Journal Pre-proof

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PII: S0272-6386(21)00055-X

DOI: https://doi.org/10.1053/j.ajkd.2020.11.029

Reference: YAJKD 57353

To appear in: *American Journal of Kidney Diseases*

Received Date: 6 August 2020

Accepted Date: 17 November 2020

Please cite this article as: Cerdeña JP, Tsai J, Grubbs V, *APOL1*, Black Race, and Kidney Disease: Turning Attention to Structural Racism, *American Journal of Kidney Diseases* (2021), doi: https://doi.org/10.1053/j.ajkd.2020.11.029.

APOL1, Black Race, and Kidney Disease: Turning Attention to Structural Racism

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The incidence of end-stage kidney disease (ESKD) is nearly three times higher in Black relative to White Americans.[1] A significant body of biomedical literature links this racial inequity to polymorphic variation in the gene encoding apolipoprotein L1 (*APOL1*). In fact, in a PubMed search of "APOL1" and "kidney disease," 86 percent of results feature abstracts mentioning African ancestry or African American, Black, or non-White race. Multiple recent articles state that *APOL1* genetic variants are found "exclusively" in people, or chromosomes, of "African" origin.[2–4] Further, an ongoing clinical trial—the *APOL1* Long-term Kidney Transplantation Outcomes Network (APOLLO) study—seeks to examine the relationship between *APOL1* genotype and racial disparities in allograft survival among deceased kidney donors and ESKD among living kidney donors.[5] Such tight coupling of *APOL1* variation and Black race lends the impression that racial disparities in kidney disease are genetically determined and homogenously distributed across persons labelled as 'Black,' a misguided hypothesis that can skew investment toward interventions with limited effect. In this editorial, we review the current literature on *APOL1*, discuss the scientific flaws of linking *APOL1* 'risk' alleles with Black race, and emphasize the role of structural racism as a determinant of racial disparities in kidney disease.

Background on *APOL1*

Genetic variation on chromosome 22q has been associated with increased susceptibility to focal segmental glomerulosclerosis (FSGS), HIV-associated nephropathy (HIVAN), and hypertension-attributed ESKD (H-ESKD). In particular, strong signals have been identified in association with two nonsynonymous coding variants (p.S342G:I384M) in the last exon of

APOL1, termed G1, and with a six-base-pair deletion that removes two amino acids (N388Y389), termed G2.[6]

Patterns of linkage disequilibrium in the region of G1 and G2 provide strong evidence for positive selection. In particular, because the *APOL1* variants evade activity of the serum-resistance associated protein of *T. b. rhodiense*—one of the vectors of African sleeping sickness—it is hypothesized that heterozygosity for these alleles confers a selective advantage against the disease.[7] Furthermore, the presence of these variants in Yoruban populations from Nigeria and in some Black Americans, and their relative scarcity in European and Asian populations, evince the likelihood of a recent selection event in West Africa.[6,8] Together, these genetic data have led clinical investigators to focus on *APOL1* polymorphisms as a key, rather than a contributory, explanatory variable in racial disparities in kidney disease. For instance, in a recent editorial, Kopp and Winkler name "variants in *APOL1* as major driver[s] of kidney disease in Blacks" and accordingly discuss recommendations for clinical testing of risk genotypes.[9] This approach, however, is based upon a misapplication of population genetics and exacerbated by conflation of genetic ancestry and race.

The Error and Harm of Linking *APOL1* Variants to Black Race

Race is a social and political construct perpetuated by those in power and should not be used as a substitute for thoughtful, hypothesis-driven genetic analyses.[10] Human genetic and phenotypic variants, including superficial physical differences like skin color and hair texture, are clinally distributed across geographic space and are not discernible by race or continent.[11,12] Researchers may lean on terms like "ancestry," which imply evolutionary history and may carry biological significance at an individual level of analysis;[13,14] however, when paired with a wide

geographical modifier (i.e., "African"), such phrases lose meaning and become little more than a substitute for race. Genetic conclusions cannot be made about the populations of entire continents or entire races; accordingly, discussing *APOL1*-associated kidney disease as a concern of—and exclusive to—people of "African descent" reflects racist practice in medicine and research,[15] even if and often done unconsciously. In this section, we identify specific flaws inherent in the logic of associating *APOL1* 'risk' alleles with Black race and outline potential harms to patients.

Sweeping associations between *APOL1* 'risk' polymorphisms and Black race risk overlooking the impact of *APOL1*-associated nephropathy on other populations. Although *APOL1* 'risk' variants are most often seen in people of West African descent, other groups—including European American, Pakistani, and Latin American patients—also carry these polymorphisms.[16–18] Even though this is likely due to admixture, these findings suggest that limiting clinical inquiries about *APOL1*-associated kidney disease to 'Black' patients inappropriately excludes patients of other racial or ethnic backgrounds. The APOLLO study, for instance, only recruits Black kidney donors, restricting insights into the role of the *APOL1* genotype on clinical outcomes to an artificially smaller population. Researchers may be reluctant to generalize their findings to White, Asian, and Latinx patients who carry G1 and G2 alleles who would otherwise benefit.

Moreover, the frequency of *APOL1* 'risk' alleles varies widely across the African continent. For instance, the frequency of G1 among the Igbo in Nigeria is 30.2 percent but 0 percent among the Lemande of Cameroon.[17] Yet, patients from both of these ethnic groups would be racialized as 'Black' in the United States. Additionally, even among genetically similar ethnic groups, significant variation in allelic frequency is evident. Genetic research comparing

the genotypes of the Yoruba of Nigeria and the Luhya of Kenya, two ethnic groups of high genetic similarity, found that no other sites were as differentiated between the two groups as G1. This large variation cannot be explained by genetic drift and instead points to a selection event occurring within a narrowly circumscribed population in West Africa.[7] Therefore, conclusions about *APOL1* polymorphisms cannot be generalized to all residents of the African continent nor to all individuals of African descent.

Because many enslaved Africans were captured from the West African coast during the trans-Atlantic slave trade, Black Americans descended from slaves may be expected to exhibit higher frequencies of G1 and G2. Indeed, current research suggests that over 20 percent of Black Americans carry one 'risk' mutant and 13 percent carry two.[19] However, recent patterns of Black African migration reveal an influx from Northern and Eastern Africa, regions where the *APOL1* 'risk' alleles are far less prevalent.[20] Accordingly, given the continued inflow of Black migrants from diverse regions of Africa—and ongoing admixture between descendants of the enslaved with genetically distinct populations—wide heterogeneity in frequency of *APOL1* variants among individuals racialized as 'Black' may be expected, depending on population sampling. In summary, sweeping attributions of kidney disease risk among Black Americans to *APOL1* 'risk' alleles overlooks the increasing genetic diversity within this community and others.

Incautious conflation of *APOL1* genotype and Black race can promote misinformed conclusions that *all* Black patients experience genetic predisposition toward kidney disease.[21] This is reflected in the Kidney Donor Risk Index (KDRI), a tool that includes Black race in its calculation of allograft longevity for donated kidneys. Substitution of *APOL1* genotype for race in the equation would improve the KDRI for 85 to 90 percent of Black donors, likely reducing

discard of high-demand kidneys.[22] Thus, generalizations about Black race and *APOL1* risk alleles are scientifically inappropriate and contribute to healthcare waste.

Finally, the link between *APOL1* polymorphisms and kidney disease is not as straightforward as some research implies. Although possessing two 'risk' alleles yields an odds ratio of 10.5 and 7.3 for FSGS and H-ESKD, respectively,[6] the overall lifetime risk is just 4 and 12 percent. Additionally, possessing two 'risk' alleles explains just 37, 18, and 7 percent of the variance in risk for HIVAN, FSGS, and H-ESKD, respectively,[19] while most reports find no association with diabetic nephropathy, the leading cause of kidney disease.[17] *APOL1* variants account for roughly 30 percent of the excess non-diabetic kidney disease in Black Americans,[23] highlighting the importance of environmental factors underpinning racial disparities in kidney disease.

Turning Attention to Structural Racism as a Determinant of Kidney Disease

Racial groups are not clearly demarcated by patterns of genetic variation; however, in the United States, histories of inequitable distribution of resources along racial lines have systematically created unequal environments and life opportunities between Black and White communities, which differentially impact their health. Structural racism refers to "the totality of ways in which societies foster racial discrimination through mutually reinforcing systems."[24] Disparities in kidney disease derive from unequal conditions in wealth, employment, residence, toxic environmental exposures, nutrition, education, healthcare access, and psychosocial stress.[25–29] Mediators of ESKD—such as diabetes, hypertension, and HIV—can be traced to racialization of the U.S. food system,[30] mass incarceration,[31] and poverty.[32] Structural determinants of health thereby deserve at least as many dedicated resources as those afforded to genetic inquiry, yet research and funding streams consistently favor investigation into biological

and genetic underpinnings of racial disparities in health over issues of racism or racialization.[33,34] In fact, a simple Boolean search of the terms “kidney disease” and “racism” in the National Institutes of Health Research Portfolio Online Reporting Tools Database for 2019 to 2020 yields just 5 results whereas pairing “kidney disease” with term “genetic” yields 754 results.[33]

Racism itself can induce multiple physiologic changes involved in the pathogenesis of kidney disease. Chronic stress from interpersonal and structural racism can initiate long-term activation of the hypothalamic-pituitary-adrenal axis, which can constitutively increase vascular tension. Such stress can also lead to failure to downregulate the inflammatory response and increased production of reactive oxygen species, which can promote interstitial fibrosis.[25] Further, epigenetic modifications—such as those resulting through fetal programming when racial discrimination increases prenatal cortisol exposure—may contribute to the excess risk for kidney disease among Black Americans.[35] Thus, although race is a poor proxy for population genetics, adverse social conditions experienced by marginalized populations are consistent and powerful contributors to disease risk. Overemphasis on racialized genetics—rather than racism—may result in insufficient examination of structural inequities as major determinants of racial disparities in kidney disease.

Future research should examine how racist—and antiracist—policies affect kidney health. Studies can assess the effects of policies like Medicaid expansion,[36,37] decriminalization,[38] or, in the future, reparations[39] on kidney health. Racism should be identified and carefully analyzed: Research that merely examines race as a ‘risk factor’—or provides a genetic basis for racial differences in health outcomes—should be scrupulously critiqued.[40] Understanding the effects of policy on health can inform both public and private action, dismantling the oppressive structures that contribute to racial disparities.

Conclusion

Carrying two *APOL1* 'risk' alleles significantly increases an individual's odds of developing kidney disease; however, even with a high-risk genotype, overall lifetime risk remains relatively low and much of the variance in risk is explained by other factors, including structural racism. Although some Black Americans carry high levels of West African ancestry due to the shameful history of chattel slavery, wide variation in *APOL1* 'risk' allele frequency is expected among all individuals racialized as 'Black.' It is therefore inappropriate to conclude that *APOL1* mutations increase risk for kidney disease among all Black Americans or to limit research or testing of *APOL1* genotypes to Black individuals: Such determinations may constrain clinical decision-making and misdirect resources to the detriment of patients. Decisions regarding *APOL1* testing in clinical care should engage key stakeholders, including a diverse group of patients, nephrologists, primary care providers, researchers, and bioethicists, considering opportunities for patient counseling and the need to develop targeted treatments.[41] Finally, since *APOL1* polymorphisms cannot fully explain the racial disparities in kidney disease, research that examines how structural racism mediates impairments in kidney function deserves closer attention.

Article Information

Support: J.P.C. is funded by the Robert Wood Johnson Foundation Health Policy Research Scholars program and the National Institute of Health Medical Scientist Training Program Grant T32GM136651.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Peer Review: Received August 6, 2020. Evaluated by 2 external peer reviewers, with direct editorial input from an Associate Editor and a Deputy Editor. Accepted in revised form November 17, 2020.

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