

New Insights into APOL1 and Kidney Disease in African Children and Brazilians Living With End-Stage Kidney Disease



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See Clinical Research on Pages 923 and 930

In 2010, the discovery that variants of the *APOL1* gene, which encodes the apolipoprotein L1 protein, confers increased risk for kidney disease was one of the most significant advances in decades in our knowledge of the pathogenesis of common kidney diseases.¹ *APOL1* genetic variants account for the majority of excess risk for hypertension-attributed end-stage kidney disease (ESKD) (7-fold), focal segmental glomerulosclerosis (17-fold), and HIV-associated nephropathy (29–89-fold).²

Two *APOL1* alleles, termed G1 and G2 (G0 is wild type), are associated with increased risk of kidney disease. The G1 allele encodes 2 missense mutations, and the G2 allele encodes a 2-amino acid in-frame deletion. Persons who are heterozygous for the G1 or G2 alleles are protected from African sleeping sickness and are not at increased risk

of kidney disease. However, those who are homozygous for G1 or G2, or are G1/G2 compound heterozygotes, have a marked increased risk of kidney diseases.¹

The *APOL1* gene is induced by proinflammatory stimuli and has roles in innate immunity. The best-characterized function of *APOL1* is to protect against African sleeping sickness, which is caused by subspecies of *Trypanosoma brucei*. Plasma *APOL1* is a constituent of HDL3, and when these HDL particles are ingested by susceptible trypanosomes, *APOL1* kills the parasites by forming pores in lysosomal membranes, leading to membrane rupture.³

The *APOL1* G1 and G2 alleles are found only in persons of African ancestry and are thought to have arisen in Africa within the past 5000 years, which is after the human ancestors who populated the other continents migrated out of Africa. The prevalence of the G1 and G2 alleles has been driven by natural selection in Africa.² Previous studies of the incidence of *APOL1* alleles in

Africa have reported highly variable frequencies of the risk alleles. The highest prevalence of *APOL1* risk alleles is found in Western Africa. In Nigeria, the frequency of the G1 and G2 alleles is as high as 49% and 17%, respectively, but these alleles are nearly absent in Eastern African countries such as Ethiopia. Whereas the G1 allele is highly concentrated in Western Africa, with markedly lower frequencies in other regions, the G2 allele is less common than G1 in Western Africa but is more widely distributed across the continent.³

The prevalence of high-risk genotypes (2 risk alleles) varies accordingly and is as high as 23% in some Western African populations. The frequency of *APOL1* risk alleles can also vary significantly among ethno-linguistic groups within local regions.³ Further, since 26 million of the 37 million HIV-positive persons worldwide live in Africa,⁴ and *APOL1* high-risk genotypes confer a 29–89-fold increased risk of HIV-associated nephropathy,⁵ it is critically important to better understand the distribution of *APOL1* risk alleles and their contribution to kidney disease risk in Africa.

Most previous studies that have examined the relationship between *APOL1* and kidney disease in Africa have focused on adults. In this issue of *Kidney International Reports*, Ekulu *et al.*⁶ report the prevalence of *APOL1* genotypes in 813 children (401 HIV-positive and 412 from the general population) recruited from Kinshasa, the capital of the Democratic Republic of the Congo and report associations with estimated glomerular filtration rate and albuminuria.⁶ Children from the general population were recruited from churches from 4 districts in Kinshasa, with efforts made to include children from socioeconomically diverse areas. Only one child was recruited from

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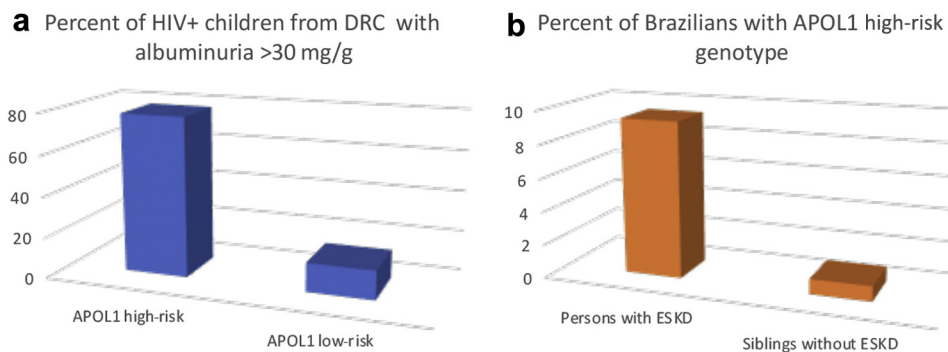


Figure 1. HIV-positive children from the Democratic Republic of Congo (DRC) with *APOL1* high-risk genotypes have an increased risk of albuminuria (a), and Brazilians with end-stage kidney disease (ESKD) receiving hemodialysis are more likely to have *APOL1* high-risk genotypes than siblings without ESKD (b).

each family. HIV-positive children not receiving potentially nephrotoxic antiretroviral medications were recruited from pediatric HIV clinics in Kinshasa, and the authors state that the children were not related to each other, although how this was determined was unclear.

Of the 412 children from the general population, the frequency of the G1 and G2 alleles was 12.4% and 10.4%, respectively, and 7% had high-risk genotypes. Those with high-risk *APOL1* genotypes had a lower estimated glomerular filtration rate (91 vs. 97 ml/min per 1.73 m²) and a nonsignificant trend toward higher levels of albuminuria.

Of the 401 HIV-positive children, the frequency of the G1 and G2 alleles was 13.5% and 9.6%, respectively, and 5.7% had high-risk genotypes. In contrast to the general population, HIV-positive children with high-risk *APOL1* genotypes did not have a lower estimated glomerular filtration rate but did have a higher prevalence of albuminuria >30 mg/g compared to HIV-positive children with low-risk genotypes (78% vs. 14%), respectively (Figure 1a). Multivariable analysis revealed that among HIV-negative children, high blood pressure, but not *APOL1* genotype, was associated with albuminuria. In contrast, in HIV-positive children, *APOL1* genotype and HIV

plasma RNA levels >1000 copies/ml were associated with increased albuminuria.

This study⁶ provides new information regarding the frequency of *APOL1* renal risk alleles in the Democratic Republic of Congo. Importantly, this is the largest study to date to examine the frequency of *APOL1* genotypes and correlate them with kidney disease in African children. Further, the authors found that *APOL1* high-risk genotypes are associated with lower estimated glomerular filtration rate values (although they are still in the normal range) in healthy children and with a markedly increased prevalence of albuminuria in HIV-positive children. They also found that incomplete suppression of HIV viremia is associated with increased albuminuria. The strong association with albuminuria in the setting of HIV infection provides evidence that HIV can serve as a potent “second hit” to promote glomerular injury in HIV-positive children, as has been reported for adults.

However, there are limitations to this study. Although the authors excluded children who were known to be related to each other, the study design was unable to exclude the possibility of population stratification, which may have accounted for imbalances in the

frequency of *APOL1* alleles. Also, given that the prevalence of *APOL1* risk alleles varies widely between ethno-linguistic groups living within the same regions within Africa, these data likely cannot be extrapolated to children elsewhere in the Democratic Republic of Congo or surrounding African countries.

In the United States, where most African Americans are of West African ancestry, the frequency of G1 and G2 alleles in African Americans is 23% and 14%, respectively, and approximately 13% of African Americans have 2 *APOL1* risk alleles.² Despite the fact that far more Africans were transported to South America than to North America during the trans-Atlantic African slave trade, little is known regarding the frequency of *APOL1* risk alleles and their contribution to kidney disease in South America. Brazil has a higher proportion of persons of African ancestry than most other regions of South America, and even within Brazil, the proportion of African ancestry varies from >50% in some northern regions to 15% in southern Brazil.⁷ Approximately 100 million Brazilians self-identify as persons of African or mixed ancestry.

Riella and coworkers, in this issue,⁸ report the results of a

case-control study comparing the frequency of APOL1 genotypes in patients receiving hemodialysis to that in first-degree family members without ESKD, and of another study in which they compared the age of ESKD onset in patients with APOL1 high-risk genotypes to that in those with low-risk genotypes. This study was performed at 3 centers in northeastern Brazil, where there is a higher prevalence of African ancestry, and 5 centers in southern Brazil, where African ancestry is less common. When the investigators compared 106 patients receiving hemodialysis with 106 unaffected relatives, the frequency of APOL1 high-risk genotypes was more than 10-fold higher (9.4% vs. 0.9%) in those receiving hemodialysis (Figure 1b). In both groups, 13% were heterozygous for either G1 or G2, and heterozygosity for these alleles was not associated with increased prevalence of ESKD. They also compared the age of ESKD onset in 34 hemodialysis patients with high-risk APOL1 genotypes versus 240 hemodialysis patients with low-risk genotypes. After controlling for multiple variables, APOL1 high-risk genotypes were associated with starting hemodialysis 9 years earlier than in those with low-risk genotypes.

This study demonstrates that APOL1 high-risk genotypes are common among Brazilians receiving hemodialysis, and that APOL1 high-risk genotypes are associated with younger age of onset of ESKD. APOL1 genotype in kidney donors is strongly associated with donor allograft function,

and it may also increase the risk of future chronic kidney disease in living donors.⁹ These data may, therefore, have important implications regarding whether genetic testing may be appropriate in Brazilians being evaluated as kidney donors. Further, since non-African genetic loci may modify the risk of kidney disease attributed to APOL1 variants,² the highly admixed and diverse population of Brazil promises to be a valuable environment for future admixture mapping studies to identify genetic loci that alter APOL1-associated risk for kidney disease.

As in the study by Ekulu *et al.*,⁶ the authors⁸ are not able to exclude the possibility that population stratification, due to differences in ancestry and not APOL1 alleles alone, contributed to the excess genetic risk attributed to APOL1. However, given that these data are similar to those reported from the United States, population substructure appears unlikely to be a major driver of the observed associations.

In conclusion, these studies provide important new insights that broaden our knowledge of the contribution of APOL1 risk alleles to kidney disease in African children in the Democratic Republic of Congo and in Brazilians living with ESKD. This information can be used to inform both future efforts to target surveillance for kidney disease in high-risk groups in Africa and South America and studies to identify novel approaches to prevent and treat kidney disease in persons with high genetic risk.

DISCLOSURE

The author declared no competing interests.

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