APOL1 Nephropathy Risk Variant Associations with Diseases beyond the Kidney
APOL1 and Sepsis

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The past decade has seen major developments in our understanding of ancestry-specific rates of CKD and outcomes after kidney donation and transplantation. Genetic association between the G1 and G2 nephropathy risk variants in the apo L1 gene (APOL1) and CKD is recognized as among the strongest in common complex disease. The odds ratio for APOL1 genetic association ranges from 7.3 (95% confidence interval [95% CI], 5.6 to 9.5) in solidified glomerulosclerosis to 89 (95% CI, 18 to 912) in HIV-associated nephropathy. Transgenic mouse studies subsequently proved that G1 and G2 cause CKD. This breakthrough changed the epidemiology in ESKD among patients with recent African ancestry, answering in part the longstanding question of why kidneys of blacks were more prone to glomerular and interstitial fibrosis than kidneys of whites.

With discovery of APOL1 nephropathy risk variants, it became evident that nondiabetic, hypertensive blacks with CKD and bland urinalyses typically had solidified glomerulosclerosis, a primary kidney disease. They did not have kidney failure related to essential hypertension; their hypertension develops secondary to reduced kidney function. The concept that the histologically classified FSGS spectrum of diseases was heterogeneous also proved to be incorrect; approximately 70% of FSGS in blacks relates to APOL1. Finally, collapsing forms of FSGS in blacks are often APOL1 associated, typified by collapsing glomerulopathy with either HIV infection or IFN administration. Variation in APOL1 also contributes to the shorter allograft survival seen in recipients of deceased donor kidneys from blacks and higher rates of ESKD after living kidney donation in blacks.

These observations coupled with APOL1 expression in organs beyond the kidney led to the performance of association analyses between APOL1 and traits that vary on the basis of population ancestry, including circulating apo concentrations, BP, and cardiovascular disease. The report by Chaudhary et al. (1) in this issue of CJASN extends these analyses to risk of sepsis. On the basis of the reduced risk of sepsis in blacks (versus whites) in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, the authors posited that APOL1 G1 and G2 nephropathy risk variants would be associated with protection from sepsis (2). However, results paradoxically supported an increased risk for sepsis with both additive and dominant genetic models; the recessive model was not significant but trended in the same direction.

The REGARDS study evaluated a large and well characterized population-based cohort. There was broad inclusion of black participants in this report, analyses were appropriate, and results were interpreted correctly (1). Consistent association was present between hospitalization for sepsis and increasing numbers of APOL1 nephropathy risk variants, including secondary analyses that were stratified on the basis of the presence or absence of diabetes mellitus and CKD.

The authors discuss potential limitations, including the possibility that some participants might have reported inaccurate hospitalization data during phone interviews and that the investigators intentionally excluded sepsis events that occurred after hospital admission. The REGARDS study participants are older than those in many studies that assessed risk of sepsis (baseline age exceeded 45 years old; current mean age is approximately 64 years old); thus, this report did not capture sepsis risk earlier in life. Nonetheless, this epidemiologic study clearly identified an association between sepsis and APOL1 nephropathy risk variants among middle-aged and older blacks in the REGARDS study. The authors noted that their results are hypothesis generating, do not prove causation, require replication, and might have been confounded by unknown factors involved in APOL1 biology. It would have been useful to report culture results and primary sites of infection when identified during chart review. Without this information, it is not clear whether there was a preponderance of sepsis events related to certain bacterial strains, such as gram-negative rods, yeast, or viruses, or with particular foci of infection.

Given that this is the first study of the role of APOL1 in sepsis, it is important to recognize that, if APOL1 G1 and G2 nephropathy variants underlie higher (or lower) risk of a condition, variable incidence rates should be present between the black population and other ancestral groups, including whites. G1 and
G2 are highly informative markers of ancestral origin, and they are present virtually only in individuals with sub-Saharan African ancestry. Different ancestries have shared and unique risk factors for sepsis. The premise of this study was that sepsis risk in the admixed black population might be due to biologic variation in APOL1 nephropathy risk variants. However, the relationship between sepsis and ancestry is confounded by preexisting medical conditions (including CKD), health behaviors and beliefs, and access to health care. Relative to whites, blacks were reportedly at higher risk for sepsis and sepsis-related mortality (3). However, the REGARDS study results supported paradoxically lower risks of infection and sepsis in blacks than whites, results that differed from prior reports (2).

APOL1 G1 and G2 nephropathy risk variants help combat trypanosomal infection and are likely selected for on the basis of their role in reducing African sleeping sickness. That explains how these two recent mutations, which developed within the past 10,000 years, have risen to such high frequency in populations with recent African ancestry, despite causing CKD later in life.

As in the general population, approximately 13% of blacks in the population-based REGARDS study possess two APOL1 nephropathy variants, and 40% have one. African sleeping sickness affects people of all ages and would have had intense effects on the population during outbreaks. It likely caused a marked contraction of the population, with great advantage for survival and future reproduction in those with APOL1 nephropathy variants. Hence, the rapid rise of these variants in sub-Saharan Africa was a result of an intense bottleneck effect. Sepsis, however, is more likely a steady pressure, and it is not fully independent of age. Thus, from a population genetics and microevolutionary standpoint, we would not expect massive effect by natural selection due to sepsis. There is no bottleneck effect but more of a slow and steady effect on human fitness and evolution.

Results from studies on cardiovascular disease suggest that we should exercise caution when extending APOL1 associations beyond kidney disease. Although blacks have higher rates of myocardial infarction and stroke than whites in the general population, they have significantly lower rates of subclinical cardiovascular disease and fewer myocardial infarctions when provided equivalent access to health care. Higher proportions of African ancestry in blacks are associated with lower levels of calcification atherosclerotic plaque (4). Several initial association studies between APOL1 G1 and G2 variants with cardiovascular disease supported a heightened risk of myocardial infarction and major adverse cardiovascular events. It was not until results of better-powered studies and a meta-analysis were available that this hypothesis proved to be incorrect (5). Recent data support no direct association between APOL1 G1 and G2 risk variants and incident cardiovascular disease; the APOL1 relationship with CKD seems to underlie the risk for cardiovascular disease.

APOL1 plays an important role in the innate immune system. Nichols et al. (6) reported that collapsing FSGS develops with therapeutic IFN infusion only in patients with two APOL1 nephropathy variants. IFNs and the toll-like receptor 3 agonist “polyIC” increase APOL1 expression up to 200-fold (6). In addition, LPS, a toll-like receptor 4 agonist, upregulates APOL1 expression in vascular endothelial cells. LPS levels are often elevated in severe gram-negative rod infections, and viral infections typically upregulate levels of IFN. Hence, it is conceivable that susceptibility to sepsis could result from variation in APOL1.

APOL1 protein is present at high levels in monocytes, comparable with those in the liver (www.genecards.org). Several effects occur when monocytes are exposed to LPS, including tolerance to endotoxins, antioxidant defenses, mitochondrial biogenesis, and increased mitophagy (7). Involvement of mitochondria, organelles regulating cellular energy homeostasis and innate immunity, is of interest, because APOL1 G1 and G2 nephropathy risk variants induce mitochondrial dysfunction, leading to CKD (8), and impair autophagy (9). Removing damaged mitochondria via autophagy or mitophagy is critical for maintaining cell function. One can hypothesize that APOL1 G1 and G2 variants might modify tolerance to bacterial endotoxin in monocytes through compromised mitochondrial function. APOL1 nephropathy risk variants may also induce aberrant THP-1 monocyte differentiation and increase eicosanoid production via enhanced expression of cyclooxygenase-2 (10), further modifying the immune response.

The intriguing observation that APOL1 G1 and G2 variants may associate with heightened risk of sepsis in black REGARDS study participants could open a new avenue of study on the nonkidney effects of this gene. APOL1 plays a major role in innate immunity and virus-associated kidney disease. The results of this study should fuel efforts to confirm findings and better define the immune effects of APOL1 G1 and G2 nephropathy variant proteins.

Disclosures
Dr. Freedman reports receiving consultant fees from AstraZeneca and RenallytixAI. Dr. Freedman also reports that he and Wake Forest University Health Sciences have rights to an issued United States patent related to APOL1 genetic testing (https://www.apol1genetest.com). Dr. Ma has nothing to disclose.

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References


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