APOL1 Nephropathy: From Genetics to Clinical Applications

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Abstract
Rates of many types of severe kidney disease are much higher in Black individuals than most other ethnic groups. Much of this disparity can now be attributed to genetic variants in the apoL1 (APOL1) gene found only in individuals with recent African ancestry. These variants greatly increase rates of hypertension-associated ESKD, FSGS, HIV-associated nephropathy, and other forms of nondiabetic kidney disease. We discuss the population genetics of APOL1 risk variants and the clinical spectrum of APOL1 nephropathy. We then consider clinical issues that arise for the practicing nephrologist caring for the patient who may have APOL1 kidney disease.

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Introduction
Rates of many types of severe kidney disease are much higher in Black individuals than in other ethnic groups. In 2010, investigators discovered genetic variants in the apoL1 gene that explained a surprisingly large fraction of this major health disparity (1,2). Over the last decade, investigators have established the basic population genetics and epidemiology of APOL1 (3,4). Understanding the biology of APOL1 risk variants has been advancing at the molecular level. Animal models have recapitulated key aspects of disease. The current clinical utility of APOL1 genotyping has been widely debated, although little consensus has emerged among clinicians. With therapeutic approaches for APOL1 kidney disease now being explored by many groups in biotechnology and academia, we consider APOL1 nephropathy from the viewpoint of the clinician both today and how it may change in the near future.

APOL1 Biology: The Basics
The APOL1 gene is one of six members of the APOL gene family on human chromosome 22 (5). Remarkably, APOL1 is absent in all nonprimates, is only known to be present in a few primate species, and has disappeared from the genome of our closest relative, the chimpanzee (5,6). Prior to its discovery as an important kidney disease gene, APOL1 was known as the trypanolytic factor of human serum that protects humans, gorillas, baboons, and some Old World monkey species against common African trypanosomes (7–9). Two disease-causing APOL1 genetic variants arose in humans in sub-Saharan Africa several thousand years ago, and the frequency of these variants rose quickly in African populations because these variants conferred enhanced protection against the virulent subspecies of trypanosomes that cause acute and chronic African sleeping sickness (1,10). Because these risk variants arose after the Out-of-Africa expansion that populated the rest of the world, the APOL1 kidney risk variants have only been observed in individuals with recent African ancestry (10).

One risk variant called G1 contains two amino acid substitutions (S342G and I384M) near the APOL1 C terminus (1,2) (Figure 1). A second risk variant called G2 is a two-amino acid deletion (del388N389Y) that occurs in the same functional domain of APOL1 as G1 (1). The nonrisk APOL1 allele is referred to as G0, although this includes several sequences with somewhat different functional properties (11). Because a person inherits one copy of the APOL1 gene from each parent, a person possesses zero, one, or two APOL1 risk alleles. Inheriting two risk variants of APOL1 (one on each chromosome) greatly increases risk of kidney disease, whereas inheriting one APOL1 risk allele confers, at most, a small increase in risk or else no increase in risk, depending on the clinical scenario. The fact that the APOL1 risk alleles seem to increase the risk of kidney disease following a mostly recessive mode of inheritance is surprising given that most evidence to date suggests that the G1 and G2 are gain-of-function variants, meaning they have acquired some ability to injure the kidneys rather than losing some essential function. One human has been reported to have no functional APOL1 but appears to have totally normal kidney function, identified because he contracted an infection by a trypanosome species that usually only infects immunocompromised hosts (12,13). APOL1 is an innate immunity gene involved in defense against pathogens that does not yet have a known role in kidney development or basic kidney function (3,14–18). It remains possible that APOL1 is required for kidney health in some environmental conditions. APOL1 circulates at high levels in the blood, whereas experimental data suggest that low levels in tissues may increase dramatically in the setting of inflammation (19–22).

How the APOL1 risk variants G1 and G2 differ in their biologic behavior from G0 is not yet clear. One
leading hypothesis is that APOL1 risk variants may create pores in kidney cell membranes in much the same way as APOL1 punches holes in trypanosomal organelles (23–27) (Figure 2). Other investigators pose that risk variant overexpression leads to mitochondrial dysfunction and injury (28–30). However, there is surprisingly little consensus about the specific molecular mechanisms that drive APOL1 kidney disease or even what cell types are injured by APOL1. Highly proteinuric forms of APOL1 kidney disease suggest that the podocyte may be the site of injury, and podocyte-specific APOL1 overexpression in mice does initiate kidney dysfunction, whereas tubular cell APOL1 overexpression does not (31). More indolent forms of APOL1 nephropathy with less proteinuria, such as hypertension-associated CKD, may not be predominantly podocyte driven. Experiments in human cells, transgenic mice, zebrafish, yeast, and flies have all been used to understand APOL1 biologic behavior, with the currently prevailing idea being that the high-risk genotype (two risk alleles) and increased expression are both required for APOL1 kidney disease to occur (32). The specific triggers capable of increasing APOL1 expression are discussed below.

**APOL1 Nephropathy: One Gene, Many Diseases across the APOL1 Spectrum**

The APOL1 risk variants cause large increases in susceptibility to multiple different types of kidney disease previously thought to represent distinct entities (Figure 3). Two risk variants confer an odds ratio of approximately 7–10 for hypertension-associated ESKD (H-ESKD), approximately 17 for FSGS, and approximately 29–89 for HIV nephropathy (1,33,34). The fact that the same alleles are an overwhelming risk factor for what are generally considered a vascular disease (H-ESKD), a glomerular disease of the podocyte (FSGS), and a disease with an infectious etiology (HIV-associated nephropathy [HIVAN]) suggests that these diseases are driven by similar, or at least overlapping, mechanisms. For this reason, it may be more useful to think of these diseases as part of an APOL1 nephropathy spectrum rather than as separate disease states in individuals with the high-risk genotype. APOL1 risk variants also have been linked to higher rates of ESKD in patients with lupus nephritis and to a collapsing nephropathy phenotype that complicates diseases such as lupus nephritis and membranous nephropathy (35–37). A collapsing glomerulopathy (also referred to as collapsing FSGS) phenotype in individuals with the APOL1 high-risk genotype can, in some rare cases, be driven by therapeutic IFN administration (21,38). High IFN states may be a common link between different types of APOL1 kidney diseases that share collapsing features.

The effect of APOL1 risk alleles varies across the age spectrum and is markedly influenced by the background rate of kidney disease. For young adults, when rates of nephropathy are typically low, the odds ratios conferred by APOL1 variants are very large, as seen with FSGS. In the original study connecting APOL1 variants to FSGS, the average age of the patients was 22 (1). In late adulthood, the odds ratios for kidney disease conferred by APOL1 are much lower, likely in part because background rates of disease are higher, but also because the most highly susceptible individuals may have already developed APOL1 kidney disease. This is demonstrated by studies where inclusion and exclusion criteria consider only individuals who have reached...
a certain age without CKD, leading to lower effects of APOL1 risk variants among participants. An example is an analysis from the Atherosclerosis Risk in Communities study that included participants enrolled between ages 45 and 64 (and excluding those with CKD at baseline) where APOL1 risk variants confer an odds ratio for incident CKD of only approximately 1.5 (39). Population-based cohorts that include younger participants, such as the Dallas Heart Study or the CARDIA study, tend to demonstrate larger effect sizes with regard to CKD and/or proteinuria (40,41). Higher odds ratios for APOL1 tend to be observed with well-defined end points such as biopsy-proven FSGS/collapsing nephropathy or ESKD, whereas lower odds ratios are typical with continuous variables such as reduced GFR or increased proteinuria (Figure 1). Much larger studies, such as the Million Veterans Program and “All of Us,” will refine our knowledge of APOL1 kidney disease across the life spectrum.

**APOL1 Risk Variants in Children**

The effect of APOL1 on kidney disease rates in Black individuals begins in childhood. Although absolute rates are low, the APOL1 risk genotype increases the likelihood of FSGS/nephrotic syndrome. Although the age of diagnosis of APOL1-mediated kidney disease among proteinuric Black children is older than from non-APOL1 causes, the disease may be more aggressive, with lower eGFR at diagnosis and larger yearly eGFR decline (in excess of 10% per year in two different cohorts) (42). Proteinuric kidney disease in children with HIV and the APOL1 high-risk genotype is greatly increased, similar to adults (43). Children and young adults with the high-risk genotype and FSGS seem more likely to progress to ESKD, whereas there is no evidence that response to treatment with standard immunosuppression regimens differs between those with and without the APOL1 risk genotype (44).

The APOL1 risk variants may exert their influence even before childhood. One study found that fetal APOL1 genotype increased risk of preeclampsia during pregnancy, whereas maternal genotype had no apparent effect. A potential role for APOL1 in the placenta is further supported by the observation that among Black children with glomerular disease, there was a more than four-fold increase rate of preterm birth among APOL1 high-risk patients (42), although APOL1 genotype did not confer any significant effect on preterm birth in general among Black children without kidney disease (45).

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**Figure 2. APOL1 mechanisms in health and disease.** (A) APOL1 is the key trypanolytic factor of human serum, providing protection against African trypanosomes. APOL1 (red) circulating on HDL complexes (yellow) or in complexes with IgM is taken up by trypanosomes in the bloodstream. APOL1 transits to the trypanosomal lysosome and inserts in the membrane, causing lysosomal swelling and leading to the death of the trypanosome. (B) The normal function of APOL1 in human kidneys is not known. Risk variant (RV) APOL1 (red) appears to be cytotoxic to kidney cells when expressed at high levels. Investigators have provided evidence to support multiple different molecular mechanisms of disease. Although the podocyte is usually proposed as the predominantly affected cell type, different mechanisms in different cell types may explain clinical presentations of APOL1 kidney disease that vary from aggressive to slowly progressive, highly or minimally proteinuric, and inflammatory or noninflammatory. E.R., endoplasmic reticulum.
Global Burden of APOL1 Nephropathy

The vast majority of reports on APOL1 epidemiology are from the United States. Additional studies from Africa make clear that APOL1 kidney disease is also common in other populations with African ancestry and that any nongenetic factors driving disease penetrance must be geographically widespread (46). In Africa, the APOL1 risk alleles are heavily concentrated in West Africa, and they are found at lower frequencies in eastern and southern Africa (15). For example, some groups within Nigeria or Ghana have combined risk variant allele frequencies that may exceed 50% (with high-risk genotypes of 25%), whereas individuals in Ethiopia, Sudan, and Somalia have very low probability of having two APOL1 risk variants. Thus, an individual from Nigeria and an individual from Ethiopia presenting for evaluation in nephrology clinic for kidney dysfunction have markedly different pretest probabilities of having APOL1 kidney disease, which may affect both clinical decision making and public health policy.

Recent studies of Black patients of mixed ancestry on dialysis in Brazil indicate that APOL1 risk alleles are also common in geographically diverse world populations and contribute to kidney disease burden in those populations (47). Because Hispanic individuals often have some degree of African ancestry, they may have the APOL1 high-risk genotype and be at risk for APOL1 nephropathy. The presence of the APOL1 risk variants varies widely between various Hispanic populations, with considerably higher frequency in Caribbean populations than in Mexican or Central American populations, in relative proportion to percentage of African ancestry (48,49). A global survey of APOL1 genotype frequency is available at http://APOL1.org (50).

How Common Is APOL1-Associated Kidney Disease?

A high-risk APOL1 genotype is present in about 75% of Black patients with FSGS (1,33). In Black patients with primary FSGS, it is much more likely than not that they have APOL1-associated disease. Similarly, approximately 50% of Black patients with hypertension-attributable ESKD have a high-risk APOL1 genotype (1). In contrast to other kidney disease variants with strong effect sizes, these variants are common. If a nephrologist is asking the clinical question "what is the cause of my patient’s disease," the answer is informed by APOL1 risk genotype status. This is true in not just African or Black individuals but also individuals from groups with significant recent African ancestry, such as Hispanics. There is evidence that some patients with FSGS who self-identify as White may have APOL1 kidney risk alleles and significant unrecognized recent African ancestry, although how frequently this occurs will require more data (33). We note that a surprising number of FSGS diagnostic testing panels still do not include APOL1 risk variants, likely leading to underdiagnosis.

The lifetime risk of clinically significant kidney disease for individuals with two APOL1 risk alleles remains uncertain.
In the pre-HAART era, approximately 50% of individuals with HIV and two risk alleles developed HIVAN. Approximately 4% of high-risk genotype individuals in the general population will develop FSGS compared with approximately 0.25% of Black individuals with the nonrisk genotype (33). Some estimates pose that the lifetime probability of developing ESKD for carriers of the high-risk genotype may be up to 15%, a number that requires refinement (51). Given that CKD and proteinuria markedly increase the risk of mortality from cardiovascular disease prior to ESKD, we suspect that the probability of clinically significant kidney disease in individuals with the APOL1 high-risk genotype may be at least twice as high as the 15% estimate for ESKD.

APOL1 risk variants are unusual in being both common and powerful (10). APOL1 nephropathy is not a Mendelian disease, but the APOL1 genotype is also much more

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**Figure 4. | Donor APOL1 genotype determines graft survival in kidney transplantation.** Transplants from APOL1 high-risk genotype donors (A) have decreased graft survival compared with kidneys from nonrisk donors. The recipient APOL1 genotype (B) does not appear to change the outcome for the survival of the donor kidney. This natural experiment indicates that it is probably kidney-expressed APOL1 rather than circulating APOL1 that injures in the kidney in the transplant setting, but it also suggests that kidney-expressed APOL1 may be the toxic factor when disease occurs in the native kidney. Some caution in making this extrapolation from transplant to native kidneys is warranted given the complex medical regimens of transplant recipients. It is not yet clear how the APOL1 genotype affects the outcome of kidney donors, but some studies suggest higher rates of GFR decline in APOL1 high-risk donors than in nonrisk donors. RV, risk variant.
predictive than most genetic variants that contribute to common complex diseases, such as diabetes, hypertension, or CKD in general. This property makes the application of APOL1 genetic testing a challenge without many clear precedents. Below, we depict a range of clinical scenarios and try to consider the benefits and pitfalls of applying APOL1 testing to clinical care. Prior to the development of APOL1-specific therapies, APOL1 testing may help a clinician understand the etiology of a patient’s kidney disease, but in most situations, it is not yet useful for guiding treatment (with the potential exception of transplantation-related decision making). We would emphasize that these examples are on the basis of clinical judgment informed primarily by existing observational datasets and, in general, will require both better data and systematic testing to validate their utility.

**Transplantation: From Mechanism to Clinical Utility**

Data from transplantation have been instrumental in understanding APOL1 biology. Multiple studies have demonstrated that APOL1 high-risk donor kidneys fail at higher rates than nonrisk kidneys, whereas the recipient APOL1 genotype has not yet been shown to affect graft survival (52–55) (Figure 4). These observations are consistent with the idea that kidney APOL1, rather than circulating APOL1 produced primarily by the liver (56), is the critical factor in driving APOL1 kidney disease. Experimental data from model systems and lack of correlation between circulating APOL1 levels and kidney disease lend further support to the human transplant data that kidney rather than circulating APOL1 is the principal driver of APOL1 nephropathy (19,57).

The clinical implications of these data are less straightforward. A major ongoing multicenter study, APOLLO, is aimed at defining APOL1 transplantation outcomes for both recipients and donors (58). Meanwhile, APOL1 genetic testing in the transplant setting has been initiated by many centers, and clinical recommendations are often on the basis of these test results.

For donors, reports suggest increased rates of kidney failure after donation associated with the high-risk APOL1 genotype compared with low-risk genotype (59). It remains unclear how much of the higher rates of disease among these donors reflects (1) the kidney donation acting as a second hit that triggers APOL1 kidney disease, (2) the loss of kidney reserve revealing preexisting subclinical kidney dysfunction, or (3) baseline higher rates of disease in high-risk genotype donors who often have family history of kidney disease (59,60). Some centers now actively discourage donation from young (<50 years) carriers of the high-risk genotype (61). It is also worth considering that the large benefit of better outcomes for recipients of a living donor kidney versus continuing dialysis (or even versus receiving a deceased donor kidney) may outweigh some level of risk to the donor in some cases. At the very least, it seems necessary that both donor and recipient should be given the option to know if there could be greater than typical risk to the donor.

Although the recipient APOL1 status does not seem to have a major effect on the graft survival, data from larger and prospectively designed trials are awaited to solidify this finding. In the meantime, recipients and transplant teams may have to weigh the APOL1 genotype of the graft in their decision to accept a kidney. Using donor kidney APOL1 genotype can alter the Kidney Donor Risk Index substantially (62). A more comprehensive understanding of the importance of APOL1 genotype across a range of donor and recipient genotypes and causes of the primary kidney disease will become clearer as more data emerge.

**Triggers of APOL1 Kidney Disease: Beyond Susceptibility**

Not all individuals with the APOL1 high-risk genotype develop kidney disease. Although there are likely to be genetic modifiers, data to date suggest that environmental influences may play a larger role (63,64). For a small fraction of cases, such as patients with HIVAN or IFN-associated glomerulopathy, we have some understanding of the triggering environmental factor. In most cases of H-ESKD or FSGS, the precipitating events are not known.

Recent reports have linked APOL1 nephropathy to infections with Parvovirus B19 (65) in native kidneys and with cytomegalovirus and BK virus in the transplant setting (66). Provocative, indirect evidence raises the possibility of a complex relationship between JC viruses, APOL1 genotype, and kidney disease, although the precise nature of this interaction is not yet fully understood (67). Acute glomerulopathy has also been observed with hemophagocytic lymphohistiocytosis, a disease driven by aberrant cytokine production (68). Recently, cases of collapsing glomerulopathy have been reported in the setting of acute SARS-CoV-2 coronavirus infection, a transient high-cytokine state (69,70). One common theme in these uncommon examples is a high-IFN state, consistent with the ability of IFNs to upregulate APOL1 in cells such as podocytes (21,22,71). Supporting this idea, APOL1 nephropathy can be induced in mice carrying a human APOL1 transgene encoding the risk variants by administration with IFN (22).

A relationship between viruses and proteinuria has long been observed in the form of nephrotic syndrome onset or relapses that occur in the wake of viral infections, such as upper respiratory illnesses (72). In general, proteinuric kidney disease in Black patients with or without a decline in GFR during or shortly after a viral illness likely warrants consideration of APOL1 status in generating a differential diagnosis.

**CKD and ESKD: When Is It APOL1 Nephropathy?**

CKD in Black individuals is often attributed to hypertension when no other risk factors are present. Although the association is clear, the direction of causality is not. The discovery that a large fraction of individuals with hypertension-attributable CKD have the high-risk APOL1 genotype has driven a rethinking of this association. It remains uncertain whether hypertension triggers APOL1-related injury to kidney vasculature or whether hypertension results from injury that starts with aberrant APOL1 behavior in the kidney microvasculature (73). Understanding the direction of causality is especially difficult because elevations of BP are detectable immediately, whereas declines in GFR lag far behind kidney dysfunction. The relatively modest effect of hypertension control on develop-
that hypertension may be the consequence rather than cause of CKD in individuals with the high-risk APOL1 genotype (74).

Clinicians are often faced with the scenario where a young Black patient presents with kidney disease, hypertension, and no other risk factors. Black patients may be less likely to undergo biopsy than similarly presenting patients of other ancestries because clinicians may make the assumption that the kidney disease is caused by chronic hypertension. Clinicians may forgo biopsy because they believe it will not change management. We believe that APOL1 genotype may alter this decision-making process. Specifically, a negative APOL1 risk genotype merits consideration of further workup that may include kidney biopsy. More routine APOL1 genotyping in the clinic and clinical studies will help clarify best practices.

The Special Case of Diabetic Kidney Disease

Although APOL1 risk variants increase the risk of several kidney diseases in Black individuals, their relationship to diabetic kidney disease (DKD) remains puzzling. Neither population-based nor case-control studies demonstrate significant effects of APOL1 on DKD prevalence (40,75). However, the risk variants appear to speed the rate of progression in individuals with DKD (74).

Because few individuals with diabetes, kidney dysfunction, and some degree of proteinuria are biopsied, it is not well defined in most cases when a Black patient has DKD versus diabetes and concurrent APOL1 nephropathy. Both diabetes and APOL1 nephropathy are common entities that are likely to occur together (independently) at a statistically meaningful rate. Understanding when a patient has DKD versus APOL1 nephropathy is needed to understand how APOL1 risk variants change the trajectory of diabetic nephropathy. Further complicating these relationships is the presence of obesity that often coexists with diabetes and can itself facilitate glomerular injury, causing both proteinuria and loss of GFR.

The questions raised here have important implications for both understanding of APOL1 biology and clinical care. Investigators studying basic biology of APOL1 nephropathy and DKD pathogenesis would benefit from knowing whether these disease processes injure the kidney through similar mechanisms. For clinicians, making the distinction between DKD versus diabetes plus APOL1 nephropathy may help weigh the risks and benefits of drugs, such as SGLT2 inhibitors, that are proving highly effective for DKD. Clinical investigators will need to formally test management strategies when diabetes and APOL1 risk genotype are both present. Assumptions that Black individuals with diabetes and kidney dysfunction have DKD should not be reflexive, especially in the absence of other complications such as retinopathy or when occurring with only modest elevations of hemoglobin A1c. APOL1 genotyping may help refine this calculation and help clarify the need for biopsy in selected individuals.

Using APOL1 to Improve Hypertension and CKD Regimens

APOL1 genotyping can help make predictions about the kidney function of populations and, perhaps, in some individuals. Its real usefulness will arise when it routinely helps improve management decisions. Until specific therapies become available, an important goal is to understand whether APOL1 nephropathy responds to any current therapies. One recent study suggests that hypertension in Black individuals may respond differently to angiotensin-converting enzyme inhibitors on the basis of APOL1 genotype, with APOL1 high-risk genotype carriers experiencing greater response in BP than noncarriers (76). To date, there is no definitive evidence that the course of APOL1 nephropathy is ameliorated by any particular regimen in either its FSGS or CKD presentations, although the larger datasets that have the power to identify optimal treatments have not yet been fully tapped. Observational data from these large datasets may guide therapy in the near term and inform prospective, randomized studies. Other studies have linked serum biomarkers to clinical progression in APOL1 high-risk carriers, improving clinical outcome prediction and potentially prioritizing patients for clinical trial selection (77).

Therapeutic Approaches to APOL1 Kidney Disease

Developing therapeutic approaches to APOL1 kidney disease has some major challenges. There is no consensus about the mechanism of APOL1 kidney disease. It is unclear which domains within the APOL1 molecule would be most amenable to targeting. Even the cell types to which therapeutic molecules would need to be delivered in different manifestations of APOL1 kidney disease are not yet known. Moreover, apolipoproteins may pose more challenges with respect to pharmacologic therapy than other types of molecules, such as receptors or kinases.

Despite these knowledge gaps, APOL1 kidney disease does have several features that give cause for optimism. APOL1 nephropathy seems to be a special case of a gain-of-function variant in a gene that can inflict damage on kidneys but is not essential for kidney development or baseline function under most environmental conditions. Inhibiting APOL1 activity may, therefore, not pose the same challenges to kidney disease treatment as blocking proteins with activities vital to kidney function, such as sodium transporters or regulators of kidney blood flow and GFR. Because it is known that at least one individual with no functional APOL1 does not have signs of kidney dysfunction, disabling the protein is less likely to induce kidney disease, possibly eliminating the need for careful modulation of APOL1 levels. APOL1 is a genetically validated target for kidney disease, meaning that nature has already demonstrated in humans that perturbing APOL1 activity directly influences kidney outcomes, as opposed to drug targets identified in animal models or cell-based systems. If studies continue to support the idea that inhibiting rather than restoring activity of APOL1 variants is the goal, one can envision intervening at the protein, RNA, or, even someday, DNA level. Although we understand relatively little about APOL1 biology, therapeutic potential is in many ways more straightforward than for diseases such as diabetic nephropathy, with decades of research data but likely much more complexity with respect to pathophysiology and genetic susceptibility as well as substantial clinical heterogeneity between patients.
The expanding tool kit for small molecule discovery, nucleic acid therapies, and gene modification are hopeful signs of progress to come. Our community eagerly awaits the day when nephrologists will be able to help their patients with targeted APOL1 therapy.

Disclosures

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