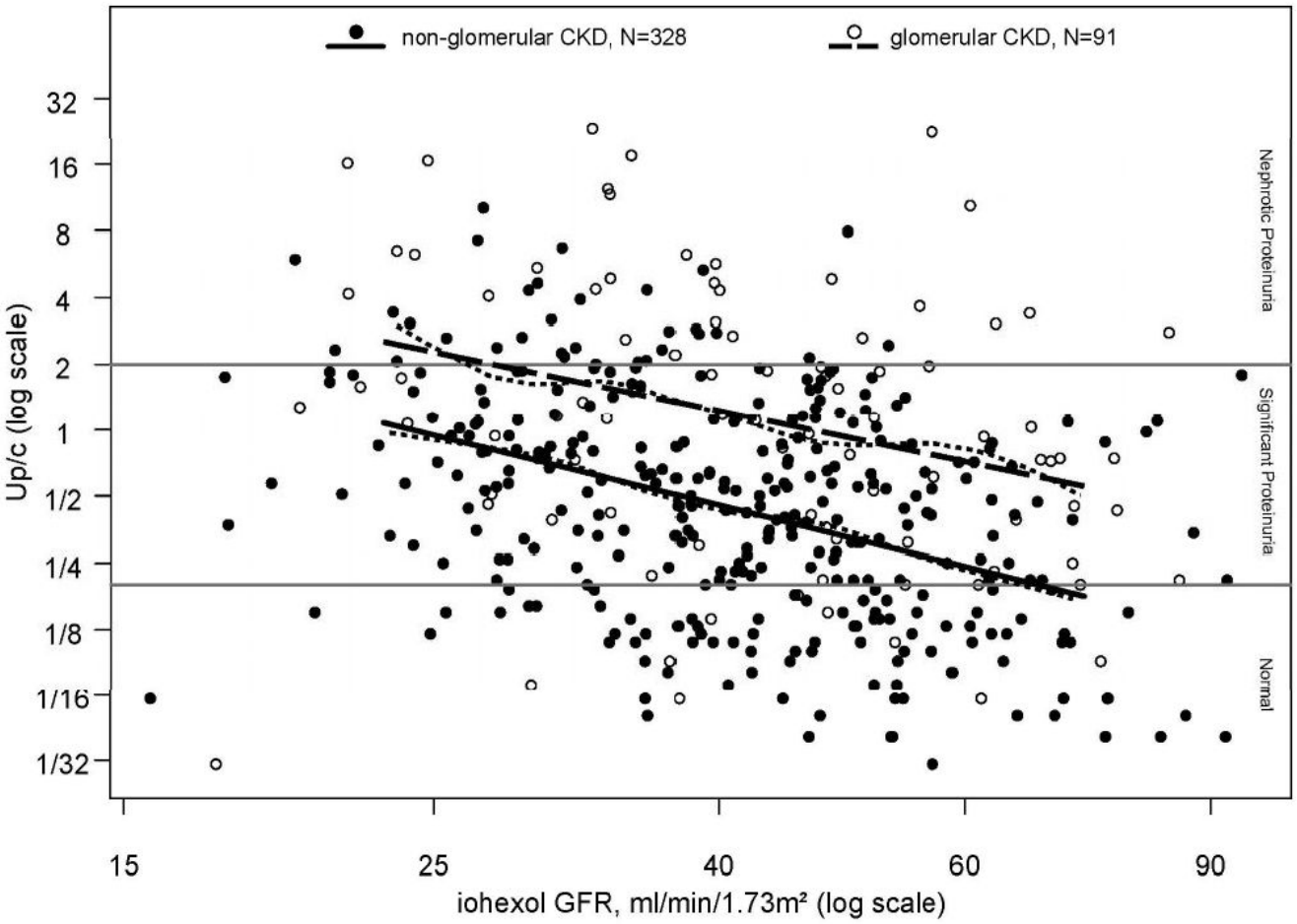

Figure 1. Level of Proteinuria by level of GFR

Urine Protein:Creatinine ratios (Up/c) by iohexol-measured glomerular filtration rate (iGFR)) for 328 non-glomerular CKD children and 91 glomerular CKD children, respectively. Non-parametric smoothing splines for the Up/c vs iGFR relationship for each of the CKD diagnosis groups are represented by the small dashed lines. Linear regression models for the non-glomerular and glomerular CKD patients are represented by the solid and large dashed straight lines, respectively. [Reproduced with permission from [26]]

Table 1
NKF-K/DOQI Classification Chronic Kidney Disease

Stage	GFR (mL/min/1.73m^2)	Description
-	≥ 90 (with CKD risk factors)	At increased risk
1	≥ 90	Kidney damage with normal or increased GFR
2	60-89	Kidney damage with mild reduction of GFR
3	30-59	Moderate reduction of GFR
4	15-29	Severe reduction of GFR
5	<15 (or dialysis)	Kidney failure

Table 2

CKiD GFR Estimating Equations

1	Original Schwartz formula: eGFR= k [a] × Ht (cm)/Scr
2	CKiD formula: eGFR[b] = $39.1[Ht(m)/Scr]^{0.516}[1.8/CysC]^{0.294}[30/BUN]^{0.169}[1.099^{male}][Ht/1.4]^{0.188}$
3	CKiD bedside formula: eGFR = 0.413 × Ht (cm)/Scr
4	CKiD longitudinal formula[c]: $eGFR_2 = 40.48\ [iGFR_1]^{0.912} \times ([Ht(m)/Scr_2] \div [Ht(m)/Scr_1])^{0.514}$

[a]The constant k is directly proportional to the muscle component of body, and varies with age. The value for k is 0.33 in premature infants through the first year of life, 0.45 for term infants through the first year of life, 0.55 in children and adolescent girls, and 0.7 in adolescent boys.

[b]Abbreviations: eGFR= estimated GFR, Ht= height, m= meters, cm=centimeters Scr= Serum creatinine, CysC= Cystatin C, BUN= blood urea nitrogen.

[c]Abbreviations: $eGFR_2$ = estimated GFR 1 year after baseline, $iGFR_1$ = iohexol GFR at baseline, $Ht(m)/Scr_2$ = height in meters divided by serum creatinine one year after baseline, $Ht(m)/Scr_1$ = height in meters divided by serum creatinine at baseline.

Table 3
Genes Associated with CKD (Non-Diabetic)

Gene	Name	Function	Biological Process
ACTN4[76,77]	Actinin alpha 4	Alpha actinins belong to the spectrin gene superfamily which represents a diverse group of cytoskeletal proteins. This gene encodes a nonmuscle, alpha actinin isoform which is concentrated in the cytoplasm.	In nonmuscle cells, the cytoskeletal isoform is found along microfilament bundles and adherens-type junctions, where it is involved in binding actin to the membrane. Mutations in this gene have been associated with an inherited form of focal segmental glomerulosclerosis.
EYA1[74]	Eyes absent homolog 1 (aka: brachio-oto-renal (BOR))	EYA1 is a regulator of mammalian organogenesis. EYA protiens do not bind DNA directly but function as coactivators of transcription in the nucleus.	EYA1 is important for pattern formation of early kidney development and works in conjunction with HOX11 and PAX2. The EYA binding domain interacts with transcriptional cofactors SIX and DACH. The binding domain also exibits a tyrosine phosphatase activity that regulates anti-apoptotic signaling with DNA damage.
GATM[72]	Glycine amidino-transferase (aka: L-arginine:glycine amidinotransfer-ase)	The gene encodes a mitochondrial enzyme that belongs to the amidinotransferase family. This enzyme is involved in creatine biosynthesis.	GATM is responsible for catalyzing the rate limiting step of creatine biosynthesis. GATM transfers the amidino group from L-arginine to glycine resulting in L-ornithine and guanidinoacetic acid (the immediate precursor to creatine).
JAG1[72]	Jagged 1	JAG1 is a single-pass transmembrane ligand for NOTCH1. Mutations of this gene is associated with Alagille syndrome.	Interactions between the extracellular domain of JAG1 with NOTCH1 triggers proteolytic cleavage of the receptor and activation of the pathway.
MTHFS[74]	5,10-methenylttrahydro-folate synthetase	MTHFS is a protein that catalyzes the transformation of 5-formyltetrahydrofolate to methenyltetrahydrofolate.	MYH9 is associated with serum creatinine level in Europeans. In African Americans it is associated with FSGS, ESRD, and in hypertensive patients albuminuria. The protein is expressed in the kidney, liver, cochlea, and platelets.
MYH9[66-70]	Myosin, heavy chain 9, non-muscle	The gene encodes the alpha isoform of non-muscle myosin heavy chain. This class of protein is an important component of the cells motor system.	MYH9 is associated with serum creatinine level in Europeans. In African Americans it is associated with FSGS, ESRD, and in hypertensive patients albuminuria. The protein is expressed in the kidney, liver, cochlea, and platelets.
NPHS2[78]	Nephrosis 2, idiopathic steroid resistant (Podicin)	This gene encodes for the glomerular protein podocin which belongs to a family of evolutionarily conserved membrane associated proteins.	NPHS2 can recruit and bind cholesterol, forming multimers. NPHS2 binds and regulates the transient receptor potential channel, TRP6.

Gene	Name	Function	Biological Process
SHROOM3[72]	Shroom family member 3	The gene encodes for an actin binding protein and associated with gamma tubulin function.	SHROOM3 associates with gamma tubulin, myosin light chain, and Rho kinase to regulate apical junction organization in epithelial cells.
STC1[72]	Stanniocalcin 1	The gene is a glycoprotein initially characterized in fish with calcium regulating properites. Human STC1 has a wide distribution of tissues and found in mitochondria. The function of STC1 has been difficult to characterize.	STC1 in humans is hypothesized to be involved in the cellular stress response. STC1 gene expression is regulated by tumor suppressors BRCA1 and p53. STC1 is upregulated by oxidative stress and IL6.
TCF7L2[75]	Transcription factor 7 like-2 (note: TCF7L2 has an alternative alias, TCF4)	This gene encodes a high mobility group box-containing transcription fctor that plays a role in Wnt signaling pathway.	Genetic variants of this gene has been implicated in blood glucose homeostasis as well as chronic kidney disease in the general population.
UMOD[72]	Uromodulin	Uromodulin is the most abundant protein in normal urine. Excretion follows proteolytic cleavage of the ectodomain on the luminal surface of the loop of henle.	Defects of the gene are associated with medullary cystic kidney disease-2 (MCKD2) and familial juvenil hyperuricemic nephropathy. Recently the gene has been associated with CKD by genome wide association in ther general population.