Apolipoprotein L1-Associated Nephropathy and the Future of Renal Diagnostics

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Apolipoprotein L1 (APOL1)-associated nephropathies comprise a spectrum of related nondiabetic kidney diseases strongly associated with the G1 and G2 coding risk variants in populations with recent African ancestry.¹ The spectrum is extremely heterogeneous, ranging from nephrotic syndrome with collapsing glomerulopathy in patients with HIV-associated nephropathy² to slowly progressive renal failure with minimal or absent proteinuria that clinically and histologically mimics hypertension-related nephropathy.³ The genetic contribution is also unique, in that the APOL1 renal risk variants have the unusual combination of a large effect size coupled with high allele frequencies in the general African-American population.⁴ In this issue of JASN, Kopp et al.⁵ carefully detail the clinicopathologic findings in the idiopathic FSGS variant of APOL1-associated nephropathy by evaluating participants in the FSGS Clinical Trial.

The clinical presentation, treatment outcome, demographics, and histopathologic lesions in the FSGS Clinical Trial were compared between those with two APOL1 renal risk alleles and those with one or zero alleles. DNA was available from 94 children and young adults; 27 (29%) participants possessed two copies of APOL1 renal risk alleles, including 23 of 32 (72%) self-reported African Americans. Interestingly, 6% (4 of 62) of participants who self-identified as non-African American had two renal risk variants, with one or zero alleles. Pairwise analysis revealed that APOL1-associated nephropathy should not immediately be excluded from the differential diagnosis in non-African Americans who have FSGS and proteinuria above 1 g/d. Collapsing glomerulopathy is the most widely recognized biopsy finding in APOL1-associated nephropathy, and not surprisingly, Kopp et al.⁵ found that it was significantly more common in those with two copies of APOL1 nephropathy risk alleles compared with those with fewer than two risk alleles. However, collapsing glomerulopathy is not the most common variant of FSGS in this cohort; 70% of participants with two APOL1 renal risk alleles had histologic evidence of a noncollapsing FSGS variant. As such, it does not seem advisable to screen for APOL1 nephropathy variants simply based on the finding of collapsing glomerulopathy on kidney biopsy in African Americans. Screening in this manner would have detected only 22% of participants with two risk alleles in this cohort.

The outcome data from the FSGS Clinical Trial, although informative, are not encouraging. Approximately 60% of participants had a transient partial or lack of response to cyclosporin or mycophenolate/dexamethasone treatment. Those with two APOL1 renal risk alleles were significantly more likely to progress to ESRD than those with fewer than two alleles. It has been reported that genetic alterations predict a lack of treatment response in patients with steroid-resistant nephrotic syndrome.⁶ However, this may not be the case for APOL1.

Little is known about the pathogenic mechanism(s) by which APOL1 renal risk alleles confer susceptibility to kidney disease with the resultant lesions of FSGS; even the primary kidney cell types involved remain uncertain. Although the effect size of renal risk alleles is quite high, the fact remains that most individuals who inherit two APOL1 renal risk variants do not develop kidney disease. For this reason, the working hypothesis is that those who ultimately manifest clinical kidney disease possess additional genetic alterations that contribute to disease (APOL1 gene–second gene interactions) or are exposed to additional modifying risk factors (APOL1 gene–environment interactions).⁷ There is no doubt that environmental conditions play a major role in several subtypes of APOL1-associated kidney disease; these disorders are labeled by modifiers, such as sickle cell nephropathy, HIV-associated nephropathy,⁵ and SLE-associated collapsing glomerulopathy.⁸ There were no clear modifiers that contributed to disease in the population described by Kopp et al.,⁵ because the FSGS Clinical Trial excluded participants with secondary conditions. Cohorts such as this provide a unique opportunity for investigation of potential novel disease modifiers that may interact with APOL1 risk alleles to produce (or prevent) CKD. Possibilities include interactions between APOL1 and second genes, which were recently described for podocin (NPHS2), serologically defined colon cancer antigen 8 (SDCCAG8), and bone morphogenetic protein 4 (BMP4),⁹ or as yet undiscovered inciting non-HIV viral triggers.⁹

Like in idiopathic FSGS, APOL1-associated focal global glomerulosclerosis with prominent interstitial and vascular changes, typically reported as arterionephrosclerosis, currently lacks known modifying factors. We reported renal histologic findings in African Americans with arterionephrosclerosis.

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on the basis of their $APOL1$ genotypes.\textsuperscript{3} This sample universally lacked nephrotic syndrome to exclude idiopathic FSGS and provides an interesting contrast to FSGS Clinical Trial participants. African Americans with two $APOL1$ renal risk alleles and arterionephrosclerosis more often lacked obsolescent glomerulosclerosis, which is the result of renal microvascular disease with reduced glomerular perfusion, subsequent ischemic collapse, and wrinkling of the glomerular basement membrane. Instead, they possessed greater degrees of solidified and disappearing glomerulosclerosis, thyroidization-type tubular atrophy, and microcystic tubular dilation relative to African Americans with fewer than two renal risk variants. Because $APOL1$ is felt to convey a higher risk for progression of nondiabetic nephropathy, the prominent tubulointerstitial changes may prove to be important in this disease spectrum. Similar to our report, FSGS Clinical Trial participants also displayed prominent tubular atrophy/interstitial fibrosis. As such, renal tubular cells are highly likely to be affected by $APOL1$ variant proteins, perhaps just as likely as the podocyte.

No existing treatments have proven efficacy for patients with progressive $APOL1$-associated nephropathy. Kopp et al.\textsuperscript{5} reported that the presence of two $APOL1$ renal risk alleles in study participants with biopsy-proven FSGS does not predict a response to immunosuppressant treatment. However, the vast majority in this report showed little (or no) response to the treatment regimens used. Unfortunately, this outcome currently exists for many subtypes of $APOL1$-associated nephropathy. Treatment and/or prevention of disease is possible in HIV-associated nephropathy, where effective antiretroviral therapy halts nephropathy progression.\textsuperscript{1} Although not proven, preventing acute flares in patients with SLE might have benefits in SLE-associated collapsing glomerulopathy. However, the vast majority of African Americans with lupus nephritis-associated ESRD who possessed two $APOL1$ renal risk variants in a recent report previously failed cytotoxic therapy.\textsuperscript{10} This may suggest limited effects of cytotoxic therapy in patients with SLE and two $APOL1$ nephropathy risk variants.

Recent clues concerning the possible pathogenesis of $APOL1$-associated nephropathy may have implications for future therapies. The lack of nephropathy in individuals with null mutations in $APOL1$ suggests that the renal risk alleles confer a toxic gain of function for this protein.\textsuperscript{11} Additionally, cell culture experiments have shown that overexpression of the $APOL1$ protein is harmful to cells and that expression of the $APOL1$ renal risk variants is more injurious than wild-type $APOL1$.\textsuperscript{12,13} Antiviral pathways may be important inducers of $APOL1$ overexpression, because this process is regulated by innate immune pathways, including signaling by IFNs and Toll-like receptors.\textsuperscript{12} Thus, treatments aimed at decreasing the expression of the renal risk alleles could alter the risk for ESRD.

Definitive diagnoses of $APOL1$-associated nephropathy are rarely made in clinical practice, because genetic testing is not routinely performed. This may be because of the fact that detecting $APOL1$ renal risk alleles provides no immediately actionable management strategy. Additionally, we practice in an increasingly pragmatic health care environment, where many payers will not reimburse molecular diagnostics that lack direct treatment implications. As a result, affected patients are often given vague diagnoses; many are mistaken for kidney disease resulting from the effects of essential hypertension and categorized as hypertensive or arteriolar nephrosclerosis. Those who have a kidney biopsy are often placed in the category of FSGS; a nonspecific lesion recognized historically that can have myriad pathogenic etiologies.

Moving forward, patients with common complex forms of severe nephropathy deserve precise diagnoses whenever possible. Precision medicine is rapidly paving the way. Affected individuals should be informed of what led to their renal diagnosis if they desire such information. As specific treatments (or clinical trials) become available for devastating forms of $APOL1$-associated nephropathy, patients and their physicians would then know that they are eligible to participate. Additionally, although no specific treatments are presently available, the diagnosis of $APOL1$-associated nephropathy provides prognostic information and will likely be important in evaluating suitable kidney donors who possess recent African ancestry.\textsuperscript{14}

The report by Kopp et al.\textsuperscript{5} enhances our understanding of a common etiology of the FSGS lesion seen on kidney biopsy in African Americans, and $APOL1$ is the most common etiology in this ethnic group. FSGS was first recognized on the kidney biopsy approximately 90 years ago.\textsuperscript{15} Despite subsequent advances in diagnostic technology, the most commonly used classification scheme of FSGS continues to rely largely on light microscopy.\textsuperscript{16} We practice in an exciting era in medicine, when diagnostic pathology is rapidly evolving with the incorporation of powerful technologies, such as next generation sequencing, allowing the simultaneous evaluation of thousands of potentially associated genes. Routine use of these new technologies will allow for more accurate pathogenesis-based classification schemes in FSGS. This will ultimately enable precise treatment options and likely improve the outcomes for many patients with CKD.

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**DISCLOSURES**

None.

**REFERENCES**


