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APOL1, Sickle Cell Trait, and Glutathione *S*-Transferase 1—More Complicated Than It Seems

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There are 2 risk alleles at the *APOL1* gene (G1 and G2, encoding S342G and I384M substitutions and N388–Y389 deletions, respectively) that account for >70% of the increased risk for nondiabetic chronic kidney disease (CKD) in individuals of Sub-Saharan African ancestry.[1] These variants have risen to high allele frequency in *Trypanosoma*-endemic regions in Africa owing to the dominant selective advantage that restores trypanolytic activity against *T brucei rhodesiense* (G2) and confers protection from active illness caused by *T brucei gambiense* (G1).[2] This protective effect confers a significant disadvantage that translates to increased CKD risk in individuals that harbor 2 *APOL1* risk alleles. A broad spectrum of kidney disease has been associated with *APOL1* risk alleles, including hypertension-attributed kidney disease, focal segmental glomerulosclerosis, HIV-associated nephropathy, accelerated kidney graft loss, progressive lupus nephritis, and collapsing glomerulonephritis owing to interferon, HIV, or COVID-19 infection.[1] Nevertheless, unlike diseases related to genetic mutations with Mendelian inheritance, *APOL1* risk alleles have a relatively lower penetrance; therefore, only a subset of individuals with the high-risk (HR) genotypes will develop clinical disease. The lifetime risk for kidney disease in individuals with HIV infection, in the absence of an antiviral therapy, can exceed 50%, whereas the lifetime risk for focal segmental glomerular sclerosis is 4%. Environmental and genetic factors may serve as second hits transforming the genetic risk into clinically evident disease.[1] Although genetic studies failed to detect significant polymorphic variants that alter *APOL1* penetrance, environmental factors that enhance the activity of the innate immune system and thereby the expression of *APOL1* do enhance CKD risk in susceptible individuals. Such environmental factors include untreated HIV infection, COVID-19 infection, and interferon treatment.[1] Other genetic and environmental factors that may modify the genetic risk are under investigation.

In the current issue of the *KI Reports*, 2 studies explored the role of sickle cell trait (SCT) with *APOL1* nephropathy. Hung *et al.*[3] investigated the relationship between SCT and kidney impairment in 2895 individuals participating in the Genetic Markers of Kidney Disease Progression in People of African Ancestry with HIV in the United Kingdom (GEN-AFRICA) study. In multivariable analysis, SCT and *APOL1* HR genotypes were associated with estimated glomerular filtration rate (eGFR) <60 ml/min per 1.73 m^2 (odds ratio [OR] 1.62 and 4.88, respectively). Surprisingly, a significant association between SCT and eGFR <60 ml/min per 1.73 m^2 was present in the subset of participants with *APOL1* low-risk genotypes (OR 2.37, $P < 0.001$) whereas no association was observed among those with *APOL1* HR genotypes (OR 0.79, $P = 0.04$). Masimango *et al.*[4] conducted a cross-sectional study in adults living in South-Kivu, located at the eastern part of the Democratic Republic of Congo (DRC). A total of 587 individuals living in urban and 730 living in rural areas were included. The authors explored the interaction of 2 different well-characterized genetic mutations, namely *GSTM1* null and SCT with CKD risk in individuals with and without 2 *APOL1* risk alleles. SCT and *GSTM1* null allele frequencies were 3.8% and 51.2%, respectively. *APOL1* G1 and G2 allele frequencies were lower than reported in west Africa and Kinshasa, the capital of DRC: 8.7%

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and 9.1%, respectively, with 3.2% carrying HR genotype. The reason for the reduced G1 allele frequency in this region may stem from different ethnicities in these areas and lower prevalence of *T brucei gambiense* (G1) in this region (east DRC) compared with Kinshasa (west DRC) and west Africa, given the protective association conferred by G1 from active illness caused by *T brucei gambiense* (G1).[2] The *APOL1* HR genotype was associated with lower eGFR in adjusted models (OR 4, $P = 0.047$). Given the low frequency of *APOL1* HR genotype, this study was underpowered to detect a similar association with albuminuria. Consistent with previous reports, SCT was associated with CKD (OR 2.4, $P = 0.031$). Nevertheless, in contrast to Hung *et al.*,[3] *APOL1* HR genotype and SCT were synergistically associated with lower eGFR (P interaction = 0.012). As opposed to this synergistic interaction and previous report,[5] *GSTM1* null was not associated with CKD, therefore, did not modify *APOL1* CKD risk.

What We Can Learn From These Findings

Oxidative stress is a significant contributor to CKD progression. Genetic factors that can mitigate the deleterious effect of reactive oxygen species may alter CKD progression. Glutathione *S*-transferase (GST) belongs to a family of phase II metabolic enzymes that are involved in attenuation of lipid peroxidation, and scavenging of free radicals, which are products of oxidative stress and key metabolites of toxins and carcinogens. *GSTM1* belongs to a superfamily of GSTs that participate in the conjugation of prooxidant xenobiotics and electrophilic species to glutathione. Loss of *GSTM1* results in increased levels of reactive aldehydes and exaggerated oxidative stress, with a consequential acceleration of CKD progression.[6]

Deletion of *GSTM1* is common in Whites and Blacks (50% and 27%, respectively).[5–7] Until now, no evolutionary advantage was found to explain this high frequency; in contrary, deleterious consequences have been suggested.[5–7] Previous studies have revealed that harboring even 1 allele impairs the amount of active *GSTM1* and the ability to neutralize reactive chemical species, leading to increased oxidative stress.[6] An association between loss of *GSTM1* (0/1 alleles) and CKD progression has been reported in the African American Study of Kidney and Hypertension and Atherosclerosis Risk in Communities,[5,6] suggesting *GSTM1* activity is crucial, irrespective of genetic background. Moreover, analysis of the African American Study of Kidney and Hypertension study revealed an increased CKD risk in individuals with null *GSTM1* and *APOL1* HR genotype.[5–7] How can we reconcile the current conflicting results on the role of *GSTM1* null in CKD? The current study is a cross-sectional study, whereas the Atherosclerosis Risk in Communities and the African American Study of Kidney and Hypertension studies were prospective with longitudinal follow-up, which therefore could capture incident CKD and progression of CKD.[5–7] In addition, previous studies have revealed that most individuals harboring *GSTM1* null were healthy, and only a small proportion experienced CKD progression, suggesting similar to *APOL1*, a second hit is required to enhance *GSTM1* null deleterious effect, leading to CKD progression. Furthermore, environmental factors that influence the availability of toxic substrates may modify the biological significance of *GSTM1* null. Such potential second hits include toxic substrates (e.g., cigarette smoking, low intake of cruciferous vegetables, and endogenous toxic metabolites). Therefore, the diversity of these factors could explain the negative association in the current study. The GST superfamily includes several members with potential redundant activity, and compensatory activity of other members of the GST family, such as GSTT1, is possible. Measurement of GST activity is needed to clarify the significance of *GSTM1* deletion and the activity of other GST members that can compensate for this deletion. In addition, in the DRC study, the mean creatinine-based eGFR was 95 ml/min per 1.73 m^2 and 0.2% of the participants had eGFR <15 ml/min per 1.73 m^2 (CKD stage 5).[4] It is postulated that the activity of *GSTM1* would be significant, especially when GFR is decreasing with the accumulation of uremic toxins and, thereby, oxidative stress. Hence, at this stage, it may be premature to definitively exclude the role of oxidative stress in general, and specifically the *GSTM1* null state, in mediating *APOL1* nephropathy and CKD risk in this population.

Although cross-sectional studies have revealed conflicting results regarding the association of SCT with CKD, a meta-analysis of 15,000 individuals from 5 population-based cohorts of African Americans and an analysis of the REGARDS (REasons for Geographic and Racial Differences in Stroke) study have revealed the association of SCT with CKD progression and incident CKD.[8,9] In that analysis and the REGARDS study analysis, SCT did not interact with *APOL1* HR genotype to further increase CKD progression.[8,9] Similarly, both studies presented in the current issue of

the *KI Reports* report the association of SCT and CKD, albeit with contrasting results on *APOL1* HR genotype and SCD interactions.[3,4] The cross-sectional design of the current studies precludes the determination of the exact nature of the observed associations. With co-inheritance of other hemoglobinopathies, such as alpha-thalassemia, hemoglobin C can alter red blood cell cycling and its effect on target organs, such as the kidney. Such interactions were not evaluated in either study. The enhanced CKD risk in individuals with *APOL1* HR genotype and SCT is biologically plausible, given the different pathways and sites of kidney injury, namely, podocyte versus medullary impairment involvement in *APOL1* injury and SCT-mediated kidney injury, respectively. These findings may carry clinical research implications. Individuals at high risk for SCT-related kidney disease and *APOL1* HR genotype may benefit from early intervention to be evaluated in clinical trials, such as the following: angiotensin-converting enzyme inhibitors that attenuate CKD progression in SCD and SGLT2 inhibitors that confer kidney-protective effects regardless of diabetic kidney disease.

DISCLOSURE

All the authors declared no competing interests.

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