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APOL1 and Nephropathy Progression in Populations of African Ancestry

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Summary

Marked familial aggregation of chronic kidney disease suggests that inherited factors play a major role in nephropathy susceptibility. Molecular genetics analyses have identified a number of genes reproducibly associated with a broad range of renal phenotypes. Most associations show polygenic inheritance patterns with limited effect size. In contrast, genetic association between the apolipoprotein L1 (***APOL1***) gene and several severe nondiabetic forms of kidney disease in African Americans approach Mendelian inheritance patterns and account for a large proportion of glomerulosclerosis in populations of African ancestry. Emerging data support an important role for ***APOL1*** in the progression of diverse etiologies of kidney disease, in concert with requisite environmental (gene*environment) and inherited (gene*gene) interactions. This article reviews the current status of ***APOL1***-associated nephropathy and discusses research questions under active investigation in the search for a cure for these severe and often progressive kidney diseases.

Keywords

African American; APOL1; FSGS; HIV; kidney disease; progression

Identification of the impressive apolipoprotein L1 (*APOL1*) association with several previously unrelated forms of nondiabetic kidney disease was a significant scientific breakthrough, one likely to advance our understanding of the pathogenesis of glomerulosclerosis with interstitial fibrosis and renal microvascular disease.[1–3] The *APOL1* G1 and G2 coding nephropathy risk variants appear to have been selected in sub-Saharan Africa within the past 10,000 years. This is based on the protection that the presence of one of these variants affords from parasitic infection with *Trypanosoma brucei rhodesiense*, a cause of the fatal disease African sleeping sickness. G1 and G2 risk variants are virtually absent in populations of European and Asian ancestry, showing their relatively recent origin, well after modern human beings departed the African continent.[4,5]

Strong nephropathy association initially was detected between polymorphisms on chromosome 22q in the nonmuscle myosin heavy chain 9 (*MYH9*) and adjacent *APOL1* genes in African Americans with biopsy-proven forms of focal segmental glomerulosclerosis (FSGS) using admixture mapping.[6–8] Odds ratios [OR] for *APOL1* association with FSGS are 17, for human immunodeficiency virus (HIV)-associated collapsing glomerulopathy (herein referred to as HIV-associated nephropathy [HIVAN]) are

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29, and for nondescript forms of end-stage kidney disease (ESKD) that historically were ascribed to high blood pressure (putative hypertension-attributed or arteriolar nephrosclerosis) are 7.3.[1,9] Table 1 contains representative ORs for *APOL1* association. A somewhat weaker association was observed in Hispanic Americans of Puerto Rican, Dominican, and other Caribbean ancestries residing in New York City.[2] These population groups had approximately 30% African ancestry, far higher than typically seen in Mexican Americans and other Hispanic Americans residing outside of the northeastern United States.

The initial *MYH9* extended-1–risk haplotype association in African ancestry populations likely reflected strong linkage disequilibrium with *APOL1* because 89% of those with *APOL1* G1 and 76% with *APOL1* G2 have *MYH9* extended-1–risk haplotypes.[1] However, residual (albeit weaker) *MYH9* association with nephropathy in European and Asian populations suggests that additional susceptibility alleles exist in this region because the G1 and G2 *APOL1* risk variants are virtually absent in these groups.[4,5,10,11] Whether additional risk variants reside in *MYH9* or reflect linkage disequilibrium with the neighboring *APOL1* to *APOL6* gene region remains unknown.

CLASSIFYING KIDNEY DISEASE IN POPULATIONS OF AFRICAN ANCESTRY: HYPERTENSION-ATTRIBUTED NEPHROPATHY RESIDES IN THE SPECTRUM OF FSGS

High blood pressure is reported by nephrologists as the inciting cause of ESKD in approximately 35% of African Americans initiating renal replacement therapy in the United States[12]; however, this clinical diagnosis frequently is incorrect.[13,14] *APOL1*-associated forms of glomerulosclerosis are present in the majority of African Americans labeled with hypertension-attributed ESKD and hypertension-attributed nephropathy.[15,16] Recent genetic analyses in African American Study of Kidney Disease and Hypertension (AASK) trial participants clearly show that this is the case.[17]

Nephropathy progression rates among AASK participants with putative “hypertensive nephropathy” were not appreciably slowed by intensive blood pressure lowering or with particular classes of antihypertensive agents including angiotensin-converting enzyme inhibitors (ACEi).[18] Although a slight benefit of ACEi and intensive blood pressure control was seen in the early years of the AASK trial,[19] using these two measures in all subjects in the AASK cohort phase saw nearly 60% of participants reach a primary study end point (death, dialysis, or doubling of serum creatinine concentration) after 10 years.[20] Clearly, blood pressure control did not slow nephropathy progression in AASK participants, suggesting that an alternative initiating cause of kidney disease was present.[21]

APOL1 showed impressive genetic association with kidney disease in all 663 AASK participants with available DNA samples (OR, 2.57; $P = 1.39E^{-8}$); association was strengthened in the subset whose nephropathy progressed to a serum creatinine concentration greater than 3 mg/dL or ESKD (OR, 4.61; $P = 5.60E^{-15}$) or with a baseline urine protein:creatinine ratio greater than 0.6 g/g (OR, 6.29; $P = 2.62E^{-14}$).[17]

Kidney biopsy specimens in a small number of AASK participants showed histologic changes that initially were interpreted as consistent with hypertension, focal global glomerulosclerosis (FGGS) and occasionally FSGS, with interstitial fibrosis and vascular changes.[22] In retrospect, these biopsy changes relate to *APOL1*-associated disease and not high blood pressure. This observation likely explains why blood pressure lowering and ACEi were poorly effective. AASK subjects have a kidney disease that lies in the spectrum

of FSGS with low relatively level proteinuria.[23] In addition, an ACEi can best slow nephropathy progression in the setting of heavy proteinuria.[24]

HIV-ASSOCIATED COLLAPSING GLOMERULOPATHY

Of all common kidney diseases, HIVAN shows the most marked African American to European American disparity in incidence rates.[25] In the early days of the acquired immune deficiency syndrome (AIDS) epidemic, AIDS was reported as a cause of FSGS in African Americans residing in the northeastern and southeastern United States.[26] Subsequent reports from the West Coast failed to detect this association, prompting many to attribute FSGS on the East Coast to the effects of intravenous drug use, not HIV infection. These geographic differences are related to the presence of *APOL1* risk variants in East Coast HIV populations with African ancestry, relative to the initial West Coast AIDS epidemic that more often impacted European Americans.[27]

In a similar vein, it is fascinating to note the relative lack of *APOL1* nephropathy risk variants in Africans from Ethiopia (whether they reside in Ethiopia or emigrated to Israel), along with their associated low frequency of HIVAN.[28] Ethiopians have approximately 50% Middle Eastern and 50% African ancestry; however, demarcation is observed in allele frequencies between Western and Eastern Africa. Consistent associations between *APOL1* risk variants and kidney disease in those with West African ancestry, and lower nephropathy risk in Ethiopians with HIV infection who lack *APOL1* risk variants, show the powerful role of variation in this one gene on nondiabetic kidney disease.[29]

Fine et al[30] evaluated renal pathology in 98 African American patients with HIV infection and nephropathy, based on *APOL1* genotypes. The frequency of FSGS was significantly higher among those with two *APOL1* risk variants, whereas immune complex–mediated glomerular diseases were more common in those without risk variants. Progression to ESKD was also significantly more common in those with two risk variants, versus zero or one.

SICKLE CELL DISEASE–ASSOCIATED NEPHROPATHY, PROGRESSIVE IGA NEPHROPATHY, AND LUPUS NEPHRITIS

Variations in *APOL1* (and MYH9) recently was shown to underlie risk for sickle cell disease (hemoglobin SS)-associated nephropathy in African Americans.[31] In addition, individuals with sickle cell trait (hemoglobin AS) do not face an increased risk of nephropathy, before or after adjustment for *APOL1*.[32] A report in Han Chinese with progressive IgA nephropathy also detected *MYH9* association.[11]

Our initial report in small numbers of African Americans with lupus nephritis (LN)-associated ESKD suggested that there was an *MYH9/APOL1* association; however, we were unable to replicate this observation when additional patients with mild forms of LN were included.[33] Lin et al[34] subsequently reported *MYH9* association with LN in EAs (and less strongly in the Gullah population), but no evidence of *APOL1* or *MYH9* association in African Americans, Asians, Amerindians, or Hispanics with non-ESKD LN.

To address the issue of severity of LN on genetic risk, a national sample of 668 African Americans with LN with ESKD was tested for chromosome 22q nephropathy risk variant associations. This study detected an OR of 2.35 (95% confidence interval 1.77-3.3; $P = 4.25E^{-9}$) for *APOL1* association with LN ESKD.[35] Significant differences were not observed in the OR for association between the 456 African American cases with kidney biopsy-proven LN and the 212 African American cases without a kidney biopsy (whose physician attributed ESKD to LN). This suggests that severe LN with ESKD is associated

with *APOL1*; leading to the evolving concept that *APOL1* risk variants underlie progression of several forms of nephropathy to end stage, but may not necessarily initiate kidney disease. Table 2 includes a list of kidney diseases associated with variation in the chromosome 22q gene region.

APOL1 ASSOCIATIONS WITH MILD NEPHROPATHY

Although African Americans have higher rates of severe kidney disease relative to European-derived populations,[12] they do not appear to have excess rates of early nephropathy.[36] This fact, along with the markedly weaker *APOL1* association with milder forms of nephropathy, strengthens the hypothesis that *APOL1* is a risk factor for nephropathy progression.

Friedman et al[37] evaluated African Americans from the large population-based Dallas Heart Study with a mean age of 44.8 years (SD, 10.3 y). Although microalbuminuria and/or MDRD GFR less than 60 mL/min per 1.73 m^2 were observed in 19.2% of nondiabetic subjects with two *APOL1* risk alleles, relative to 6.7% of those with fewer than two risk variants, it is important to note that the mean GFR and urine albumin to creatinine ratio (UACR) were similar and within the normal range in participants from both genotype groups. Shriner et al[38] also reported a weak association of the *APOL1* G2 risk variant with eGFR in a population-based sample of African Americans residing in the Washington, DC, area; evidence of G1 association was not detected in these individuals lacking advanced nephropathy.

As in the Dallas Heart Study, we observed weaker *APOL1* association with mild nephropathy in first-degree relatives of African Americans with nondiabetic forms of ESKD.[8] Although high-risk relatives were enriched for APOL1 risk variants (23% had two risk variants and 46% had one risk variant, compared with 12% and 39% of the general African American population), MDRD GFR less than 60 mL/min per 1.73 m^2 and/or UACR greater than 30 mg/g were present in 22.9% of those with two risk variants and in 21.1% of those with fewer than two risk variants. A major difference between our family based results and those in the Dallas Heart Study was seen in those with fewer than two *APOL1* risk variants; lower frequencies of kidney disease were detected in the Dallas Heart Study compared with high-risk first-degree relatives of index cases with ESKD. Based on the robust evidence of *APOL1* association with severe forms of nephropathy and weaker association with mild disease, we conclude that *APOL1* likely contributes to more rapid progression from early stage kidney disease to ESKD (Fig. 1).

GENETIC PREDICTION OF OUTCOMES AFTER KIDNEY TRANSPLANTATION

APOL1 variation appears to underlie the poorer allograft survival rates in kidney transplants from deceased African American donors, relative to European Americans.[39] As for the caveolin 1 and the drug transporter P-glycoprotein genes (encoded by the adenosine triphosphate-binding cassette, subfamily B, member 1 gene) on kidney allograft survival transplant outcomes, effects are associated with donor genotypes, not those of recipients.[40,41]

APOL1 risk variants were genotyped in 106 African American deceased kidney donors at one center and graft survival was assessed in 136 resulting transplants.[39] Cox proportional hazard models were used to test for association between time to graft failure and donor genotypes. Sixteen percent of transplanted kidneys (22 of 136) were from high-risk donors with two *APOL1* nephropathy risk variants. Overall, 25 grafts failed during follow-up

evaluation, 32% (8 of 22) of them had two *APOL1* risk variants. In a multivariate model accounting for donor *APOL1* genotypes, genome-wide African ancestry, expanded criteria versus standard criteria donation, recipient age and sex, HLA mismatch, cold ischemia time (CIT), and panel reactive antibody titer, graft survival was significantly shorter in donor kidneys with two *APOL1* risk variants (hazard ratio, 3.84; $P = .008$) and higher HLA mismatch (hazard ratio, 1.52; $P = .03$), but not overall African ancestry excluding *APOL1*. Kidneys from African American deceased donors that harbored two *APOL1* risk variants failed far more rapidly after transplantation than those with zero or one risk variant.

This effect held true only for the genotypes of kidney donors. In a subsequent study, long-term effects on graft survival were not observed based on *APOL1* genotypes of kidney transplant recipients.[42] Although this result makes it tempting to speculate that an important pathophysiologic role exists for *APOL1* gene expression in kidney cells (possibly in podocytes) leading to glomerulosclerosis, and that resulting kidney disease or allograft failure is less likely related to aberrant circulating ApoL1 protein or high-density lipoprotein (HDL) cholesterol, we do not believe that firm conclusions should be drawn from the kidney transplant model. Kidney transplants are impacted by the effects of prolonged CIT and nephrotoxin exposure including calcineurin inhibition. As such, subclinical nephropathy that may have been present at the time of organ harvesting may be accelerated to graft failure by CIT and nephrotoxin exposure.

It remains difficult to determine exactly what processes lead to subclinical kidney disease in donors; this remains an area of intensive investigation. It is not difficult to appreciate that some deceased individuals screened for kidney disease before organ donation could have undetected mild nephropathy. *APOL1* association with nonproteinuric mild nephropathy in AASK participants and relatives of cases with non-diabetic ESKD show this phenomenon.[8,17]

As a result of this work, debate has arisen over whether to screen potential African American living kidney donors for *APOL1*. Cohen et al[43] argued persuasively that this is the most ethical approach because kidney donors may face higher risk for subsequent ESKD if they donate half of their renal mass. In addition, recipients of these kidneys may not fare as well. It is true that African American live kidney donors have somewhat higher rates of ESKD than European ancestry donors.[44] However, overall rates of ESKD postdonation remain low.[45] This suggests that the current evaluation process works fairly well; but *APOL1* genotyping may further inform patients, family members, and transplant physicians. We await replication of our initial finding in the deceased kidney donor population. If this finding is replicated, we would encourage *APOL1* genotyping in potential African American living kidney donors, as well as in deceased African American kidney donors if it can be performed rapidly. As such, *APOL1* genotypic data ultimately may transform the kidney donor evaluation process.

SECOND HITS AND MODIFYING FACTORS

All individuals inheriting two *APOL1* risk variants will not develop nephropathy. For example, HIVAN develops in approximately 50% of untreated African Americans with HIV infection.[9] A smaller percentage of non–HIV-infected individuals with two *APOL1* risk variants are expected to develop kidney disease. Therefore, modifying factors such as environmental exposures or second gene interactions likely are involved in *APOL1*-associated nephropathy.[46–48] We believe that different modifiers likely lead to the observed histologic findings in this disorder, from collapsing glomerulosclerosis seen with HIV infection to idiopathic forms of FSGS and FGGS, likely related to other modifying factors.[14]

Variants in the glomerulosclerosis-associated podocin gene (*NPHS2*), and other genes, could induce nondiabetic ESRD in concert with *APOL1*.[49] Although such gene*gene interactions are likely, environmental exposures that interact with *APOL1* potentially may be amenable to treatment and lead to novel prevention strategies.

We screened for the presence of viral infections with characteristics similar to HIV (eg, lymphotropism and persistent urinary tract/renal reservoirs of infection) that could interact with *APOL1*, as in HIVAN.[50] Evidence of active infection with two lymphotropic viruses (Human Herpes Virus 6 and cytomegalovirus) and two viruses with urinary tract reservoirs (JC polyoma virus [JCV] and BK polyoma virus) were assessed in 300 first-degree relatives of African American index cases with nondiabetic ESKD, a population enriched for *APOL1* risk variants. Although bloodstream infection with Human Herpes Virus 6 and cytomegalovirus were extremely rare, 30% and 9.7% of relatives, respectively, had detectable JCV and BK polyoma virus in the urine. Adjusting for familial age at nephropathy, sex, and ancestry, JCV genomic DNA in the urine and *APOL1* risk alleles were associated negatively with renal phenotypes, including increased cystatin C ($P = .006$), UACR greater than 30 mg/g ($P = .0002$), and kidney disease defined as an eGFR less than 60 mL/min per 1.73 m^2 and/or UACR greater than 30 mg/g ($P = .000017$) in an additive model. BK viruria was not associated with kidney disease. Hence, African Americans with two *APOL1* risk variants and JC viruria had a lower prevalence of kidney disease, suggesting that JCV interacts with *APOL1*. Potential mechanisms might include inhibition of urinary tract replication by other more nephropathic viruses or impact on gene expression profiles that may alter susceptibility to *APOL1*-associated nephropathy. This observation requires replication; however, it provides hope that modifiable or preventable viral infections may one day reduce the rates of nondiabetic nephropathy in individuals with two *APOL1* risk variants.

DISEASE PATHOGENESIS

Mechanisms underlying the development of progressive nephropathy in individuals with two *APOL1* risk variants remain unknown (Table 3). There appears to be a consensus developing that *APOL1* is expressed in podocytes and ApoL1 protein is present in these cells.[51–53] It is less clear whether the gene is expressed in renal tubular cells, glomerular endothelial cells, and intimal and medial cells of small intrarenal blood vessels. Only a few small studies have been performed to date and results are equivocal. Differences in gene expression based on *APOL1* genotypes have not been observed. Several cell lines have been transfected with wild type, G1, and G2 *APOL1* transcripts. In general, cells transfected with nephropathy risk variants appeared to have higher rates of autophagic cell death and shorter survival,[54,55] as initially postulated in the landmark study by Genovese et al.[1]

Another potentially important observation is that ApoL1 protein is detectable in renal tubular and vascular cells, although it may not be expressed in those cells.[52] If the protein is not produced within these cells, circulating and/or filtered ApoL1 protein may be taken up by these cells with potentially toxic consequences. Again, it will be important to detect genotype-specific effects.

ApoL1 protein travels in the circulation in association with HDL cholesterol. Nondiabetic nephropathies include arteriolar changes that are consistent with vascular damage. Hence, it is conceivable that altered properties of HDL cholesterol based on ApoL1 content could lead to small-vessel and glomerular endothelial cell injury. *APOL1* genotype impacts HDL particle concentration; as a result, HDL could play a role in glomerulosclerosis and renal microvascular injury.[23] *APOL1* genotypes also were associated with race-specific relationships between HDL cholesterol concentration and kidney function.[56] Higher HDL

level was associated with higher eGFR in Han Chinese and European American populations, whereas an inverse association between HDL and eGFR was seen in African Americans and West Africans. The effect was significant only in African Americans who had *APOL1* risk genotypes (not in West Africans). The authors concluded that the disease mechanisms underlying *APOL1*-associated nephropathy could involve HDL cholesterol.

RESPONSE TO TREATMENT

APOL1-associated nephropathies are often severe, lead to rapid progression of chronic kidney disease, and present with earlier ages at onset of ESRD.[57,58] Although little is known about response rates to standard therapies for FSGS, Kopp et al[9] reported that after 8 or more weeks of steroid therapy, African American patients with FSGS and two *APOL1* risk variants had a 29% (12 of 42) response rate, relative to 33% (5 of 15) of patients with 0/1 risk variants ($P > .5$). FSGS associated with other Mendelian genetic mutations, including the recessively inherited podocin gene (*NPHS2*), typically are resistant to glucocorticoid therapy.[59]

The FSGS Controlled Trial randomized children and young adults with glucocorticoid-resistant FSGS to either 1 year of cyclosporine plus low-dose daily steroids or mycophenolate pulse oral dexamethasone and low-dose daily steroids.[60] Only 32 study subjects were African American (of those, 23 [72%] had two *APOL1* risk alleles); an additional four study subjects had two *APOL1* risk alleles (two were Hispanic). Subjects with two *APOL1* risk alleles had a lower eGFR, a higher frequency of severe lesions (collapsing FSGS, cortical atrophy/fibrosis, arteriosclerosis), and similar levels of proteinuria relative to those with fewer than two risk alleles. Although remission rates to the cyclosporine and mycophenolate-based regimens were not significantly different based on genotypes in this small series, the risk for progression to ESKD during follow-up evaluation was significantly higher (by three-fold) in those with two *APOL1* risk variants versus those with fewer than two risk variants.[60] Additional trials evaluating responses to existing and novel treatments for *APOL1*-associated nephropathy are required.

CONCLUSIONS

Much of the existing epidemiology regarding non-diabetic ESKD in African Americans was based on the assumption that mild to moderate essential hypertension commonly initiated nephropathy. Instead, it is now clear that a spectrum of *APOL1*-associated proteinuric and nonproteinuric disorders manifesting as FSGS and FGGS with interstitial and vascular changes exists in those previously labeled with hypertension-attributed nephropathy. These disorders relate to selection for trypanolytic gene variants protective of African sleeping sickness. Risk variants appear to predispose to severe kidney disease from a variety of nondiabetic systemic and renal-limited diseases. As such, it appears likely that they promote progression of nondiabetic forms of nephropathy to ESKD. The mechanisms whereby *APOL1* accelerates nephropathy progression remain to be determined; however, modifying genetic and environmental triggers appear necessary and different modifying factors likely determine the final histopathology (eg, collapsing FSGS, nonspecific FSGS, or FGGS). This molecular genetics breakthrough is likely to lead to novel treatments for FSGS and related nondiabetic renal disorders in those with African ancestry. Novel therapies will be critical for the nephrology community because nondiabetic nephropathies in African Americans previously have proven relatively refractory to existing treatments.

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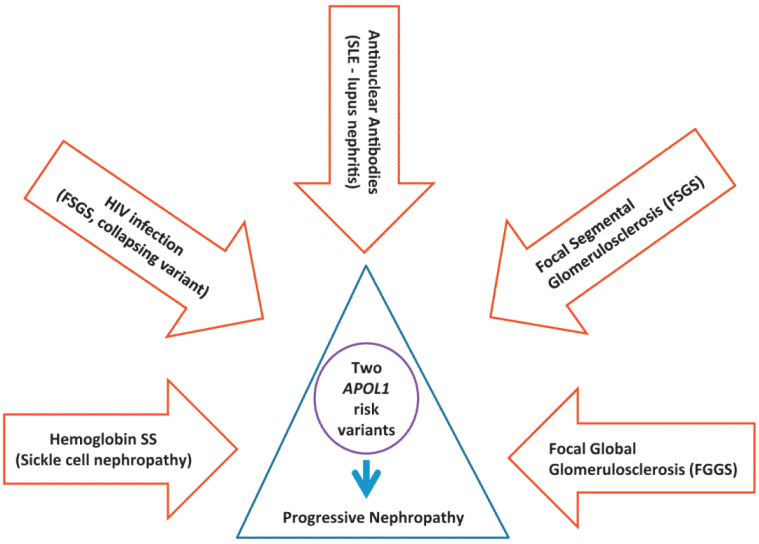

Figure 1.
The spectrum of APOL1-associated progressive nephropathy. SLE, systemic lupus erythematosus.

Table 1

Reported Odds Ratio (Recessive Model) for ***APOL1***-Associated Forms of Nephropathy

Kidney Disease	Clinical Features	Odds Ratio (95% CI)
HIVAN[9]	Collapsing glomerulopathy	29.2 (13.1-68.5)
Idiopathic FSGS[9]	—	16.9 (11.0-26.5)
FGGS with interstitial and vascular alterations[17]	All participants in AASK with putative hypertension-attributed nephropathy	2.6 (1.9-3.6)
FGGS with interstitial and vascular alterations[17]	AASK participants with eventual increase in serum creatinine level > 3 mg/dL	4.6 (3.1-6.8)
FGGS with interstitial and vascular alterations[17]	AASK participants with baseline urine protein: creatinine ratio > 0.6 g/g	6.3 (3.9-10.1)
Nondiabetic ESKD in African Americans[1]	Putative hypertension-attributed ESKD (African ancestry)	7.3 (5.6-9.5)
Sickle call nephropathy[31]	Proteinuria	3.4 (not reported)
Lupus nephritis–associated ESKD[35]	African ancestry	2.4 (1.8-3.3)

Abbreviation: CI, confidence interval.

Table 2

Kidney Diseases Associated With ***APOL1*** (and ***MYH9***)

Histopathology	Clinical Diagnosis	Population Group (s)	Comments
FSGS	Idiopathic FSGS	African and European	1,2,9
HIV-associated collapsing glomerulopathy	HIV-associated nephropathy	African	9
Nondiabetic ESKD (likely FGGS and FSGS)	Hypertension-attributed ESKD	African and Hispanic	Hispanics from New York City had significant African admixture[1,2]
FGGS with arteriolar changes and interstitial fibrosis	Hypertension-attributed nephropathy	African	1,2,17
Sickle cell nephropathy	Sickle cell nephropathy	African	31
Lupus nephritis-associated ESKD	Advanced lupus nephritis with ESKD	African	35
Progressive IgA nephropathy	Advanced IgA nephropathy	Chinese	***MYH9*** association[11]
Diabetic and nondiabetic CKD	Nondiabetic CKD (nonspecific glomerulosclerosis)	European	***MYH9*** association[4,5,10]

Abbreviation: CKD, chronic kidney disease.

Table 3

Potential Mechanisms Underlying ***APOL1***-Associated Nephropathy

Potential Mechanism	Primary Site (Effect)	Additional Sites
Expression in the kidney	Podocyte (? autophagy)	Glomerular endothelium and tubules
Expression in small arterioles	Media	Intima
Altered circulating ApoL1 protein	Glomerular filtration, subsequent proximal tubule reabsorption	Direct effects on glomerular endothelium
Altered HDL cholesterol	Effects on glomerular and vascular endothelium	—