

APOL1-Associated Kidney Disease in Brazil



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Introduction: Coding variants in apolipoprotein L-1 (APOL1) are associated with an increased risk of end-stage kidney disease (ESRD) in African American individuals under a recessive model of inheritance. The effect of the APOL1 risk alleles on kidney disease has been observed in studies in African American and African populations. Despite the 130 million individuals of recent African ancestry in South America, the impact of APOL1 has not been explored.

Methods: In this case-control study, we tested APOL1 genotype in 106 Brazilian HD (hemodialysis) patients with African ancestry and compared risk allele frequency with 106 healthy first-degree relatives. The association of risk alleles and ESRD was calculated with a linear mixed model and was adjusted for relatedness and additional confounders. In a broader survey, the age of dialysis initiation and APOL1 variants were analyzed in 274 HD patients.

Results: Two APOL1 risk alleles were 10 times more common in patients with ESRD than in controls (9.4% vs. 0.9%; odds ratio [OR]: 10.95, SE = 1.49, $P = 0.0017$). Carriers of 2 risk alleles initiated dialysis 12 years earlier than patients with zero risk alleles.

Conclusion: The APOL1 risk variants were less frequent in dialysis patients of African ancestry in Brazil than in the United States. Nonetheless, carriers of 2 risk variants had 10-fold higher odds of ESRD. Age of dialysis initiation was markedly lower in 2-risk allele carriers, suggesting a more aggressive disease phenotype. The Brazilian population represents an opportunity to identify different sets of genetic modifiers or environmental triggers that might be present in more extensively studied populations.

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KEYWORDS: age of dialysis initiation; APOL1; APOL1-associated kidney disease; end-stage kidney disease; genetics; South America

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African American individuals have a 3- to 4-fold higher risk of end-stage renal disease (ESRD) when compared with white individuals.¹ Genetic studies have demonstrated that specific apolipoprotein L-1 (APOL1) coding variants are linked to increased

risk of nondiabetic chronic kidney disease, focal segmental glomerulosclerosis, and HIV-associated nephropathy in patients of recent African ancestry.^{2–5} Two allelic variants have been identified, named G1 (S342G and I384M, 2 missense variants) and G2 (N388del:Y389del, a 6 base pair deletion), which both result in altered APOL1 protein sequence within a domain responsible for anti-trypanosome activity.³ These APOL1 variants appear to confer resistance to trypanosome infection that caused their frequency to rise in sub-Saharan Africa.^{6,7} Whereas 2 risk variants are required to increase the risk of kidney disease, 1 risk allele appears sufficient to protect against African sleeping sickness. Notably, G1 and G2 risk alleles are not observed in populations without recent African ancestry.⁸

Unlike genetic variants that cause monogenic diseases and are defined by a low allele frequency with

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high penetrance or common complex disease variants that are common but individually have weak effects, APOL1 risk variants are both common and relatively strong. Thirteen percent of African American individuals carry 2 risk alleles and their risk of many forms of kidney disease is dramatically higher than those who carry 0 or 1 risk allele.^{3,9–11} Not all individuals with 2 risk alleles develop kidney disease, indicating that important genetic modifiers or environmental factors remain to be discovered.^{5,12} Although cell and animal models are important for discovering APOL1 pathophysiology, human studies remain critical for understanding the real-world correlates of experimental systems. Studying APOL1 in a range of different populations and environments may lead to insights about APOL1 biology that have more immediate implications for preventing kidney disease.

During the period of the Atlantic slave trade, the slave traffic between Africa and Portuguese Americas (now Brazil) was more than double the volume to the British Americas (North America).¹³ It is estimated that more than 130 million people of African ancestry live in South America.¹⁴ The different trade routes and subsequent differing patterns of admixture have led to a black population in South America that differs significantly from US black populations. Although we expect APOL1 to be present in Brazil, the frequency and the impact on kidney disease is unknown. Brazil, the most populous country in South America with more than 200 million people, was primarily a Portuguese colony and has mixed ethnicity, with approximately 48% primarily European ancestry, 8% primarily African ancestry, 43% of mixed ancestry, and 1% Asian ancestry, although frequencies can vary widely depending on the geographic region.¹⁵ Despite the presence of more than 120,000 dialysis patients in Brazil, with more than 106 million individuals being of African or mixed ancestry, there are no reported estimates of APOL1 frequency or whether the APOL1 risk variants have similar effects on kidney disease as observed in the United States.¹⁶ High rates of focal segmental glomerulosclerosis in Brazil, with similar enrichment of disease in Brazilians of recent African origin, suggested APOL1 was likely to be important in this understudied population.^{17,18} To begin answering these questions, we performed genetic studies of APOL1 in Brazilian HD patients and their unaffected relatives to determine whether APOL1 nephropathy represents a public health problem in Brazil similar to the United States. We then broadened our study to a wider population of HD patients and asked whether APOL1 genotype led to earlier age at HD initiation, suggestive of a more aggressive disease.

METHODS

Study Participants

We examined for eligibility a total of 1124 HD patients in 8 different dialysis centers. Recruitment and sample collection took place between July 2015 and April 2017. Institutional review board approval was obtained from Beth Israel Deaconess Medical Center (Boston, MA) and the National Committee for Ethics in Research (Brasilia, Brazil). We acquired written informed consent from all participants. After the initial screening, 445 patients self-identified as having African ancestry. A total of 151 patients did not meet disease inclusion criteria (obstructive, autoimmune, or genetic etiology, below the age cutoff of 18 years) and 20 patients declined to participate. A total of 274 HD patients were included in the study but only 106 had a matched first-degree relative and therefore were included in the ESRD outcome analysis. Age of dialysis initiation analysis included the 274 patients. First-degree relatives of enrolled patients were invited to volunteer as controls. The participating dialysis centers are located in 2 distinct regions of Brazil, 5 in Curitiba, in the southern part of Brazil, and 3 in Maceió, located in the northeastern area of the country. The clinical data were collected by nurses and physicians who were part of the study protocol. Blood samples were collected in EDTA tubes and kept at -20°C until DNA extraction.

Genotype Analysis

DNA from blood was extracted with the QIAamp Blood Maxi Kit (Qiagen, Hilden, Germany) protocol. After extraction, we assessed DNA integrity with Nanodrop 260/280 ratio. The samples were diluted down to 20 ng/ μl , the final concentration used for the reverse-transcriptase polymerase chain reaction. The assay consisted of 2 reactions, with 2 sets of TaqMan probes each. The G1 assay has 1 probe complementary to the G1 site and another complementary to the G0 sequence at the same single nucleotide variant coordinate. The same principle is applied to the G2 assay, with 1 probe detecting the G2 sequence and another G0 at the same coordinate of the 6 base pair deletion. Each probe is tagged with a different fluorophore, therefore allowing it to be multiplexed with 2 probes per well. Each assay plate run included human positive controls for the combination of genotypes: G0/G0, G0/G1, G0/G2, G1/G1, G2/G1, G2/G2, assayed with both G1 and G2 TaqMan probes. Genotype calling was then made based on the positive controls with 98.4% to 100% allele call accuracy. Amplification results were interpreted with the QuantStudio Real-Time PCR Software V1.2 (Applied Biosystems, Foster City, CA).

Statistical Analysis

The statistical analysis was performed with the software STATA, version 14 (Stata Corp, College Station, TX). The sample size was estimated for a matched case-control study with the following parameters: power of 0.8 and alpha of 0.05, an OR of exposure of 4, a probability of exposure of 0.1, which outputted an estimated sample size of 94 cases. Regarding the **Table 1** significance analysis, a *t*-test was used for all normally distributed continuous variables and reported as mean and SD; non-normally distributed variables were displayed as median and interquartiles. A χ^2 test was used to determine distribution of categorical variables across groups. Multivariable linear regression was used with continuous dependent variables such as the age of dialysis initiation. Gemma software (Xiang Zhou Lab, University of Michigan, Ann Arbor, MI) was used to run a linear mixed model to determine the relationship between ESRD outcome and APOL1 risk variants. The model was adjusted for age, gender, body mass index, smoking history, diabetes status, and relatedness by genetic relationship matrix. The beta value from the linear mixed model was transformed to OR with the Shiny application (<http://cnsgenomics.com/shiny/LMOR/>). In respect to subgroup analysis, linear regression model followed by *F* test was used to determine the significance of age of dialysis initiation distribution for each genotype. There were no variables with missing values in the logistical or linear regression analyses. The Hardy-Weinberg equilibrium test was performed by a likelihood ratio test (HWLratio) in the R package of "HardyWeinberg."¹⁹

RESULTS

Baseline Characteristics and APOL1 Variants Frequency

A total of 106 patients with ESRD and 106 first-degree relative controls were included in the first phase of the study. An additional 168 HD patients were enrolled in the study and genotyped for analysis of age of dialysis initiation. The mean age of the ESRD group was 53.6 years as compared with 40.5 years in the controls. There were more women in the control group than in the ESRD group. As expected, comorbidity rates were higher in the ESRD group, with higher rates of diabetes, hypertension, coronary artery disease, and mean systolic blood pressure (**Table 1**). With regard to smoking history, 21.7% of the ESRD group were active smokers versus 13.3% of controls. The frequency of genotypes with 1 risk allele (G0/G1 or G0/G2) did not differ between groups. In contrast, the 2-risk allele frequency (G1/G1, G2/G2, or G1/G2, termed high-risk [HR] genotype hereafter) was more than 10 times higher in the ESRD group (9.4% vs. 0.9%) (note that

Table 1. Participant characteristics

Variables	Controls (n=106)	HD patients (n=106)	P
Age (yr), mean (\pm SD)	40.5 (13.1)	53.6 (16.4)	<0.001 ^a
Women, n (%)	70 (66)	52 (49.1)	0.012 ^b
Systolic BP (mm Hg), mean (\pm SD)	124.2 (24.3)	144.3 (26.7)	<0.001 ^a
Diastolic BP (mm Hg), mean (\pm SD)	80.2 (12.9)	80 (10.6)	0.91 ^a
Body mass index, mean (\pm SD)	28.9(6.3)	24.6(4.25)	<0.001 ^a
Race, n (%)			0.192 ^b
Black	34(32)	24(22.9)	
Mixed	72(68)	81(77.1)	
Household income (times minimum wage), n (%)			0.6 ^b
<1	28 (26.4)	35 (33)	
1–3	56 (52.8)	48 (45.3)	
3–5	11 (10.4)	13 (12.3)	
>5	3 (2.9)	5 (4.7)	
Did not answer	8 (7.5)	5 (4.7)	
Education, n (%)			<0.001 ^b
Illiterate	0 (0)	12 (11.3)	
Elementary school	39 (36.8)	60 (56.6)	
High school	45 (42.5)	28 (26.4)	
Postsecondary education	18 (17)	6 (5.7)	
Did not answer	4 (3.7)	0 (0)	
Hypertension, n (%)	26 (24.8)	92 (86.8)	<0.001 ^b
Diabetes mellitus, n (%)	5 (4.8)	36 (34)	<0.001 ^b
Smoking status, n (%)			0.025 ^b
Active	14 (13.3)	23 (21.7)	
Former	3 (2.9)	10 (9.4)	
Coronary artery disease, n (%)	1 (0.95)	13 (12.3)	0.001 ^b
Congestive heart failure, n (%)	1 (2.1)	7(14.6)	0.27 ^b
Creatinine, blood ^c (mg/dl), median (IQR)	0.79 (0.71–0.95)	–	–
eGFR MDRD ^c (ml/min), mean (\pm SD)	115.9 (28.4)	–	–
Albumin-to-creatinine ratio ^c (mg/g), median (IQR)	4 (2–22)	–	–
APOL1 genotypes, n (%)			0.079 ^b
G0G0	91 (85.9)	82 (77.4)	
G0G1	11 (10.4)	12 (11.3)	
G0G2	3 (2.8)	2 (1.9)	
G1G1	1 (0.9)	5 (4.7)	
G2G2	0	0	
G1G2	0	5 (4.7)	
Number of APOL1 risk alleles, n (%)			0.001 ^b
1 risk allele	14 (13.2)	14 (13.2)	
2 risk alleles	1 (0.9)	10 (9.4)	

APOL1, apolipoprotein L-1; BP, blood pressure; eGFR, estimated glomerular filtration rate; HD, hemodialysis; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease.

^aThe *t*-test was used for normally distributed continuous variables and reported as mean \pm SD.

^bChi-squared test was used to determined distribution of categorical variables across groups.

^cNon-normally distributed variables are displayed as median and interquartile (IQR).

G1 and G2 are located on 2 different haplotypes and are generally mutually exclusive, thus they are rarely if ever present on the same chromosome). Risk alleles were present at higher frequencies in patients without diabetes, both 1 and 2 copies (**Table 2**).

Table 2. Relationship of diabetes status and risk alleles in hemodialysis patients

Diabetes status	Number of risk alleles				P
	0 risk alleles	1 risk allele	2 risk alleles	Total	
					0.044 ^a
No diabetes, n (%)	124 (66)	35 (18.6)	29 (15.4)	188 (100)	
Diabetes present, n (%)	68 (79.1)	13 (15.1)	5 (5.8)	86 (100)	
Total	192 (70.1)	48 (17.5)	34 (12.4)	274 (100)	

^aChi-squared test was used to determined distribution of diabetes status across groups.

The APOL1 High-Risk Genotype Was Associated With Higher Odds of ESRD

We computed a linear mixed model to quantify the risk associated with the presence of the HR genotype on ESRD outcome. Under a recessive model, the HR genotype conferred 10.95 higher odds of ESRD when compared with 1 and 0 risk allele genotypes (SE 1.49, $P = 0.0017$). To control for confounding factors, other ESRD risk factors were included as covariates in the model (age, gender, body mass index, smoking history, diabetes status). Hypertension was not included in the model because it is confounded with APOL1-associated kidney disease.^{20,21} The presence of 1-risk allele (dominant model) did not confer significant risk for ESRD (data not shown).

Patients With the HR Genotype Initiated Hemodialysis 12 Years Younger Than Non-HR Genotype Carriers

Age of dialysis initiation is a proxy for disease aggressiveness. To extend our power, we included 168 additional patients with ESRD for a total of 274 individuals (cohort characteristics in Table 3) to study this question. In an unadjusted analysis, HR genotype carriers started HD 12 years younger than non-HR genotype carriers (coefficient -12.3 , $P < 0.001$, 95% confidence interval [CI]: -18.1 to -6.5) (Figure 1). A single risk allele did not achieve statistical significance but showed a weak trend toward starting HD earlier (coefficient -2.96 , $P = 0.255$, 95% CI: -8.09 to 2.15). We then modeled the age of HD initiation with multivariable linear regression to better understand the effect of confounders. After adjusting for gender, smoking history, body mass index, and diabetes mellitus, HR genotype carriers started HD 9 years younger than non-HR genotype carriers (coefficient -8.97 , $P < 0.001$, 95% CI: -14.39 to -3.56). Last, we compared the individual genotype combinations for the age of HD initiation. Genotypes G1/G1 and G1/G2 were significantly associated with younger age at HD initiation (G1/G1: coefficient -13.8 , $P < 0.001$ and G1/G2: coefficient -11.1 , $P = 0.017$). There were not enough

Table 3. Full hemodialysis patient cohort characteristics

Variables	Full patient cohort (n = 274)
Age (yr), mean (\pm SD)	52.1 (15)
Woman, n (%)	117 (43)
Systolic BP (mm Hg) mean (\pm SD)	141 (26)
Diastolic BP (mm Hg) mean (\pm SD)	79.3 (11)
body mass index, median (IQR)	23.9 (21–27)
Race, n (%)	
Black	53 (19.6)
Mixed	208 (77)
Hypertension, n (%)	240 (87.6)
Diabetes mellitus, n (%)	86 (31.4)
Smoking status, n (%)	
Active	60 (25.1)
Former	23 (8.4)
Coronary artery disease, n (%)	21 (7.6)
Congestive heart failure, n(%)	10 (8.2)
APOL1 genotypes, n (%)	
G0G0	192 (70.1)
G0G1	38 (13.8)
G0G2	10 (3.6)
G1G1	19 (6.9)
G2G2	2 (0.7)
G1G2	13 (4.7)
Number of APOL1 risk alleles, n(%)	
1 risk allele	48 (17.5)
2 risk alleles	34 (12.4)
Age of dialysis initiation, mean (\pm SD)	
0/1 risk alleles	46.1 (16.5)
2 risk alleles	33.7 (13.2)

APOL1, apolipoprotein L-1; BP, blood pressure.

G2/G2 homozygotes to make a meaningful comparison but individuals with this genotype also reached ESRD at younger ages, consistent with studies in the United States (Figure 2).

CONCLUSION

APOL1 risk alleles arose in West Africa several thousand years ago, rose to high frequency quite

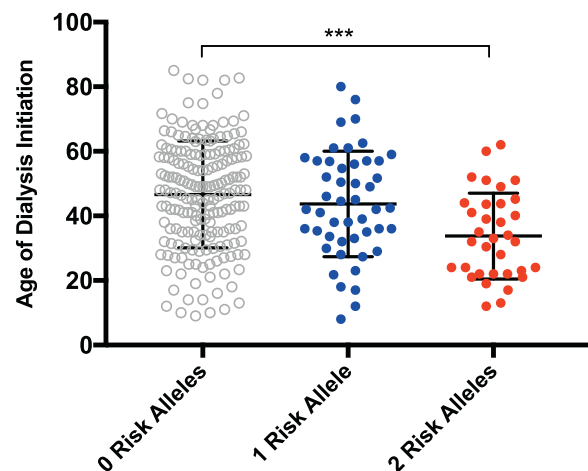


Figure 1. Age of dialysis initiation by number of APOL1 risk alleles. *** $P < 0.001$.

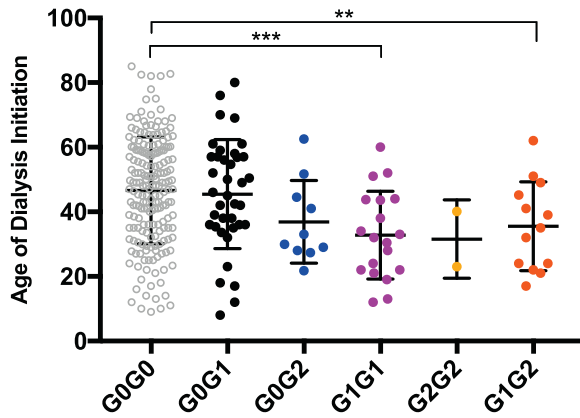


Figure 2. Age of dialysis initiation by APOL1 genotype. ** $P = 0.017$; *** $P < 0.001$.

quickly driven by enhanced activity against trypanosomes, and subsequently spread beyond the regions where they originated.^{7,22,23} These alleles moved eastward and southward in Africa during the Bantu expansion and were carried to the New World in slave ships starting approximately 500 years ago. APOL1 risk alleles are now relatively common in the Americas, and particularly enriched in patients with kidney disease. The impact of these alleles on kidney disease in the United States has been widely chronicled.^{3,5,24,25} Here, we show that they also have powerful effects in carriers in South America, specifically Brazil, where more than 100 million people have recent African ancestry. We find that though the risk alleles are less frequent in Brazilians of African ancestry than in the United States (Table 4), they do confer a strong predisposition to the development of kidney disease and also cause particularly aggressive kidney disease phenotypes.

We found that individuals with the high-risk APOL1 genotype were enriched by more than 10-fold among HD patients compared with their unaffected

first-degree relatives. Although our sample size is too small for accurate estimates of ORs, the effects in Brazil appear to be of a similar order as in the United States, where case-control series in African American individuals demonstrate large effect sizes for hypertension-attributed ESRD (OR: 7.3),³ focal segmental glomerulosclerosis (OR: 17),^{4,5} lupus collapsing glomerulopathy (OR: 5.4),²⁶ and HIV-associated nephropathy (OR: 29)⁵ (Table 5). Among Hispanic American individuals with African ancestry, APOL1 risk allele frequency is lower than among self-identified black individuals, but APOL1 effect size for 2 risk alleles remains at least as large.^{10,11} Our complex admixed population in Brazil includes both individuals of predominantly African ancestry but likely many more with self-reported mixed ancestry that often includes more than 2 ancestral populations.¹⁵ Unlike US populations in which African American individuals tend to have approximately 80% African ancestry and 20% European ancestry regardless of region, in Brazil there is much more heterogeneity, with considerably more African ancestry in the north of Brazil than the south.^{27,28}

Of the 274 total HD patients studied for age of initiation, patients with 2 APOL1 risk alleles needed dialysis approximately 12 years earlier than those with 0 or 1 risk allele. Adjustments for other risk factors attenuated this difference to approximately 9 years. The early age of dialysis in patients with 2 APOL1 risk variants does suggest that APOL1 kidney disease is more severe than non-APOL1-associated types, either in earlier onset or more rapid progression. In either case, the results suggest that 10-fold increased OR for disease occurrence underestimates the human impact of these alleles on kidney disease because younger people are disproportionately affected. These results are similar to studies in the United States that also show earlier age of HD initiation in 2 risk variant carriers.^{29,30} Our sample was not large enough to help clarify whether the reported effect of a single risk allele on dialysis initiation age in other studies is signal or noise.^{5,29,30}

Table 4. APOL1 risk allele frequency across healthy populations

Country	Population	n	% of G1	% of G2	Reference
Brazil	Mixed ancestry	106	6	1.4	Current study
Central Africa Republic	Biaka Pygmy	36	4	8	HGDP ^a
Ethiopia	Afar	76	0	0	U.C.L. ^b
Ghana	Akan	171	47	11	Thomson <i>et al.</i> ²²
Kenya	Kikuyu	112	5	6	Thomson <i>et al.</i> ²²
Nigeria	Yoruba	113	38	7	Hapmap
Senegal	Mandenka	24	5	20	HGDP ^a
Somalia	Somali	30	5	7	Thomson <i>et al.</i> ²²
South Africa	Mixed ancestry	859	3.6	5.8	Matsha <i>et al.</i> ²¹
USA	African American	3067	22	13	Foster <i>et al.</i> ²
USA	African American	3764	21	13	Udler <i>et al.</i> ¹¹
USA	African American	1825	22	15	Friedman <i>et al.</i> ⁹

^aHuman Genome Diversity Project.

^bThe Center for Anthropology at University College London.

Table 5. Case-control studies and odds of kidney disease

Year	Reference	Type of outcome	Odds ratio
2010	Genovese <i>et al.</i> ³	Focal segmental glomerulosclerosis	10.5
2010	Genovese <i>et al.</i> ³	Hypertension-attributed ESRD	7.3
2011	Kopp <i>et al.</i> ⁵	HIV-associated nephropathy	29
2011	Kopp <i>et al.</i> ⁵	Focal segmental glomerulosclerosis	17
2011	Papeta <i>et al.</i> ⁴	Focal segmental glomerulosclerosis and HIV-associated nephropathy	10.9
2013	Larsen <i>et al.</i> ²⁶	Lupus collapsing GN	5.4
2019	Current study	Diabetic and nondiabetic ESRD	10.95

ESRD, end-stage kidney disease; GN, glomerulonephritis.

Our study, designed as a pilot exploration of APOL1 in Brazil, has limitations. First, our sample was not large enough to determine accurate ORs for APOL1 risk variants. Second, our use of unaffected first-degree relatives as controls mitigates but does not eliminate concerns about population stratification.^{31,32} However, the similarity of the effects of APOL1 in the United States and Brazil, and the unusually large ORs (>10) for disease risk make false associations due to ancestry very unlikely. As expected, and as seen in US-based studies, APOL1 risk alleles are in Hardy-Weinberg equilibrium in controls but not in cases, with similar rates of heterozygotes between groups but very different rates of risk homozygotes, supporting an association driven by enrichment of HR homozygotes among cases. The use of first-degree relatives as controls may cause the tendency toward underestimation of the associated risk of HR genotype and ESRD outcome.³¹ This occurs because relatives of HR genotype carriers are more likely to have 1 or more risk alleles than a person selected at random from the general population.^{31,33}

In the future, this highly admixed population in Brazil with considerable genetic heterogeneity and wide range of micro-environments may be highly advantageous in the search for genetic and environmental modifiers of APOL1. Common infections with tropical febrile diseases (e.g., dengue, zika, yellow fever, malaria) may be a good opportunity to study environmental triggers of APOL1 kidney disease. Our current study justifies deeper interest in APOL1 in Brazil and throughout the wider region of Latin America.

DISCLOSURE

MRP and DJF have filed patents related to APOL1-associated kidney disease, and DJF and MRP own equity in ApoLo1 Bio, LLC. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

STROBE Statement.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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