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# APOL1-Mediated Kidney Disease

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## Introduction

According to the United States Renal Data System 2020 Annual Data Report, 30% of patients with end-stage kidney disease (ESKD) in the US are Black individuals, although they comprise only 13% to 14% of the population. In 2010, researchers identified 2 common variants of the *APOL1* (apolipoprotein L1) gene (G1 and G2), which account for much of the excess nondiabetic chronic kidney disease (CKD) risk among Black individuals in the US.[1,2] This review explains the evolutionary origin of *APOL1* high-risk genetic variants, defines APOL1-mediated kidney disease (AMKD), and discusses recommendations for AMKD screening and management.



## *APOL1* and Trypanosomiasis

The wild-type *APOL1* gene (G0) was identified in 2003 as the component of human serum that confers resistance to *Trypanosoma brucei*, the cause of African trypanosomiasis (sleeping sickness). The *APOL1* gene encodes an innate immune pore-forming protein that inserts into the trypanosome's lysosomal membrane, inducing osmotic stress and ultimately lysing the trypanosome. Approximately 10 000 years ago, 2 novel *T brucei* strains emerged in Africa that were resistant to the G0 immune response and therefore caused African sleeping sickness. The G1 and G2 variants of the *APOL1* gene restored immune protection against the novel *T brucei* strains and underwent positive selection in West Africa.

## Genetics of *APOL1*

The risk of kidney disease associated with the *APOL1* G1 and G2 alleles follows a recessive inheritance pattern. Individuals who are heterozygous for a G1 or G2 variant (G1/G0 or G2/G0) are resistant to African sleeping sickness but do not have increased risk of kidney disease. However, individuals with 2 alleles of *APOL1* G1 or G2 variants (G1/G1, G2/G2, or G1/G2) have an increased risk of kidney disease and are collectively known as the *APOL1* high-risk genotype.[1]

The allele frequencies of G1 and G2 vary across different populations worldwide. The prevalence of these high-risk alleles is highest in West African populations. In different populations in Nigeria, G1 allele frequency has been reported to be 37% to 45%, and G2 frequency has been estimated to be 7.5% to 17%.[2] Among Black individuals in the US, the G1 allele frequency is 22% and G2 allele frequency is 13%.[2] Approximately 13% of Black individuals in the US (more than 5 million people) have a high-risk *APOL1* genotype.[3] High-risk alleles are also found frequently in sub-Saharan African, Western African, Caribbean, Central American, and South American populations.[4]

## *APOL1*-Mediated Kidney Disease

Recent experimental evidence suggests that the G1 and G2 variants may cause kidney injury by increased transport of monovalent cations—similar to the mechanism by which G1 and G2 provide resistance to *T brucei*.[5,6]

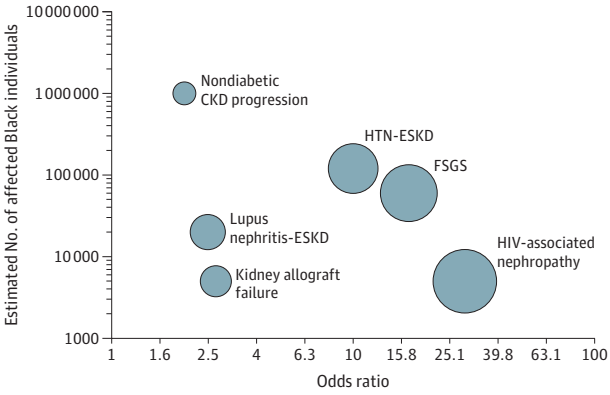
Individuals with a high-risk *APOL1* genotype have been estimated to have a 15% to 30% lifetime risk of developing ESKD.[3] The basis of this variable penetrance is currently unknown. AMKD is diagnosed when an individual with a high-risk *APOL1* genotype develops nondiabetic kidney disease. There is no established glomerular filtration rate (GFR) cutoff to diagnose AMKD. Proteinuria (urine albumin to creatinine ratio >30 mg/g) is often present but is not a requirement for the diagnosis of AMKD.

Approximately 75% of Black individuals in the US with focal segmental glomerulosclerosis (FSGS) have been estimated to have a high-risk *APOL1* genotype.[4] Black individuals in the US with a high-risk *APOL1* genotype are also more likely to develop hypertension-attributed ESKD, lupus nephritis–attributed ESKD, FSGS, and HIV-associated nephropathy compared with Black individuals who have a low-risk *APOL1* genotype (**Figure**). A recent study reported that 25.8% of patients with COVID-19–associated kidney injury had collapsing glomerulopathy, and 91.7% of these patients had a high-risk *APOL1* genotype.[7]

## Screening for High-Risk *APOL1* Genotype and AMKD

Screening of asymptomatic individuals in the US for high-risk *APOL1* genotype is not currently recommended. Individuals identified as

**Figure. APOL1-Mediated Kidney Disease in Black Individuals in the US**




Bubble plot shows the odds ratio of APOL1-mediated kidney disease (AMKD) in Black individuals in the US with a high-risk *APOL1* genotype compared with Black individuals with a low-risk *APOL1* genotype. The area of each bubble represents the population attributable risk—the proportion of the incidence of each type of kidney disease that is attributed to high-risk *APOL1* genotype.

Odds ratios from Friedman and Pollak.[3] Estimated number of affected individuals was extrapolated from United States Renal Data System. Population attributable risk was calculated from odds ratio and the frequency of high-risk *APOL1* genotype in the Black US population.

CKD indicates chronic kidney disease; HTN-ESKD, hypertension-attributed end-stage kidney disease; and FSGS, focal segmental glomerulosclerosis.