LETTER TO THE EDITORS

APOL1 screening of potential living kidney donors in resource-limited countries: an initial experience in Antigua & Barbuda and Nigeria

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Dear Editors,

The Apolipoprotein L1 (*APOL1*) gene plays an important role in determining risk for chronic kidney disease (CKD) and is prevalent in countries with large populations of African ancestry [1,2]. The effects of the presence of high-risk variants pose a challenge when considering kidney transplantation in endemic populations due to the potential detrimental effects on recipients and donors alike. For recipients, grafts from both living and deceased donors with two *APOL1* risk variant alleles are associated with shorter graft survival and decreased glomerular filtration rate (GFR) in comparison to those with zero or one variant [3]. Similarly, living donors with two risk variant *APOL1* alleles experience significantly decreased pre and postdonation GFR when compared to those with zero or one variant, precipitating the introduction of *APOL1* risk variant screening of potential living kidney donors (pLKDs) across many institutions in resource-rich settings such as the United States [4,5]. This is the first study to screen for *APOL1* risk variants in pLKDs located in Nigeria, and Antigua & Barbuda, countries with large populations of African descent.

In 2017, we initiated living donor transplantation pilot programs in Antigua & Barbuda and southeastern Nigeria. In establishing screening criteria for potential donors, *APOL1* testing was included and high-risk variants were determined to be an absolute contraindication (primarily due to lack of both deceased donation and access to kidney transplantation should a high-risk donor develop kidney failure). This letter reports our findings of *APOL1* risk variants among pLKDs during the course of establishing pilot living kidney transplant programs in the respective resource-limited countries.

Over a three-year period (2017–2020), pLKDs presenting to the pilot programs in both countries gave informed consent and were screened. Prior to the availability of testing, which began in 2018, four patients in Nigeria and two patients in Antigua & Barbuda proceeded with donation and were retrospectively tested. All other potential donors were prospectively screened. High-risk genotype was defined as two copies of an *APOL1* risk variant (e.g., G1G2, G1G1, G2G2). Patient samples were sent to Wake Forest Innovations for determination of *APOL1* high-risk status and genotyping was performed using QuantStudio 3 qPCR™ system. pLKDs were presented with results, counseled by the transplant surgeon, nephrologist, and transplant coordinator (if coordinators were available) on the decision to proceed with donation or not.

A total of 33 pLKDs were assessed for *APOL1* genotype, 21 from Nigeria and 12 from Antigua & Barbuda. Nigerian group, 76% ($n = 16$) were male and 24% ($n = 5$) were female, Antigua & Barbuda group 33% ($n = 4$) were male and 67% ($n = 8$) were female. The average ages were 32.4 (SD 9.1) and 35.9 (SD 10.1) for the Nigerian, and Antigua & Barbuda groups, respectively.

Regarding *APOL1* genotype, 42.8% (95% CI 0.217–0.640) of the Nigerian group and 41.7% (95% CI 0.138–0.696) of the Antigua & Barbuda group had high-risk *APOL1* genotype. Of the Nigerian group, 33.3% ($n = 7$) were homozygous for the G1 risk variant, while 9.5% ($n = 2$) of patients were compound heterozygous (G1/G2) and no patients were homozygous for the G2 risk variant. In Antigua & Barbuda, 16.7% ($n = 2$) of patients were homozygous for the G1 risk variant, 8.3% ($n = 1$) were homozygous for the G2 risk variant, and 16.7% ($n = 2$) were compound heterozygous (G1/G2). Of note, 83.3% ($n = 10$) of the

doi:10.1111/tri.13815

Antigua & Barbuda group and 76.2% ($n = 16$) of the Nigerian group had at least one high-risk *APOL1* allele. Of the patients who were retrospectively tested, one from Antigua & Barbuda and one from Nigeria were homozygous for high-risk *APOL1* variants. These donors who were retrospectively found to have two high-risk alleles have not had greater than expected loss of renal function after donation but are being monitored on an ongoing basis. Genotype prevalence is further reported in Table 1.

We report a high prevalence of high-risk *APOL1* genotype in potential kidney donors in Antigua & Barbuda (41.7%) and Nigeria (41.8%). High-risk genotype rates from this study are higher than those reported in black donors in the United States (14%), as is expected in endemic regions such as Nigeria and Antigua & Barbuda [6]. As a caveat, the average potential donor age in both Nigeria and Antigua & Barbuda is younger than the average donor in the United States.

The high prevalence of *APOL1* high-risk variants in potential kidney donors in this pilot study highlights an unmet need for screening of potential kidney donors in Nigeria, and Antigua & Barbuda. In the United States, a recent survey showed that 50% of transplantation programs offered *APOL1* testing, with some providers citing presence of two risk variants as an absolute contraindication to donation [7].

In resource-limited countries with large populations of West-African ancestry, where access to kidney transplantation and donors is severely limited, the presence *APOL1* high-risk variants could further exacerbate access to a life-saving operation in this setting. Preliminary findings in donors with two high-risk variants show lower baseline GFR and faster rates of renal function decline. Lifetime risk of developing focal segmental glomerulosclerosis or hypertension attributed ESRD in African Americans with two risk variants and no other significant comorbidities is estimated at 15%, leaving over 80% of African Americans with no significant loss of GFR [8]. Furthermore, comorbid conditions that may contribute to poorer outcomes such as obesity, hypertension, and diabetes are less prevalent in these resource-limited settings, which may act to counterbalance increased risks attributed to *APOL1* high-risk variants. The use of homozygous *APOL1* risk variants as an absolute contraindication to donation in resource-limited countries, estimated to exclude as many as 23% of potential African American donors in the United States, could exclude an important supply of donors who may not experience decreased GFR and further exacerbate the shortage of donors and lack of access to RRTs experienced in these settings [7,9]. Further information on absolute risks in donors with two high-risk variants and normal GFR at baseline is warranted.

Table 1. *APOL1* genotype prevalence by country.

	Prevalence % (*n*)	
Genotype	Antigua & Barbuda	Nigeria
G1/G1*	16.7 (2)	33.3 (7)
G2/G2*	8.3 (1)	0.0 (0)
G1/G2*	16.7 (2)	9.5 (2)
G1/normal	33.3 (4)	28.6 (6)
G2/normal	8.3 (1)	4.8 (1)
normal/normal	16.7 (2)	23.8 (5)
Total	100 (12)	100.0 (21)
High risk	41.7 (5)	42.8 (9)

*Indicates high risk genotype.

This feasibility study is the first to assess pLKDs in resource-limited countries with endemic presence of *APOL1* risk variants. Our findings suggest a high prevalence of high-risk *APOL1* genotype in potential kidney donors in both Nigeria, and Antigua & Barbuda. The limited sample size and emerging utilization of kidney transplantation in these settings provide insight, but not conclusion. A large, prospective study examining the long-term outcomes in donor-recipient pairs with variations in donor and recipient *APOL1* genotypes in the United States is currently underway [10]. Due to the complexity of APOL1 risk variant effects on outcomes, however, results from African Americans may not be applicable in these settings, and further studies are necessary in Antigua & Barbuda, Nigeria, West-Africa and other settings with a large population of African ancestry. The ethical considerations of *APOL1* screening have been discussed elsewhere and are beyond the scope of this letter. We invite further discussion regarding these implications in resource-limited settings going forward.

Funding

The authors have declared no funding.

Conflict of interest

The authors have no conflicts of interest to disclose at this time.

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Transplant International 2021; 34: 590–592