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***APOL1*-Associated Nephropathy: A Key Contributor to Racial Disparities in CKD**

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Abstract

Genetic methodologies are improving our understanding of the pathophysiology in diverse diseases. Breakthroughs have been particularly impressive in nephrology, where marked disparities exist in rates and etiologic classifications of ESKD between African Americans and European Americans. Discovery of the apolipoprotein L1 gene (*APOL1*) association with focal segmental glomerulosclerosis, HIV-associated nephropathy, lupus nephritis, sickle cell nephropathy, and solidified glomerulosclerosis, as well as more rapid failure of transplanted kidneys from donors with *APOL1* renal-risk genotypes has improved our understanding of non-diabetic nephropathy. Environmental factors acting via natural selection in sub-Saharan African populations likely underlie this association. This article describes the discovery of chromosome 22q renal-risk variants and their worldwide distribution, reviews the epidemiology and pathology of *APOL1*-associated nephropathies, and explores several proposed mechanisms of renal injury identified in cell culture and animal models. Detection of the *APOL1* associations with kidney diseases and delineation of injury pathways brings hope for effective treatment for these kidney diseases.

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Keywords

African Americans; APOL1; apolipoprotein A1; chronic kidney disease (CKD); focal segmental glomerulosclerosis (FSGS); disparities; HIV-associated nephropathy (HIVAN); race/ethnicity; genetic determinants; renal risk variant; African ancestry; genotype; review

Genetic epidemiology of end-stage kidney disease in African Americans

Prior to the era of genomic medicine, several lines of evidence supported unique susceptibility to progressive non-diabetic chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in African Americans. These included the greater propensity for progression of early-stage CKD to ESKD in this population,¹ continued high incidence rates of ESKD relative to other racial/ethnic minority groups despite improvements in therapy, pronounced familial aggregation of ESKD that was independent from socioeconomic status,^{2–4} and clustering of disparate kidney diseases in families.^{3,5,6} Therefore, it was proposed that a common nephropathy susceptibility gene variant might preferentially exist in African Americans that would cause ESKD independently from hypertension, diabetes mellitus, systemic lupus erythematosus (SLE), or human immunodeficiency virus (HIV) infection.^{7,8,9}

Although met with skepticism, this hypothesis ultimately proved correct. Many African Americans with non-diabetic etiologies of ESKD have nephropathy caused by the G1 and G2 renal-risk variants in the apolipoprotein L1 gene (*APOL1*).^{10,11} Renal histology reveals lesions in the spectrum of focal segmental glomerulosclerosis (FSGS) and solidified (global) glomerulosclerosis, often with pronounced vascular and interstitial changes.¹² Many of these patients continue to be labeled as having kidney disease related to effects of mild-to-moderate hypertension, particularly among the African American population. This misattribution of kidney disease to hypertension relates in part to physician misunderstanding of disease mechanisms.¹³ Recent trials reveal that aggressive blood pressure control using angiotensin-converting enzyme inhibitors fails to slow nephropathy progression in patients with kidney disease attributed to hypertension and that non-hypertensive etiologies of kidney disease are often present.^{14,15} The African American Study of Kidney Disease and Hypertension (AASK) concluded that there was no additional benefit of slowing progression of non-diabetic CKD with intensive blood pressure control, particularly in those with urinary protein-creatinine ratios <0.22 g/g.¹⁶ Intensive blood pressure control was found to be of potential benefit to participants with higher degrees of proteinuria and ACE inhibitors were observed to be more effective than beta-blockers or calcium channel blockers. Thus independent from *APOL1* genetic risk variants, factors such as smoking, dyslipidemia, inflammation, obesity, as well as the effects of blood pressure, contribute to vascular injury in the setting of systemic hypertension.¹⁷

With identification of *APOL1* renal-risk variants, it became apparent that a spectrum of non-diabetic kidney diseases was associated with *APOL1* variants; odds ratios (ORs) revealed magnitudes never before observed in a complex disease. Kidney diseases in the spectrum include FSGS with and without nephrotic-range proteinuria, HIV-associated nephropathy (HIVAN), interferon-associated FSGS, severe lupus nephritis (LN), sickle cell nephropathy,

and solidified glomerulosclerosis with low-level proteinuria.^{8–11,18–21} In addition, more rapid failure of transplanted kidneys from African American deceased donors has been reported to relate to variation in *APOL1*.²²

Discovery of the chromosome 22q ESKD susceptibility locus

Individuals with recent African ancestry carry an excessive burden of CKD and ESKD compared to individuals of other ancestries, even after adjusting for socioeconomic status, lifestyle and clinical factors (e.g. diet and hypertension).¹ This suggests genetic factors contribute to the racial disparity. In 2008, two groups used a strategy of mapping by admixture linkage disequilibrium (MALD) to investigate the genetic bases of this ancestry-driven health disparity in the recently admixed African American population.^{23,24} Using <1,500 ancestry-informative markers spread across the genome for which the allele frequencies widely differ between European and African populations, they estimated local chromosome ancestry to map the genetic loci associated with FSGS/HIVAN and non-diabetic ESKD. Both groups identified a striking association on the 22q locus encompassing dozens of genes and centered on the non-muscle myosin heavy chain IIA gene (*MYH9*). *MYH9* appeared to be a good causal candidate because it is expressed in podocytes and mutations in this gene were previously associated with glomerular diseases.²⁵ However, plausible functional variants within *MYH9* could not be identified; only intronic variants were associated.²⁶ A study revealed extended linkage disequilibrium and haplotype length in the *MYH9* genetic locus, suggesting a recent selection event in sub-Saharan African populations and opening the possibility that *MYH9* haplotypes could be tracking the effect of causal variants in neighboring genes.²⁷

In 2010, the 1000 Genomes Project, which contained DNA sequence data for hundreds of individuals including Africans and Europeans, became available. Two groups with access to this database discovered newly available coding genetic variants within the *APOL1* gene that were in strong linkage disequilibrium with *MYH9* risk haplotypes and exhibited even stronger associations with FSGS,¹⁰ hypertension-attributed ESKD,¹⁰ and non-diabetic ESKD.¹¹ *APOL1* is located less than 14 kilobases directly upstream of *MYH9*. The *APOL1* renal risk alleles are located in the 3' end of the gene and were termed G1, for the rs73885319 nonsynonymous coding variant (leading to a serine to glycine substitution at amino acid 342 [p.S342G]), and G2, for the rs71785313 two amino-acid deletion (p.N388_Y389del).¹⁰ After adjusting for both G1 and G2 renal risk alleles, no residual significant association was found in *MYH9* or any other neighboring genes.¹⁰

The G1 and G2 alleles are nearly always mutually exclusive, ie located on homologous chromosomes, not having undergone recombination due to their close proximity. When considered together, they exhibit a strong recessive pattern of inheritance; the *APOL1* renal high-risk genotype being defined as two G1 risk alleles (homozygous G1/G1), two G2 risk alleles (homozygous G2/G2), or one G1 and one G2 risk allele (compound heterozygous G1/G2). To date, the *APOL1* renal high-risk genotype characterizes the strongest associations discovered for common variants with a complex disease (ORs of 17 for FSGS and 29–89 for HIVAN).^{9,21}

The aforementioned high ORs were reported in case-control studies. However, longitudinal cohort studies also reveal important effects of *APOL1* on the progression of kidney disease, with ORs below 2. In the Atherosclerosis Risk in Communities (ARIC) study, rates of incident ESKD were found to be higher among African Americans in the *APOL1* high-risk group compared with the *APOL1* low-risk group ($p < 0.05$ in fully-adjusted analysis).²⁸ Results from the longitudinal Chronic Renal Insufficiency Cohort (CRIC), the Coronary Artery Risk Development in Young Adults (CARDIA) study, and AASK also revealed that African Americans with *APOL1* high-risk genotypes have significantly faster rates of decline in kidney function, more frequent development of ESKD, and higher incidence rates of albuminuria than European Americans.^{29–31} Variable rates of decline in kidney function were observed in African Americans with *APOL1* low-risk genotypes across reports.

Worldwide distribution of *APOL1* renal-risk alleles

APOL1 renal risk alleles have only been reported on African-derived chromosomes, including individuals from Africa and recently admixed individuals from the U.S. or Caribbean.³² Approximately 13% of the U.S. African American population carries the *APOL1* high-risk genotype. The highest G1 and G2 allelic frequencies were described in Western sub-Saharan Africa, with frequencies $>40\%$ for G1 in Ghana and Nigeria, and 24% for G2 in Nigeria.^{32,33}

The G1 and G2 variants are believed to have reached these high frequencies in West Africa due to recent events of positive selection.^{10,34} The driving selecting force is thought to be the African *Trypanosoma* parasites, which are transmitted by the tsetse fly and responsible for African sleeping sickness or trypanosomiasis. Indeed, both G1 and G2 can restore *in vitro* *APOL1* trypanolytic activity against *Trypanosoma brucei* (*Tb rhodesiense*), the parasite distributed across East and Central Africa and causing the acute form of the disease (2% of all trypanosomiasis cases), and delay its parasitemia *in vivo* in mouse models. Moreover, G2 was recently associated with a protection from *Tb rhodesiense* infection in a population from Uganda, when G1 was shown to restrict the severity of *Tb gambiense* trypanosomiasis in Guineans. The chronic form of African sleeping sickness is caused by the western *Tb gambiense* parasite and accounts for 98% of cases.^{10,35} Surprisingly, G2 exhibited an opposing association, with a faster progression to *Tb gambiense* trypanosomiasis.³³

Overall, these studies demonstrate a major role for *APOL1* variants in the fight against trypanosomiasis. The G1 prevalence overlaps with the *Tb gambiense* distribution, making this parasite subspecies a credible candidate as the selection driving force for G1 as a factor protecting from a lethal course of infection (Figure 1). However, several gray areas remain in untangling the selection story. It is puzzling that some of the highest G2 frequencies are in West Africa, where *Tb gambiense* is endemic, when G2 correlates with an increased *Tb gambiense* clinical severity and a strong protection against the eastern *Tb rhodesiense* infection. If *Tb rhodesiense* was the selection driving force for G2, we can imagine that the parasite endemicity could have shifted due to an environmental pressure or to the rising frequency of this protective variant. Such a theory has yet to be proven. An alternative hypothesis is that another pathogen would have selected the G2 variant. This hypothesis is supported by the fact that *APOL1* seems to play a broader protective role in innate immunity

as it is upregulated by proinflammatory cytokines²⁰ and ameliorates *Leishmania* infection³⁶ and *in vitro* HIV replication.^{37,38} This could explain why G1 can lyse *Tb rhodesiense* *in vitro* and delay parasitemia in a mouse model, but showed no protection against *Tb rhodesiense* in a population of infected individuals.^{10,35}

Renal pathology in *APOL1*-associated kidney diseases

African Americans with heavy proteinuria/nephrotic syndrome typically undergo kidney biopsy, which often reveals *APOL1*-associated diseases including primary FSGS, collapsing glomerulopathy (e.g. HIVAN), and lupus nephritis. However, far larger numbers of patients have sub-nephrotic proteinuria (or lack proteinuria) and typically do not undergo kidney biopsy; as these individuals may be labeled as having hypertension-attributed CKD or unspecified CKD, this contributes to disease misclassification.³⁹ Several common *APOL1*-associated histologic findings are seen in patients with variable clinical presentations including low-level proteinuria and nephrotic syndrome, as well as in transgenic mouse models of human disease. Lesions include solidified (global) glomerulosclerosis, collapsing glomerulopathy (a variant of FSGS), and microcystic tubular dilation. They are highlighted below and in Table 1.¹²

Larsen *et al.*¹² reported *APOL1* genotype-phenotype correlations in 196 African Americans with progressive CKD characterized by chronic tubulointerstitial injury and arteriosclerosis; their disease was originally labeled arterionephrosclerosis. Exclusion criteria included nephrotic syndrome (likely reflecting a podocytopathy such as FSGS), diabetes mellitus, and systemic diseases associated with CKD except for hypertension. Solidified and disappearing forms of glomerulosclerosis, thyroidization-type tubular atrophy, greater degrees of interstitial fibrosis, and greater percentages of microcystic tubular dilation were observed to be present in patients with two (vs 0 or 1) *APOL1* renal-risk variants. Individuals with *APOL1* renal-risk genotypes were also younger. Differences in presence of the “not otherwise specified” and perihilar variants of FSGS were not observed based on *APOL1* genotype. A trend toward more severe arteriosclerosis and severe arteriolar hyalinosis was observed in patients *without* *APOL1* renal-risk genotypes; hence, arteriolar lesions do not likely reflect *APOL1*-associated disease; however, contrasting conclusions have been reported.⁴⁰ A striking feature in this report was solidified glomerulosclerosis,¹⁷ also seen in AASK participants and other reports in African Americans³⁹ and in an *APOL1* transgenic mouse model.⁴¹

Kopp *et al.*⁴² examined renal histology in 94 FSGS Clinical Trial participants with nephrotic syndrome; this kidney disease was excluded by Larsen *et al.*¹² *APOL1* risk genotypes were present in 27 of 94 individuals, 23 self-reported as African American (of the remainder, 2 were European American and 2 were European American, Hispanic). In the full sample, those with *APOL1* risk genotypes were older and had lower baseline estimated glomerular filtration rates. Individuals with *APOL1* risk genotypes had higher frequencies of segmental glomerulosclerosis collapsing variant and more severe tubular atrophy/interstitial fibrosis; they also had lower frequencies of glomerular tip lesions. As in Larsen *et al.*,¹² arteriosclerosis scores did not differ based on *APOL1* genotype. *APOL1* risk genotypes associated with significantly higher rates of progression to ESKD. Although overall

proteinuria responses to treatment were poor regardless of genetic risk, *APOL1* genotype did not significantly alter the proteinuria response to treatment with cyclosporine or mycophenolate mofetil/dexamethasone.

In addition to *APOL1* variant association with idiopathic FSGS⁴² and solidified glomerulosclerosis,¹² strong association is seen with HIVAN, a secondary form of FSGS collapsing variant with strikingly high ORs (29–89).^{9,21,43} African Americans with HIV infection and CKD having fewer than two *APOL1* renal-risk alleles typically lack FSGS-associated disorders such as HIVAN, more often having HIV-associated immune complex disease. A link appears to exist between chromosome 22q renal-risk genotypes and the collapsing glomerulopathy variant of FSGS as in HIVAN because collapsing lesions are reported in genetically susceptible patients who receive interferon,²⁰ and in those with lupus nephritis,¹⁸ membranous nephropathy,⁴⁴ and C1q nephropathy⁴⁵ (considered a form of minimal change disease and FSGS). As with solidified glomerulosclerosis, microcystic tubular dilation is another prominent feature of *APOL1*-associated collapsing glomerulopathy.¹²

APOL1 risk genotypes are frequent in patients with lupus nephritis-associated ESKD in the absence of FSGS, collapsing variant. These patients often have typical lupus membranous and focal and/or diffuse proliferative glomerulonephritis.⁸ Finally, although chromosome 22q renal-risk variants are not associated with classic diabetic kidney disease,^{23,24} they contribute to more rapid CKD progression in African Americans with diabetes.²⁹ This likely reflects *APOL1*-associated lesions in patients with co-existing diabetes.⁴⁶

***APOL1* gene expression and protein content in the kidney and vasculature**

With discovery of the *APOL1* association with nephropathy, it became necessary to determine whether endogenous (renal) or circulating APOL1 protein contributes to initiation of CKD. *In vivo* systems documented the presence and localization of APOL1 variant proteins in the human kidney, establishing a biological connection between *APOL1* gene products and kidney disease. Madhavan *et al.* reported that APOL1 protein was present in podocytes, glomerular endothelial cells, and renal tubule cells from human formalin-fixed paraffin-embedded kidney sections using immunohistochemistry.⁴⁷ Ma *et al.* confirmed this observation using immunofluorescence on human kidney cryo-sections.⁴⁸ In these studies, endogenous *APOL1* messenger RNA (mRNA) and protein were detected in human podocyte cell lines, and in primary proximal renal tubule and primary glomerular endothelial cells using reverse transcription-polymerase chain reaction amplification and immunoblotting. *APOL1* mRNA was also present in human podocytes, glomerular endothelial cells, and renal tubule cells independently of *APOL1* genotype. APOL1 protein and mRNA are not present in mesangial cells.

Kidney transplantation studies implicated endogenous (renal) APOL1 variant proteins and not circulating APOL1 as the cause of shorter kidney allograft survival after receiving deceased donor kidneys from African Americans compared to European Americans.^{49–51} The transplant model is likely to mimic development of native CKD.

Circulating APOL1 is present in protein complexes⁵² primarily produced and secreted by the liver. *In vitro* studies show that non-complexed APOL1 can be taken up by human podocytes.⁴⁸ However, *APOL1* genotypes of African American kidney transplant recipients do not impact allograft survival, suggesting little role for circulating APOL1 protein in shorter renal allograft survival.⁵³ This concept was supported by lack of association between serum APOL1 protein concentrations with *APOL1* genotype in first-degree relatives of African Americans with non-diabetic ESKD⁵² and lack of correlation between plasma APOL1 protein levels with CKD.⁵⁴ These data suggest that *APOL1* genotypes do not regulate circulating APOL1 protein concentration. We believe that *APOL1* G1 and G2 renal-risk variant protein structures likely produce cellular dysfunction because intracellular *APOL1* transcript levels do not associate with *APOL1* genotypes in non-diseased primary renal tubule cell lines from African Americans (L.M., unpublished observation, 2018). These data provide the background for subsequent cell model and whole animal experiments to determine the intracellular function of *APOL1* renal-risk variants.

Animal models of *APOL1*-associated nephropathy

The *APOL1* gene is unique to certain primates; thus, humans, gorillas, and baboons have the gene, but our nearest neighbor, the chimpanzee, lacks it. One possible explanation for this surprising fact is that APOL1 protein may have toxicity under certain circumstances and that if its anti-parasite activity is not needed in particular environments or is redundant with another host defense mechanism, there is natural selection for the gene to be deleted from the genome.⁵⁵ While mice lack the *APOL1* gene, several sets of transgenic models bearing the *APOL1* gene have been developed (Table 2).

Mechanisms of cellular injury in *APOL1*-associated kidney disease

Diverse mechanisms have been proposed to explain the damage that APOL1 renal risk variants inflict on podocytes and possibly other renal cells in vivo (Table 3). Much of the data comes from studies in cultured cells and so further confirmatory studies from human patients are needed, including those using tissues or serum, plasma, or urine. First, cell culture studies suggest that APOL1 acts as a channel or pore, with the risk variants associated with greater flux.⁵⁶ The loss of intracellular potassium is associated with activation of stress kinases. Second, the risk variants have been shown to impair mitochondrial function and mitochondrial membrane potential, reduce maximum respiratory rate, and reduce reserve respiratory capacity; effects were evident prior to intracellular potassium depletion.^{57,58} Third, cell culture and transgenic mouse studies support a model in which APOL1 variants perturb endolysosomal function and promote autophagic cell death.^{41,59,60} Fourth, emerging data suggest that APOL1 has a splice variant (termed B3) and the risk variant G2 activates the NLRP3 inflammasome (J.B.K., unpublished observation, 2018). Fifth, emerging data suggest that the risk variants, via extended double-stranded RNA structures, activate protein kinase R, leading to reduced protein synthesis and promoting cell death (J.B.K., unpublished observation, 2018). Finally, it has recently been reported that APOL1, serum urokinase type plasminogen activator receptor, and $\alpha v \beta_2$ integrin form a tripartite complex on the podocyte cell membrane, leading to cell injury and proteinuria in transgenic mice.⁶¹ This list of cell injury pathways will likely continue to expand. The

challenge is to determine which pathways are clinically relevant in patients with *APOL1*-associated nephropathy. This will require analysis of biological samples from patients and, ultimately, targeted interventions.

***APOL1* and kidney transplantation**

Striking racial differences exist in outcomes after transplantation of kidneys from deceased donors. Allograft survival is shorter in recipients of kidneys from African American donors, relative to those donated by European Americans. This observation holds regardless of the race of the recipient. *APOL1* genotypes in African American deceased kidney donors clearly contribute to shorter allograft survival after transplantation,^{49–51} whereas genotypes of recipients do not (Table 4).⁵³

A single-center study assessing African American deceased donors detected markedly shorter renal allograft survival among recipients of kidneys from two *APOL1* renal-risk variant donors; recipients of kidneys from donors with zero or one *APOL1* risk variant fared as well as those from European American donors.⁴⁹ Renal histology in failed allografts revealed that the vast majority of failed *APOL1* high-genetic risk kidneys displayed *APOL1*-associated lesions, whereas this was not the case in failed allografts from low-genetic risk donors. Based on the limitations of this single center study, subsequent analyses included 1,153 kidney transplants from 624 unique donors performed at 113 transplant programs.^{50,51} Multivariate analyses assessed effects of *APOL1* genotype, donor and recipient age, recipient sex, cold ischemia time, HLA match, recipient sensitization based on panel reactive antibodies, standard vs. expanded criteria donor, and transplant center on outcomes. Donor *APOL1* genotypes were found to be significantly associated with shorter renal allograft survival (hazard ratio, 2.05; $p=0.0003$), the only other variables with significant effects were recipient and donor age. Recipients of kidneys from donors with *APOL1* high-risk genotypes were found to have twice the rate of allograft failure at six years post-transplantation. These results support the major effect of deceased donor *APOL1* genotypes on kidney transplant outcomes and have stimulated a debate regarding whether rapid genotyping of deceased donors with recent African ancestry should be performed to assist decisions on organ allocation.^{62,63}

The Kidney Donor Risk Index (KDRI) was created to assess the quality of kidneys for transplantation and improve matching of deceased donor kidneys with recipients to prolong allograft survival and reduce rates of recipient death with a functioning allograft. It was developed prior to identification of the *APOL1* effect in CKD. As such, KDRI includes ten donor variables including race of deceased donors, but not their *APOL1* genotype, in risk assessment. KDRI reduces the “apparent” quality of kidneys from all African American donors; whereas newer data reveal that approximately 13% possess two *APOL1* renal risk variants and have higher risk of shortened allograft survival. Despite concerns that replacing donor race with *APOL1* genotype could increase organ discard and reduce the numbers of transplantations from African American donors,⁶⁴ effects of using genotypic data appear likely to better define risk associated with kidneys transplanted from deceased African American donors, substantially improve the predictive power of the KDRI score for 85–90% of kidneys offered, and enhance the link between donor quality and recipient need.⁶² These

are precisely what the KDRI attempts to achieve. It is likely that fewer kidneys would be discarded with more accurate estimation of donor quality based on *APOL1*.⁶² Kidneys from the approximately 13% of African American deceased donors harboring high-risk *APOL1* genotypes could be allocated as expanded criteria donor kidneys because they may function for prolonged periods. It is likely that the *APOL1* discovery will have its earliest clinical use in transplantation medicine.

Rates of post-donation ESKD are also higher in African American living kidney donors than in European American living kidney donors.⁶⁵ In live donor kidney transplantation, *APOL1* is implicated in development of progressive FSGS with allograft failure in recipients, and with ESKD in previously healthy African American donors.^{66–68} Beyond case reports, little objective data exist for *APOL1* genotyping in living donor transplantation, although one study suggests benefit.⁶⁹ Based on these reports, widespread *APOL1* genotyping in African American potential living donors has been called for, as well as for deceased kidney donors (see above).

APOL1 genotyping could stratify risk for future ESKD in potential live kidney donors with recent African ancestry and improve kidney transplantation outcomes in recipients of live and deceased donor kidneys.^{70,71} The National Institutes of Health initiated the *APOL1* Long-term Kidney Transplantation Outcomes Network (APOLLO) to provide critical information on these topics.⁷²

Conclusions

Racial disparities in a disease state may reflect poverty, with consequent reduced access to health care, medical insurance, and high-quality nutrition. Although these socioeconomic factors contribute to the higher rates of advanced kidney disease in African Americans, discovery of genetic association between two coding *APOL1* variants demonstrate that inherited factors underlie the majority of the excess risk for non-diabetic ESKD in populations with recent African ancestry. This unusual situation provides hope for the development of novel therapies to reduce rates of non-diabetic nephropathy in the African American community.

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Figure 1: Geographic distribution of *APOL1* renal risk alleles and *Trypanosoma brucei* subspecies. Shown are the distributions of G1 (left) and G2 (right) alleles among population groups, mostly in sub-Saharan Africa, together with the population ranges for *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* (ranges based on information from WHO⁸¹). The Great Rift Valley is shown as a line running from southwest to northeast. The population numbers refer to Table 1 from Limou et al³². Reproduced from Limou et al³² with the permission of the copyright holder, Elsevier, Inc.

Table 1.

Histopathologic findings in the APOL1-associated spectrum of nephropathy

Lesion	Description and associated findings	Reference
FSGS	Interstitial fibrosis and tubular atrophy	10
Collapsing glomerulopathy, FSGS variant	Microcystic tubular dilation; Idiopathic cases or seen in association with HIV infection, interferon treatment, lupus nephritis, membranous glomerulonephritis, and C1q nephropathy	73
Solidified (global) glomerulosclerosis	Solidified and disappearing glomerulosclerosis, and thyroidization-type tubular atrophy	12
Severe lupus nephritis	FSGS, collapsing variant has been reported; focal proliferative, diffuse proliferative, and membranous glomerular lesions frequent	8, 18
Sickle cell nephropathy	FSGS, vascular changes	19

FSGS, focal segmental glomerulosclerosis; APOL1, apolipoprotein L1

Table 2.

Transgenic models of APOL1 disease

Species	Alleles expressed	Promoter/Model	Anticipated expression level*	Pathology	Reference
Mouse	G0	Human <i>APOL1</i>	Physiologic	NA	74
Mouse	G0	Hydrodynamic gene delivery	Uncertain, possibly high	NA	36
Mouse	G0	Hydrodynamic gene delivery	Uncertain, possibly high	NA	75
Mouse	G0, G2	Nephrin	Physiologic	Eclampsia, podocyte depletion (G2)	76
Mouse	G0, G1, G2	Nephrin	Physiologic	Glomerulosclerosis (G1, G2)	41
Zebrafish	G0, G1, G2	Suppression of <i>APOL1</i> orthologue	Not applicable	Podocyte loss, glomerular filtration defects	77,78
Fly	G0, G1	Nephrin	Physiologic	Nephrocyte hypertrophy, cell death (G1>G0)	79
Fly	G0, G1, G2	Dot-Gal4; <i>dh-GAL4</i> ; GMR-GAL4	Uncertain**	Nephrocyte-specific defects and death, pupal-pharate adult lethality, rough eye and wing phenotypes (G1, G2)	80

Note: Various reports have described *APOL1* expression in experimental animal models. Three involved renal-risk variants and all manifested injury to podocytes or nephrocytes (in flies). In one model, this led to glomerulosclerosis, as noted.

* Anticipated expression level is with the caveat that *APOL1* is absent from the mouse genome and there is no physiologic level of expression in this species.

** GAL4/UAS is a method to study gene expression in the fly, using the yeast transcriptional activator Gal-4, used here under the control of Dorothy enhancer (DOT) or Glass multiple promoter (GMR). *APOL1*, apolipoprotein L1

Table 3.

Pronosed mechanisms of APOT1-induced cell and tissue injury

Mechanism	Allele	Experimental system
Channel or pore	G1, G2	Cell culture
Mitochondrial dysfunction	G1, G2	Cell culture
Endolysosomal dysfunction	G1, G2	Cell culture, transgenic mice
NLRP3 inflammasome activation	G2	Cell culture, transgenic mice
Protein kinase R activation	G1, G2	Cell culture, transgenic mice
$\alpha_v\beta_3$ integrin activation	G1, G2	Cell culture, transgenic mice

NLRP3, NLR family pyrin domain containing 3; APOL1, apolipoprotein L1

Six mechanisms by which APOL1 proteins or RNA may damage cells are shown, as well as the experimental systems that support these mechanisms. References provided in the text.

Table 4.*APOLI*-based outcomes in deceased donor kidney transplantation

Genotype in	No. of African Americans	No. of DDKTs	<i>APOLI</i> risk genotype outcome	Ref.
Donor	106 donors	136	Shorter allograft survival with donor risk genotype (HR, 3.84; p=0.008)	⁴⁹
Donor	368 donors *	675	Shorter allograft survival with donor risk genotype (HR, 2.26; p=0.001)	⁵⁰
Donor	624 donors *	1,153	Shorter allograft survival with donor genotype (HR, 2.05; p=0.003)	⁵¹
Recipient	119 recipients	119	No effect of recipient risk genotype (HR, 0.96; p=0.84)	⁵³

* some kidney donors overlap with earlier reports; DDKT – deceased donor kidney transplants; HR – hazard ratio