**COMMENTARY**

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

Etty Kruzel-Davila¹ and Sethu M. Madhavan²

¹Department of Nephrology, Galilee Medical Center, Nahariya, Israel; and ²Department of Medicine, The Ohio State University, Columbus, Ohio, USA

Kidney Int Rep (2022) 7–10; https://doi.org/10.1016/j.ekir.2021.12.038 © 2022 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

See Clinical Research on Page xxx.

There are 2 risk alleles at the APOL1 gene (G1 and G2, encoding S342G and 1384M substitutions and N388–Y389 deletions, respectively) that account for >70% of the increased risk for non-diabetic chronic kidney disease (CKD) in individuals of Sub-Saharan African ancestry. 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 gambiensens (G1). 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 glomerular sclerosis, HIV-associated nephropathy, accelerated kidney graft loss, progressive lupus nephritis, and collapsing glomerulonephritis owing to interferon, HIV, or COVID-19 infection. 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. 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. Other genetic and environmental factors that may modify the genetic risk are under investigation.

In the current issue of the *Kidney Reports*, 2 studies explored the role of sickle cell trait (SCT) with APOL1 nephropathy. Hung et al. 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 m² (odds ratio [OR] 1.62 and 4.88, respectively). Surprisingly, a significant association between SCT and eGFR < 60 ml/min per 1.73 m² 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. 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%,

---

**Correspondence:** Etty Kruzel-Davila, Department of Nephrology, Galilee Medical Center, 89 Nahariya-Cabri, Israel. E-mail: ETTYK@gmc.gov.il; or Sethu M. Madhavan, Department of Medicine, The Ohio State University, 473 W 12th Avenue, HLRI 325 Columbus, Ohio 43210, USA. E-mail: sethu.madhavan@osumc.edu
respectively. APOL1 G1 and G2 allele frequencies were lower than reported in west Africa and Kinshasa, the capital of DRC: 8.7% 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, 3 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). 3–7 Until now, no evolutionary advantage was found to explain this high frequency; in contrary, deleterious consequences have been suggested. 3–7 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 m² and 0.2% of the participants had eGFR <15 ml/min per 1.73 m² (CKD stage 5). 8 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. 5,6 In that analysis and the REGARDS study analysis, SCT did not...
interact with APOL1 HR genotype to further increase CKD progression.\textsuperscript{8,9} Similarly, both studies presented in the current issue of the \textit{KI Reports} report the association of SCT and CKD, albeit with contrasting results on APOL1 HR genotype and SCT interactions.\textsuperscript{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.

**REFERENCES**


