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INVITED REVIEW ARTICLE

Kidney disease and APOL1

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Introduction

Globally, chronic kidney disease (CKD) represents an important non-communicable disease with significant morbidity and mortality. An estimated 10% of the world's population had CKD in 2015 with approximately 1.2 million deaths in 2017 (1,2), and the burden is expected to rise at the rate of 6% per annum (3,4). By 2030, more than 70% of patients suffering from end-stage kidney disease (ESKD) worldwide will be in low and lower middle income countries of the world including African countries (5). Significant disparities in the burden of CKD exist worldwide, where economically disadvantaged communities, notably those on the African continent and those of the African diaspora, continue to bear a disproportionate burden of the disease (2,6). This disparity is fueled by a convergence of genetic and environmental risk factors (7,8). A recent meta-analysis showed an overall prevalence of CKD of 15.8% in the general population in Africa, with up to 4.6% of adults having moderate to severe kidney dysfunction (9). In Africa, more than 80% of the continental burden of CKD is in sub-Saharan Africa (SSA), with the highest prevalence in West Africa (8). The burden of CKD among African Americans, who share substantial genetic ancestry with West Africans (10), is similarly high; African Americans represent 13% of the USA population, but account for 35% of the patients on dialysis (11).

Genetic Susceptibility

It has long been noted that African Americans have an increased risk of progressive CKD and ESKD relative to their non-African counterparts, even after accounting for health disparities (12–14). A familial risk of chronic renal failure, often with different underlying etiologies, was noted in African American families (12,15). CKD has been observed to have higher incidence and faster progression rates in African Americans compared to Americans of European descent, consequently the risk of developing ESKD is 4-fold higher in African Americans (13,14,16–18). This is independent of socioeconomic status or the presence of traditional clinical risk factors.

These observations prompted a search for genetic risk for the development of CKD in people of African descent. Employing an admixture mapping approach to exploit the mixed African-European ancestry of African Americans, focal segmental glomerulosclerosis (FSGS) and HIV-associate nephropathy (collapsing nephropathy) was linked to a region on chromosome (chr) 22 and replicated for non-diabetic ESKD (19). A second group identified the same chr 22 association with non-diabetic ESKD, but notably, not with diabetic ESKD (20). Subsequently, Genovese and colleagues identified two alleles, termed G1 and G2 in the *APOL1* gene, encoding apoliprotein L1, which were responsible for the chr 22 admixture signal (21). Carriage of any combination of the two *APOL1* risk alleles accounts for about 70% of excess risk of development, progression and severity of CKD in the African American population (22).

APOL1 Gene and Protein

APOL1 functions as part of the innate immune system and is regulated by antiviral pathways; notably, it is potently upregulated by interferons (23,24). Of the 6 members of the *APOL* gene family, only APOL1 has acquired a secretory signal peptide permitting

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cellular export of the APOL1 protein into the blood stream (25). Intracellular APOL1 protein lacking a signal peptide is retained within the cell; it is this protein isoform that leads to kidney injury (26,27). Circulating APOL1 is largely produced by the liver and is a minor component of high-density lipid particles that are incorporated into trypanosome lytic factor (TFL), which, after ingestion by African trypanosomes, lyses the parasite (28,29). Unlike most common variants that tend to have small effect sizes, *APOL1* G1 and G2 variants have large effect sizes, which is not atypical for mutations that have undergone balancing selection by lethal pathogens (i.e. sickle cell and malaria) (30). Among African primates, only the baboon, gorilla and humans retain a functional *APOL1* gene and the gene is absent in all other mammals (31). In addition, one human completely lacks both copies of a functional *APOL1* gene but shows no evidence of kidney disease, indicating that APOL1 protein is not essential for life or for kidney homeostasis (32).

APOL1 Protein and African Trypanosomiasis

Although APOL1 protein protects humans from infection by *T.b. brucei,* humans are susceptible to infection and disease by *T.b. rhodensiense* and *T.b. gambiense*, the pathogens causing acute and chronic human African trypansomiasis (HAT), respectively, affecting millions of Africans (33). *T.b. rhodensiense and T.b. gambiense* have evolved different mechanisms to escape APOL1 lysis. *T.b. rhodesiense* expresses a serum resistance associated (SRA) protein that binds and inactivates APOL1 protein, while *T.b. gambiense* resist lysis by a hydrophobic β-sheet of the *T.b. gambiense*-specific glycoprotein (TgsGP) (21,34–36). The *APOL1* G2 variant, located within the serum resistant associated (SRA) binding site, restores partial ability of the APOL1 protein to lyse *T.b. rhodesiense* through its low affinity for SRA, conferring a selective advantage against acute trypanosomiasis (21,36,37). The G1 variant protein does not prevent infection by *T.b. gambiense or T.b. rhodensiense*, but the G1 allele is associated with asymptomatic *T.b. gambiense* infection and undetectable parasitemia in individuals from West Africa (38). The *APOL1* G1 allele and, to a lesser extent the G2 allele, underwent a selective sweep in west Africa within the last 10 000 years and are prevalent in populations throughout sub-Saharan Africa and the African diaspora (21,39,40). These findings support the prevailing hypothesis that G1 and G2 variants have been subject to balance selecting in West Africa, with heterozygous advantage against trypanosomiasis and homozygous disadvantage in susceptibility to CKD.

Distribution Of *APOL1* Variants

The *APOL1* renal risk variants are found exclusively on African-derived chromosomes and are not present on European or Asian chromosomes (39,41). The G1 and G2 variants arose independently in separate events on two different haplotypes of chromosome 22 and have not undergone a recombination event; hence, G1 and G2 are not observed on the same haplotype (21). As shown in Figure 1, the highest prevalence of the *APOL1* high-risk variants was found in West African populations notably in Ghana and Nigeria where a prevalence is as high as 40% among the Yoruba and Igbo people of southwestern Nigeria (39,42). East African populations appear to have lowest prevalence of the high-risk alleles in Africa (21,39,43). It is important to note that even within a country, the frequencies of the G1 and G2 variants may vary considerably among ethnic groups (39).

APOL1 G1 and G2 risk variants are found throughout the African diaspora in individuals with recent African ancestry (40). During the 16th to 19th century, ~12 million Africans from West Africa were brought to enslavement in the Caribbean and the Americas during the trans-Atlantic slave trade, driving gene flow from Africans to Americans. As a result of this relocation, admixture with European populations and Native Americans caused a mixed genomic profile of the population now referred to as African American (44). Approximately 50% of African Americans carry at least one *APOL1* risk allele and ~13% of African Americans carry two *APOL1* risk alleles (45). In African Americans, the frequency for G1 is 20–42% and 13–15% for G2 (46). The high G1 and G2 frequencies from African individuals from the Atlantic coast of Africa are reflected in African Americans, in African and Hispanic Caribbeans and in South Americans, particularly in Brazil (47,48). Hispanics who migrated from the Caribbean to New York also carry the G1 and G2 variants, but at lower frequencies (41).

APOL1 Associations with CKD in the USA and SSA

In spite of the high frequencies of *APOL1* G1 and G2 risk variants in the African population, there are limited data on *APOL1*-associated diseases in Africans residing on the African continent. Hence, most current knowledge about the role of *APOL1* genetic variants on diseases are extrapolations from studies on Africans in the African diaspora, mainly African Americans in the USA.

Although most individuals with *APOL1* high-risk genotypes do not develop disease, the lifetime risk of CKD for carriers is estimated to be approximately 20%. *APOL1* is associated with a spectrum of progressive chronic kidney disease ranging in severity from arterionephrosclerosis to the most severe form of focal segmental glomerulosclerosis (FSGS), collapsing glomerulopathy, which is often fulminate, frequently irreversible and rapidly progressive (Fig. 2) (49). The *APOL1* renal risk variants are most strongly associated with FSGS and HIV-associated nephropathy (HIVAN) with odds ratios (OR) of 17 and 29, respectively (46). Approximately 70% of African Americans with FSGS and HIVAN carry high-risk genotypes in contrast to 13% in the general US black population (46). Both conditions are characterized by podocyte effacement and detachment, which suggests APOL1-mediated injury to the kidney podocyte, a key component of the tripartite renal filtration barrier (50–52). African American patients with systemic lupus erythematosus (SLE) have a 5.4-fold greater odds of developing a collapsing glomerulopathy (53,54). In addition to untreated HIV infection, other viral infections, including cytomegalovirus and BK polyoma virus infection in recipients of kidney allografts from *APOL1* high-risk donors, have been associated with de novo collapsing glomerulopathy (55). Treatment with therapeutic interferon-gamma has also been associated with collapsing nephropathy in those with *APOL1* high-risk genotypes, which remits upon cessation of the drug (23). These findings suggest that 'second hits' that potently activate interferon pathways or high levels of exogenous interferon trigger collapsing glomerulopathy, likely by upregulating *APOL1* levels in the kidney to a critical threshold (23).

APOL1 risk alleles are strongly associated (OR ~ 2–7) with end-stage kidney disease attributed to hypertension (OR 2–7), but not with diabetic ESKD (19–21,56,57). The predilection of African Americans with hypertension-attributed CKD to progress to ESKD likely results from APOL1-mediated arterionephrosclerosis and global glomerulosclerosis (58,59). *APOL1* high-risk genotypes are associated with higher rates of progression to ESKD and steeper decline in estimated glomerular filtration rate (eGFR)

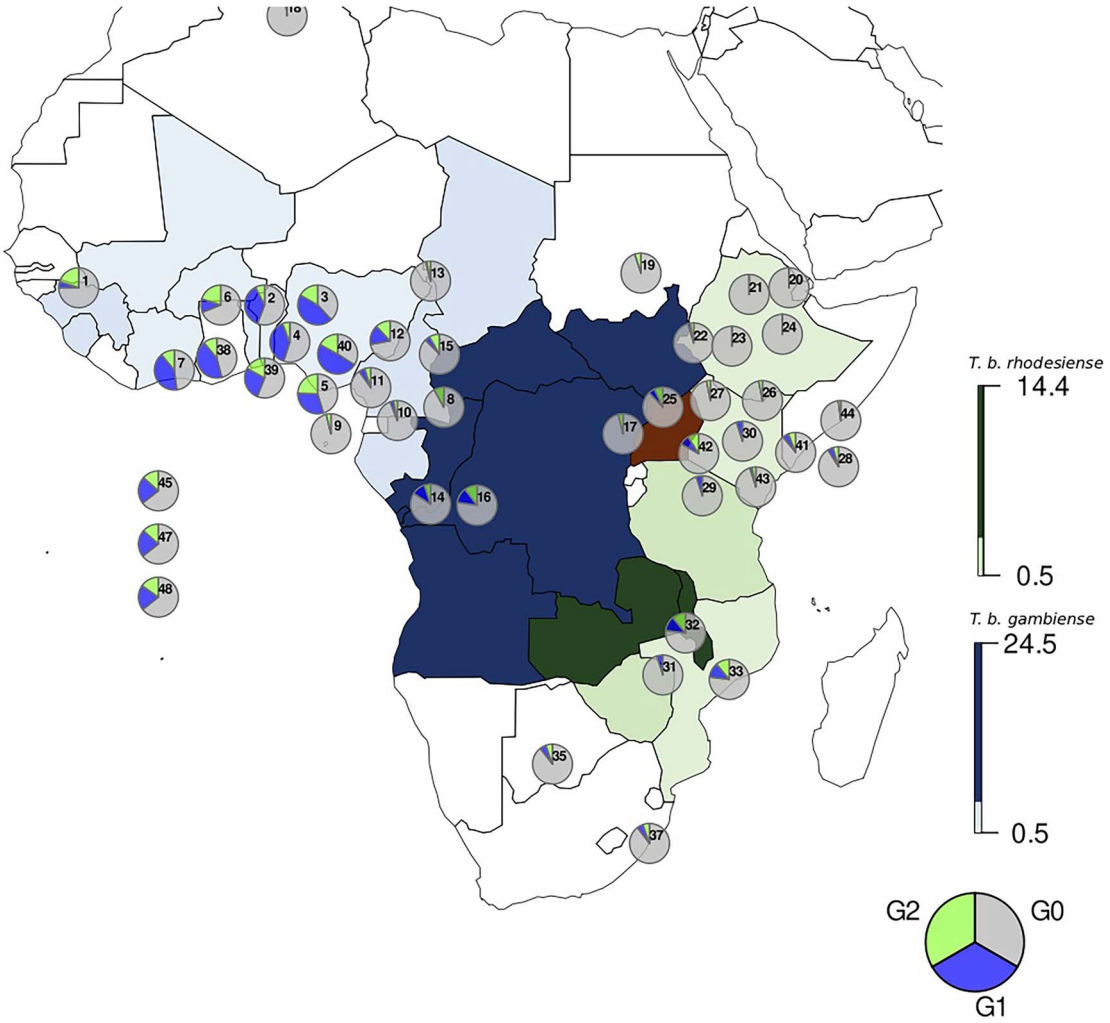

Figure 1. Distribution of human African trypansomiasis (*T.b. gambiense* and *T.b. rhodesiense*) and *APOL1* G1 and G2 allele frequencies in Africa. The distribution of G1, G2 and GO frequencies are represented by pie charts and overlap the distribution of *T.b. gambiense* (blue), *T.b. rhodesiense* (green) and both (red) as presented in Franco *et al.* 2020 (97). Supplementary Material, Table S1 lists the haplotype frequencies and location of the sampled populations. For countries where *T.b. gambiense* and *T.b. rhodesiense* cases have not been reported recently, the frequency of infections has been set to 0.5%. These include Benin, Mali, Nigeria and Togo for *T.b. gambiense*, and Mozambique, Ethiopia and Kenya for *T.b. rhodesiense* (97).

in African Americans with established chronic kidney disease, regardless of diabetes status (60). The finding of a more rapid rate of progression in patients with CKD secondary to diabetes may be due to undetected *APOL1*-associated arterionephrosclerosis or FSGS in diabetic patients, since renal biopsies were not performed (60). Renal biopsies of patients with *APOL1* high-risk genotypes and progressive or late-stage CKD may resolve the role of *APOL1* in patients with diabetic nephropathy. *APOL1* variants are also associated with earlier onset of proteinuria in both pediatric and adult sickle cell populations (61,62). In African Americans with CKD attributed to hypertension, those with *APOL1* high-risk genotypes were 80% more likely to develop proteinuria and once proteinuria is established, it is the dominant risk factor for decline in eGFR regardless of *APOL1* risk status (63). Similarly, in young to middle-aged adults with preserved kidney function, there is no significant difference in eGFR decline by *APOL1* risk status; however, *APOL1* high-risk status is associated with earlier onset of proteinuria, followed by a downward eGFR trajectory (64). It is important to note that among both those with preserved kidney function and in those with reduced kidney function, in the absence of proteinuria, eGFR slopes are similar between carriers of *APOL1* high-risk and low-risk genotypes (64). These studies support accumulating evidence that the first manifestation of APOL1-mediated kidney injury is proteinuria resulting from podocyte injury.

Surprisingly few case–control studies and no longitudinal studies for *APOL1* associations with kidney disease have been reported in sub-Saharan Africa (see Table 1). A small study of adults in the DRC comprising 83 controls and 79 cases with hypertension-attributed CKD reported that 12.7% of cases carried high-risk genotypes compared to only 2.4% of the controls (OR 7.7) (65). A recent study of 412 healthy children from the general population and 401 HIV-positive children living in Kinshasa, Democratic Republic of Congo (DRC), reported that children from the general population with *APOL1* high-risk genotypes had lower eGFR (91 vs 97 mL/min/1.73m^2); however, children with HIV had much higher prevalence of albuminuria and

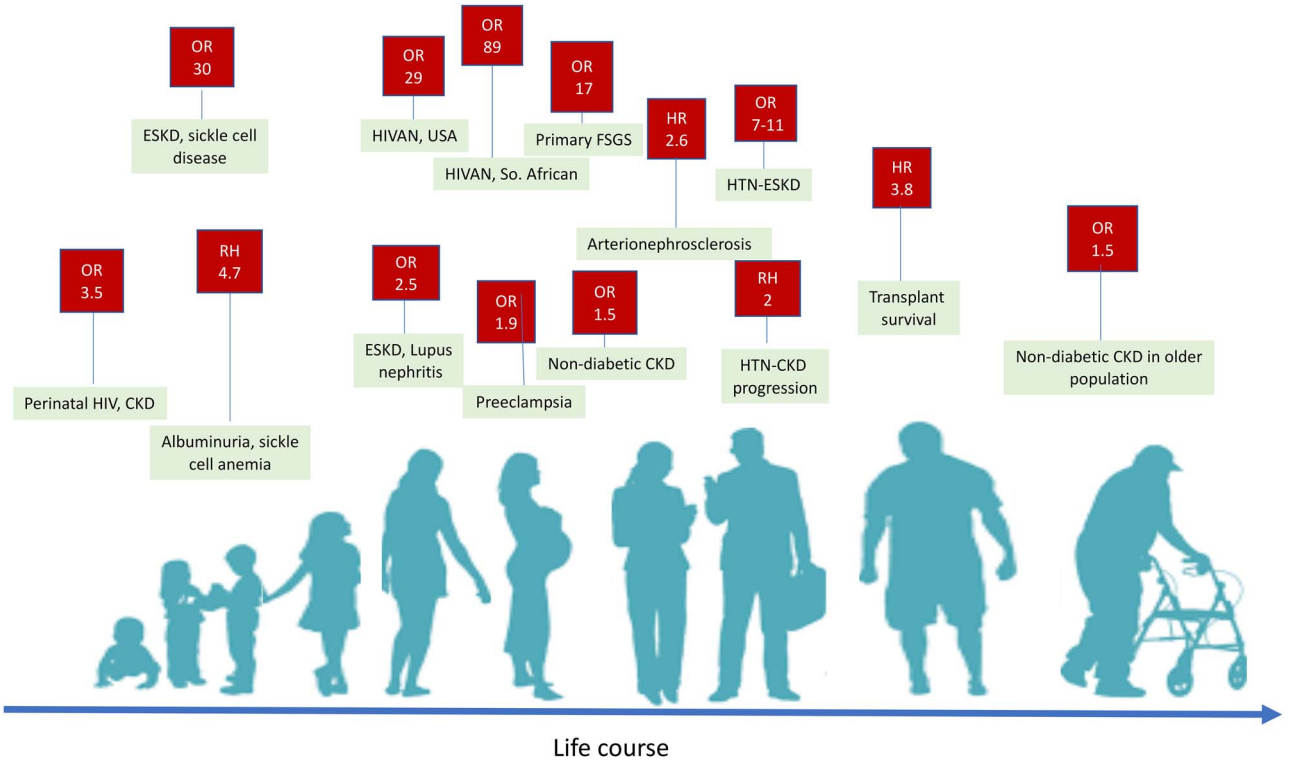

Figure 2. Shown are conditions and diseases and their point ORs and relative hazards (RHs) associated with *APOL1* high-risk genotypes across the life course. Peak years of onset are from adolescence to middle age, after which risk of CKD decreases (46). Risk of preeclampsia is determined predominately by carriage of *APOL1* high-risk genotypes of the fetus, although maternal genotype may also contribute to risk (88–90).

levels of albuminuria were higher with incomplete suppression of viral load (66). A large, cross-sectional study representing multiple ethnic groups from the Atlantic coastal region of Nigeria reported that over 70% of participants carried *APOL1* high-risk genotypes; however, *APOL1* high-risk genotypes were only associated with CKD in the setting of HIV infection (OR 2.5) (67). In the absence of HIV infection, there was no reported association between CKD and *APOL1* high-risk genotypes (67). However, since this study only reported the associations for G1 or G2 alleles and not carriage of 2 risk alleles in the compound heterozygous state, effect sizes are likely underestimated. Kasembeli et al. reported that among HIV-infected adults living in South Africa, 79% of participants with biopsy confirmed HIVAN carried high-risk *APOL1* genotypes compared to only 3.3% of the HIV-positive control group (OR 89) (68). In contrast, in African Americans, the OR for biopsy-confirmed HIVAN is 29 (46). The difference in effect sizes may represent differences in genetic background, circulating HIV strains or viral burden or other environmental influences. The striking association of *APOL1* high-risk genotype and kidney disease in children and adults with HIV infection provides additional support that HIV infection is a strong 'second hit' promoting podocyte injury and glomerulosclerosis. Further sufficiently powered case–control studies for renal phenotypes and longitudinal cohort studies across different ethnic groups, risk groups and geographical regions of Africa are warranted to quantify *APOL1* effect sizes and rates of progression to clinical endpoints. Performing these studies in multiple ethnic groups and geographical regions should identify genetic and environmental factors that attenuate or exacerbate *APOL1* penetrance.

APOL1 and Kidney Transplantation

Studies have shown that donor *APOL1* high-risk allele status significantly affects kidney allograft survival in the recipient, with shorter survival in kidneys from donors with two high-risk alleles compared to those with one or no risk allele (27). In contrast, the *APOL1* risk status of the kidney recipient has no influence on allograft survival (69). *APOL1* high-risk status may also have consequences for the kidney donor. Studies have shown that living kidney donors with high-risk genotypes have lower eGFR at donation and lower eGFR rebound following kidney donation, experience more hypertension than *APOL1* low-risk kidney donors and may be at increased risk for ESKD post-donation (70,71). The *APOL1* long-term Kidney Transplant Outcomes Network (APOLLO) study is designed to assess the effects of *APOL1* renal risk variants on outcomes for living donors and for recipients of kidneys, following deceased and living kidney transplantation (72,73).

APOL1 and Other Disease Associations

The association of *APOL1* risk alleles with cardiovascular disease (CVD) is conflicting; the earliest studies showed that the *APOL1* high-risk genotype is associated with a range of CVD conditions including incident myocardial infarction, stroke, heart failure, cardiac revascularization and cardiovascular death (74,75). However, others have not observed statistically significant associations between *APOL1* high-risk genotypes and increased risk of CVD in cohort studies of African Americans or in a two-stage meta-analysis of 23 305 individuals (76–78).

Table 1. Case–control studies showing ORs for *APOL1* high-risk genotypes associated with kidney disease in the Americas and sub-Saharan Africa for kidney disease

Phenotype	Country	Setting	No. of cases	No. of controls	OR	Ref.
Non-diabetic ESKD	USA	Adults on dialysis	1002	923	7.3	(21)
ESKD	Brazil	Adults on dialysis	106	106	10.95	(48)
Stage 5 CKD	SA	Adults, mean eGFR 8 (4–12)	70	58	0.85[a]	(98)
CKD	DRC	Adults, hypertensive CKD	79	83	7.7	(65)
CKD	Nigeria	Adults	44	43	4.8	(42)
FSGS	USA	Adults	192	176	10.5	(21)
FSGS	USA	Mostly adults	217	383	17	(46)
FSGS	SA	Adults	22	108	2.1[a]	(68)
HIVAN	USA	Adults, HIV+	54	237	29	(46)
HIVAN	SA	Adults, HIV+	78	108	89	(68)
Albuminuria	USA	Young to middle-aged adults	2.9		2.9	(64)
Albuminuria	DRC	Pediatric population	2.1	40	412	(66)
Albuminuria	DRC	Pediatric population, HIV+	22.0	72	329	(66)

[a]Not statistically significant. SA, South Africa; USA, United States of America; DRC, Democratic Republic of the Congo.

Preeclampsia is a common complication of pregnancy characterized by systemic hypertension, albuminuria and maternal endothelial dysfunction in pregnancy, which results from placentation defects with imbalance in angiogenic factors (79–81). The overall model-based incidence rate of preeclampsia is 4.6%, with the highest incidence in African countries (5.6%) (82). Preeclampsia accounts for 16% of maternal deaths; in sub-Saharan African, prevalence rates as high as 26% have been reported (83,84). Mothers of African descent in Africa and the Africa diaspora have higher rates of pregnancies complicated by preeclampsia (84). Globally, preeclampsia accounts for 900 000 infant deaths per year, with the largest burden being in sub-Saharan Africa (83). A role for *APOL1* in preeclampsia is supported by several lines of evidence: 1) APOL1 mRNA and protein is highly expressed in the placenta (85); 2) circulating autoantibodies against APOL1 protein are present in the blood of women experiencing preeclampsia (86); and 3) dams of transgenic mice pups constitutively expressing reference or variant *APOL1* develop a preeclampsia-like phenotype with smaller than expected litter sizes (87). Two recent studies found that carriage of *APOL1* risk variants by the fetus, but not the mother, increases the odds of maternal preeclampsia by 50–90% (88,89). The first study reported a recessive inheritance in two independent cohorts of African American mother–baby pairs, while the second study reported associations for additive and recessive modes of inheritance (88,89). A third study from South Africa that had DNA from mothers, but not babies, reported that carriage of one *APOL1* risk allele by the mother was associated with increased risk of preeclampsia (90), whereas two previous studies found no significant association with maternal carriage of 1 or 2 risk alleles for preeclampsia. This finding is not in conflict with the previous studies, since the mothers are obligate carriers of at least one *APOL1* risk allele for fetuses carrying 2 risk alleles (88,91). Given that preeclampsia is a significant cause of infant and maternal mortality and may therefore affect reproductive fitness, it is interesting to speculate that modifying genes may attenuate *APOL1* penetrance for preeclampsia in West African populations with high prevalence of *APOL1* risk alleles.

Summary

APOL1 renal risk alleles have profound influence on a spectrum of kidney disease in individuals of recent African descent over the life course. *APOL1* risk variants require 'second hits' (e.g. viral infection, auto-immune diseases, sickle cell anemia, glomerular hyperfiltration) for renal disease to manifest; upregulation of *APOL1* by interferons is a potent second hit. However, beyond exposure to therapeutic interferon and certain viral infections, it is still unclear why most individuals with *APOL1* high-risk status never develop kidney disease. Africa comprises 1000s of ethnolinguistic groups with extensive genetic diversity living on a continent undergoing epidemiological transition. The study of *APOL1* associations in case–control studies and longitudinal studies in SSA may shed new light on genetic and environmental exposures that initiate CKD and/or modify CKD progression. In addition, knowledge of *APOL1* prevalence and disease associations may inform public health policies and resource allocation. Recent advances in understanding the pathophysiological mechanisms of *APOL1*-associated CKD may lead to new therapeutic options (92,93). An *APOL1* antisense drug targeting *APOL1* has been shown to ameliorate proteinuria in animal models (94). If particular drug therapies (e.g. blood pressure lowering drugs that block the renin angiotensin aldosterone system) are proven effective in clinical trials, knowledge of at-risk populations susceptible to *APOL1*-related kidney disease may justify screening for *APOL1* or for biomarkers of APOL1-mediated renal injury (95). *APOL1* risk variants provide fertile soil for the development of severe glomerulopathies and progressive kidney disease and warrant further study in sub-Saharan Africa and in the African diaspora (96).

Supplementary Material

Supplementary Material is available at *HMG* online.

Contributions

The initial draft was written by all authors.

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