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APOL1 Kidney Risk Alleles: Population Genetics and Disease Associations

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Abstract

APOL1 kidney disease is a unique case in the field of the genetics of common disease: 2 variants (termed G1 and G2) with high population frequency have been repeatedly associated with nondiabetic CKDs, with very strong effect size (odds ratios 3–29) in populations of sub-Saharan African descent. This review provides an update on the spectrum of APOL1 kidney disease and on the worldwide distribution of these kidney risk variants. We also summarize the proper way to run a recessive analysis on joint and independent effects of *APOL1* G1 and G2 kidney risk variants.

Keywords

Glomerular disease; Apolipoprotein L1; African admixture; *APOL1* demographics; Chronic kidney disease

Introduction

In 2010, 2 *APOL1* genetic variants (termed G1 and G2) were identified, which are both very frequent on African-derived chromosomes and strongly associated with FSGS and HIV-associated nephropathy (HIVAN).^{1,2} These associations were confirmed and extended to other glomerular diseases, emphasizing the importance of ApoL1 variant proteins for podocyte and, perhaps, kidney microvascular injury. ApoL1 evolved as an innate resistance factor against trypanosomes and, possibly, other pathogens.^{3–6} Although the mechanism of ApoL1-mediated pathogen lysis is fairly well worked out,^{4–6} its role in podocyte or other kidney cells remains elusive. This review will provide an update on the demographics of the APOL1 trypanolytic variants and on the spectrum of APOL1-associated nephropathies. Finally, we will discuss the recessive model of inheritance for the kidney risk alleles and provide advice on the correct way to analyze the joint and independent effects of *APOL1* variants.

APOL1 Variants and Haplotypes

The *APOL1* gene encodes the ApoL1 protein, which protects against human African trypanosomiasis (HAT, the cause of African sleeping sickness) by lysing the disease-causing trypanosomes.^{4,7} ApoL1 trypanolytic activity is determined by 3 protein domains encoded by the terminal *APOL1* exon: a pore-forming domain, a pH-sensitive membrane-addressing domain, and the serum resistance-associated protein (SRA)-interacting domain (Fig 1A). The *APOL1* kidney risk variants are located in the terminal exon of *APOL1* within the SRA-binding domain.¹ The G1 allele is composed of 2 missense variants in nearly absolute linkage disequilibrium: G1^G (p.S342 G) and G1^M (p.I384 M). The G1^G missense variant is located within the SRA-binding domain but outside the SRA-binding epitope. In contrast, the G1^M variant and the G2 6 base pair deletion, which results in the deletion of p.N388/Y389, occur precisely within the SRA-binding epitope comprising amino acids 370 to 392.^{1,5} However, the resistance to trypanosome infection was shown to be mostly driven by G1^G, suggesting a different molecular mechanism for G1 and G2 isoforms.¹ The G1 and G2 variants arose independently on separate chromosomes. Because of the close physical proximity of the 2 variants—the G1^M and the G2 variant sites are separated by only 12 base pair—they have not undergone a recombination event that would bring them together on the same chromosome,¹ so there is no haplotype carrying both G1 and G2 (Fig 1B).

As discussed subsequently, the occurrence of the 2 variants on separate chromosomes has important implications when testing for genetic associations. Although the G1 variants are in near-absolute linkage disequilibrium and usually occur together on the same chromosome, G1^G is infrequently observed in the absence of G1^M. For simplicity, we will consider common G1^{GM} haplotype to be “G1.” By analogy with the G1/G2 nomenclature, the wild-type or ancestral haplotype is termed G0. The G1/G2 variants and haplotype frequencies, shown in Figure 1B, are for African Americans; however, these same haplotypes have been observed throughout sub-Saharan Africa in surveys of African ethnic groups represented in the Human Genome Diversity Project and International HapMap Project (C.A.W., unpublished Sanger sequence data).² As a practical matter, deviations from these expected haplotypes indicate genotypic, database, or sample handling errors rather than recombination events.

Population Genetics of *APOL1*

Recent data have clarified the frequency distribution of G1 and G2 variants in Africa and worldwide (Table 1, Fig 2).^{2,8–13} The G1 and G2 alleles are most frequent in Western Africa, with the highest G1 allele frequencies found in Ghana and Nigeria (>40%). The G2 variant also showed similar frequency clines, again with the highest frequencies in Ghana and Nigeria (allele frequency 6%–24%). There are distinctive west-east and west-south clines for both the G1 and G2 alleles. The prevailing hypothesis is that the *APOL1* variants arose in the last 10,000 years on sub-Saharan Africa chromosomes, likely in West Africa,¹ where they have been subject to intense recent positive selection.³ Interestingly, only the Yoruba people from Nigeria sampled by the Human Genome Diversity Project and the International HapMap Project show convincing evidence of a recent selective sweep, in the

form of extended haplotype homozygosity in the region of chromosome 22 harboring the *APOL1* alleles.^{1,14}

The variants are found outside Africa at high frequencies only in persons of recent African ancestry. The trans-Atlantic slave trade, lasting primarily from the 16th to 19th centuries, resulted in the forced diaspora of more than 11 million Africans from the Atlantic coastal regions of Africa and to a lesser degree from southeast Africa to the Caribbean and the Americas.¹⁵ The high allele frequencies of *APOL1* G1 and G2 variants in African Americans and in African and Hispanic Caribbeans reflect the *APOL1* G1 and G2 frequencies along the Atlantic coast of Africa, the source of the Atlantic slave trade (Table 1).¹⁶ Among 3 surveys of African Americans, G1 variants were found on 20% to 22% of chromosomes and G2 variants were found on 13% to 15% (Table 1); approximately 10% to 15% of African Americans carry 2 *APOL1* kidney risk alleles. Hispanics from the New York region, many of whom migrated from the Caribbean and have African admixture, also carry *APOL1* risk alleles but at much lower frequencies.^{9,17}

***APOL1* G1 and G2 Prevalence Is Not Coincident With *Trypanosoma brucei rhodesiense* Endemic Regions**

The World Health Organization reports that HAT is restricted to the 36 sub-Saharan countries within the geographical range of the transmitting tsetse fly.¹⁸ *Trypanosoma brucei rhodesiense* occurs in 13 of the countries in east and central Africa, causing acute HAT and accounts for only 2% of cases. A second subspecies, *Trypanosoma brucei gambiense*, is widely distributed across 24 countries in West and Central Africa, causes chronic HAT, and accounts for the vast majority of cases of African sleeping sickness. Uganda is the only country where both forms of HAT are found: *T brucei rhodesiense* HAT is found in the northwestern region of the country and *T brucei gambiense* HAT in the southeastern region.^{18,19} The Democratic Republic of Congo accounted for 83% of reported HAT in 2012; elsewhere HAT is either under-reported because of the lack of surveillance or transmission has declined or stopped.

Of the 36 HAT endemic countries, *APOL1* genotypes have been determined for 34 populations in 14 countries, representing 2204 individuals, that is, 4408 chromosomes (Fig 2 and Table 1). Of the 34 African populations with genotypic data, G1 variants were detected in 23 (68%), 7 of which were from *T brucei rhodesiense* endemic regions. The G2 variant was observed in 27 of 34 (79%) different ethnic groups. It remains a mystery why G2 has not been as strongly selected as G1, given that G2 is a more potent killer of *T brucei rhodesiense* and arose earlier than G1.¹ This suggests that there may be aspects of the evolutionary story that remain to be learned.

Although the G1 and G2 variants restore trypanolytic potential only against *T brucei rhodesiense*, the African ethnic populations with the highest prevalence of G1 and G2 variants are found in *T brucei gambiense* endemic regions in West Africa, and this subspecies is resistant to lysis by the G1 and G2 protein isoforms. There are several possible scenarios that might explain this puzzle. First, the tsetse fly vectors for *T brucei rhodesiense* may have been displaced by the tsetse fly vector for *T brucei gambiense* because of environmental changes (eg, climate or forest depletion) in West Africa. Of the 8 tsetse fly

species that transmit *T brucei rhodesiense* or *T brucei gambiense*, only *Glossina fuscipes*, the forest tsetse fly, is a vector for both subspecies.^{19,20} Second, the *APOL1* variants may have been sufficiently prevalent in human populations to reduce the burden of *T brucei rhodesiense* below a threshold for transmission efficiency. Third, the *APOL1* variants may have been selected for in West Africa by extracellular or intracellular pathogens other than *T brucei rhodesiense*. Whatever the pathogenic cause of the selective sweep on these variants, they have risen to extremely high frequency in West Africa and have introgressed into the gene pool of many sub-Saharan African ethnic groups from recent human migrations, likely from the Bantu expansion out of West Africa that has occurred over the past 5000 years.¹⁶

The map of frequency distribution drawn from various sources indicates that *APOL1* G1 and G2 alleles are found throughout sub-Saharan Africa, albeit with widely differing frequencies (Fig 2).^{2,8–13} It also graphically shows the paucity of *APOL1* genotypic data from central Africa, particularly where *T brucei rhodesiense* is endemic. The punctuated distribution of *APOL1* alleles and the blank spots on the map highlight the critical need for extensive sampling of genome sequences among diverse African ethnic groups throughout Africa to catalog the extent of genetic diversity and to find clues for human diseases, some of which may result from pathogen-selected genes. The National Institutes of Health and the Wellcome Trust have funded the Human Heredity and Health in Africa (H3Africa) initiative to carry out large-scale population studies to reveal the extent and character of diversity throughout Africa. The long-term objective is to gain further understanding of the intersection of genetic variation and environmental factors, such as human pathogens, with diseases including kidney diseases.²¹

Spectrum of *APOL1*-Associated Kidney Disease

Table 2 presents *APOL1* associations with specific kidney diseases and histopathologies. Case-control studies highlight the strong effect sizes (up to 29) and high frequency (up to 72%) of cases that carry 2 risk alleles for HIVAN, primary focal segmental glomerulosclerosis (FSGS),² Lupus collapsing glomerulopathy,^{22,23} sickle cell disease nephropathy,²⁴ and hypertension-attributed arterionephrosclerosis.²⁵ Also shown in Table 2 are the correlations of 2 *APOL1* risk alleles with specific histopathologies in a series of biopsies from HIV-positive patients with kidney disease. Carriage of 2 *APOL1* risk alleles was highly elevated in HIVAN patients with collapsing glomerulosclerosis (62%).²⁶ Among individuals with non-HIVAN kidney disease, the presence of 2 *APOL1* risk alleles was elevated for FSGS (63%).²⁷ Of the group of HIV-positive patients carrying 0 or 1 risk allele, only 12% had FSGS, but more than 40% had HIV immune complex disease (HIVICK). HIVICK appears not to be associated with *APOL1* risk variants, although an association with HIVICK cannot be excluded because of the limited sample size. In addition to these specific histopathologies, carriage for 2 risk alleles was also associated with increased risk of proteinuria (> 200 mg/g) in HIV-positive women enrolled in the Women's Interagency HIV Study.²⁸

These studies reveal the uniqueness of *APOL1* associations with specific kidney histopathologies. In contrast to most other complex disease genes, *APOL1* variants are both very frequent and have substantial penetrance. It is a widely held tenet in the field of human

genetics that common variants generally have small effect sizes (low penetrance), whereas rare variants have the potential to have moderate-to-high penetrance as natural selection will tend to eliminate deleterious alleles from the gene pool.²⁹ Although this concept is generally borne out, in a situation of strong selection by lethal, endemic pathogens that lead to selective sweeps on the protective variant, pathogenresistant variants with deleterious properties may rise to high frequency, as is the case for the sickle cell trait and the *APOL1* trypanolytic G1 and G2 alleles.¹ In the heterozygote state, *APOL1* variants protect against trypanosomes and likely other pathogens, but in the homozygous or compound heterozygote state (“recessive” model), the variants contribute to kidney injury.^{1,2}

The strongest effect size reported for *APOL1* associations with kidney disease is for HIVAN (odds ratio [OR] = 29, Table 2).³⁰ Interestingly, Skorecki and colleagues speculated years before the discovery of the chromosome 22 association with glomerular disease that Ethiopians would lack the “African renal susceptibility gene.”³¹ This was based on the observation that HIVAN was never diagnosed in black HIV-positive Ethiopians, in contrast to other African ancestry populations where HIVAN was a frequent manifestation of untreated HIV-1 infection.³² All 4 populations lacking both *APOL1* G1 and G2 variants are located within Ethiopia (Fig 2), supporting a causal role for *APOL1* G1 and G2 variants in HIVAN development.⁹

Additional studies have shown that the *APOL1* G1 and G2 are strongly associated with nondiabetic end-stage kidney disease (ESKD) and hypertension-attributed ESKD (OR ~7), but no association has been reported for diabetic ESKD in case-control studies, consistent with studies identifying the chromosome 22 region only with nondiabetic ESKD.^{25,33–36} *APOL1* G1 and G2 variants are also recessively associated with overall burden of nondiabetic CKD, but not diabetic CKD, in the Dallas Heart Study a large population-based cohort study.³⁷ In the Atherosclerosis Risk in Communities study *APOL1* risk alleles were associated with a 1.5-fold increased risk for CKD, and among those who developed CKD, there was a 1.9-fold increased risk of progression to ESKD regardless of diabetic status at study entry.³⁸ Recently, carriage of 2 *APOL1* risk alleles was associated with increased rate of *progression* to clinical end points in African Americans enrolled in the Chronic Renal Insufficiency Cohort, nearly half of whom had diabetes, and the African American Study of Kidney disease and hypertension.³⁹ This was the first report showing an *APOL1* association with declining estimated glomerular filtration rate and more rapid progression to clinical end points in African American patients with diabetes.

Finally, *APOL1* risk variants were recently associated with atherosclerotic cardiovascular disease (CVD) in 2 independent cohorts, the Jackson Heart Study and the Women’s Health Initiative.⁴⁰ Although CKD is a risk factor for CVD, these results were independent of CKD or traditional CVD risk factors.⁴⁰ Therefore, the approximately 14% of African Americans bearing 2 *APOL1* risk alleles (Fig 1B) are at substantially greater risk of developing CKD and possibly CVD compared with those carrying no or 1 *APOL1* risk allele or compared with European Americans.

Recessive Model

Most reports argue for a strong recessive model of inheritance for *APOL1* kidney risk alleles. Although effect size is much stronger for the recessive model, there are reports of additive or dominant associations for G1 but not for G2,⁴¹ and of a main effect for G1 but not for G2,⁴² suggesting that G2 might have a weaker or no independent effect. However, the apparent lack of association for the G2 allele is largely because of a statistical analysis artifact introduced by the failure to account for the presence of the second risk variant as advised by Kopp and colleagues² (see detailed analytical description subsequently). Kopp and colleagues² reported a weak association for G1 with FSGS (OR = 1.9) for carriage of 1 risk allele vs 0 risk allele, but the association with FSGS was much stronger for the G1 recessive model (OR = 23) for carriage of 2 risk alleles compared with 1 or no risk allele. In addition, the authors showed that the combination of any 2 risk alleles, in the homozygote or compound heterozygote state (G1/G2), is equivalent in effect size, reinforcing the argument for a strong recessive model. However, we cannot completely exclude that there might be an additive or dominant inheritance model for other kidney phenotypes or that there may be permissiveness for kidney injury for heterozygotes.^{2,10,43,44} Along this line, in 2 independent studies, the age-of-onset for dialysis for nondiabetic ESKD was a decade earlier for carriers of 2 risk alleles and 5 years earlier for carriers of a single G1 risk allele compared with carriers of a single G2 allele or to G0 homozygotes.^{10,44}

Statistical Analysis of *APOL1* Kidney Risk Alleles

Because the G1 and G2 alleles always occur on separate chromosomes and have equivalent effect sizes for kidney disease,² the independent frequencies for G1 and G2 can be added to calculate the burden of risk variants in a population.¹ To assess the joint effects of G1 and G2, the number of G1 and G2 risk alleles carried by each individual is summed; each individual will carry 2, 1, or 0 risk alleles: G1 and G2 homozygotes and G1/G2 compound heterozygotes represent 2 risk alleles, G1/G0 and G2/G0 heterozygotes represent 1 risk allele, and G0/G0 corresponds to 0 risk allele as shown in Figure 3A for normal controls and primary FSGS.

If one tries to assess the recessive effect of G1 by itself (2 G1 alleles, ie, G1/G1 – vs 0 or 1 G1 allele), the alternative G2 risk genotypes in the comparison group will weaken the recessive association of G1 with the phenotype while creating a spurious dominant effect because of the G1/G2 genotypes included among individuals with 1 copy of G1 (Fig 3B). Similarly for assessing the recessive effect of G2, G1 risk genotypes will be included in the comparison groups, and because G1 is more frequent in many populations, the G2 association may be obscured leading to the false conclusion that G2 has a weak or no association with the phenotype (Fig 3C).

To determine G1 or G2 independent effects, it is necessary to remove all individuals carrying the other risk allele from the analysis; the alternative of stratifying by the other factor is problematic since the associations, for example, 1 copy of G1 may be expected to be radically different depending on whether G2 is present.

Conclusions

The recessive association of *APOL1* G1 and G2 risk variants with nondiabetic CKD is an unusual story of high-frequency variants with strong effect size, contrary to the “common disease-common variant” paradigm.^{45,46} There is evidence that *APOL1* risk variants are associated with more severe disease in diabetic and hypertensive patients with CKD, the 2 leading causes of ESKD; whether this is evident that *APOL1* variants are progression factors or that *APOL1*-associated kidney disease tends to progress more rapidly than other forms of glomerular injury remains to be determined. The burden of CKD and ESKD in the United States because of carriage of 2 risk alleles is considerable, but it may be much higher in sub-Saharan Africa, where the G1 and G2 alleles are found in most of the populations surveyed, rates of HIV infection are among the highest in the world, and treatment options are limited. For these reasons, it is essential to continue collecting data on *APOL1* G1 and G2 variants in sub-Saharan African populations and deciphering the molecular mechanisms that damages kidney cells to translate *APOL1* genetic data to the nephrology clinic.

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CLINICAL SUMMARY

- *APOL1* kidney risk alleles (G1 and G2) are common throughout sub-Saharan Africa and in individuals with African admixture.
- *APOL1* risk alleles protect against trypanosome infection and increase risk for CKD.
- Approximately 14% of African Americans carry 2 *APOL1* risk alleles.
- *APOL1*-mediated kidney disease follows a recessive mode of inheritance.
- *APOL1* G1 and G2 risk alleles are strongly associated with many forms of CKD and those with 2 risk alleles experience more rapid progression to end-stage kidney disease.

Figure 1. ApoL1 protein structure and haplotype distribution among African Americans. (A) Domain structure of ApoL1 protein, with the location of the G1 allele (S342 G and I384 M) and G2 allele (NYK388–389K). (B) Haplotype and variant frequencies for the general African American population.² For the G1 alleles, the G1^{GM} refers to the genotype with both mutations and G1^{GI} refers to S342 G without I384 M. Abbreviations: BH3, Bcl2 homology domain 3; SRA, serum resistance antigen (of *Trypanosoma brucei rhodesiense*).

Figure 2.

Geographic distribution of *APOL1* risk alleles and of *Trypanosoma brucei* subspecies.

Shown are the distributions of G1 and G2 alleles among population groups, mostly in sub-Saharan Africa, together with the population ranges for *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*.¹⁸ The Great Rift Valley is shown as line running from southwest to northeast. The population numbers refer to Table 1.

Figure 3.

Importance of considering both G1 and G2 alleles in the genetic analysis. Spurious or attenuated associations occur when *APOL1* G1 or G2 are considered separately. (A) Analysis by count of risk alleles; bars show frequency of each genotype among FSGS controls and cases.² Genotypes with 2 risk alleles (red) are strongly associated; genotypes with 1 or no risk alleles (yellow) show weak or no associations. There is no significant difference in disease susceptibility between subjects carrying 1 and no risk alleles. Analysis that considers G1 or G2 separately confounds the association by bringing risk genotypes—genotype with 2 risk alleles—into the groups carrying 1 or no copies of G1 or G2, respectively. (B) Analysis considering the number of copies of G1. Here a significant difference is observed in frequency of FSGS between individuals with 1 copy of G1 and individuals with no copies, suggesting a dominant effect. However, this is driven by the high frequency of individuals with the G1/G2 genotype—individuals with 2 risk alleles, but only 1 copy of G1—among FSGS cases. (C) Analysis considering the number of copies of G2. A much weaker recessive disease association is seen—this is significant with the data shown but may not be with weaker data or smaller effect sizes for a particular phenotype—because of the rarity of the G2/G2 genotype and because the more frequent G1/G2 and G1/G1 genotypes occur only in the comparison (one and no copies of G2) groups.

Table 1

Prevalence of *APOLI* G1 and G2 Variants in Global Populations

Map Ref.	Population	Country	%G1 ^G		%G1 ^M		%G2		Source	References
			p.S342	G	p.I384	M	p.N388/Y389			
West Africa										
1	Mandenka	Senegal	5		2.4		21.4		HGDP	Kopp et al ²
2	Yoruba	Nigeria	45.2		45.2		7.5		HapMap	Kopp et al ²
2	Yoruba	Nigeria	45.2		45.2		16.7		HGDP	Kopp et al ²
2	Yoruba	Nigeria	39		39		6		–	Ko et al ⁸
3	Igbo	Nigeria	30.2		30.2		24.4		–	Ulası et al ¹¹
4	Bulsa	Ghana	11.4		11.4		21.4		–	Tzur et al ¹⁰
5	Asante	Ghana	40.9		41.2		12.9		–	Tzur et al ¹⁰
West Central Africa										
6	Fulani	Cameroon	0		0		8		–	Ko et al ⁸
7	Lemende	Cameroon	0		0		3		–	Ko et al ⁸
8	Mada	Cameroon	3		3		3		–	Ko et al ⁸
9	Bakola	Cameroon	5		5		5		–	Ko et al ⁸
10	Somie	Cameroon	16.4		15.3		12.3		–	Tzur et al ¹⁰
11	Far North-CMR/Chad	Cameroon	0.8		0		3.3		–	Tzur et al ¹⁰
12	COG	Republic of Congo	10.9		9.3		4.5		–	Tzur et al ¹⁰
Central Africa										
13	Biaka	Central African Republic	4.2		4		10.0		HGDP/Kidd	Kopp et al ²
14	Mbuti	Democratic Republic of Congo	0		0		3.8		HGDP/Kidd	Kopp et al ²
North Africa										
15	Mozabite	Algeria	1.8		1.8		0		HGDP	Kopp et al ²
16	Kordofan	Sudan	0		1.7		5		–	Tzur et al ¹⁰
17	Afar	Ethiopia	0		0		0		–	Tzur et al ¹⁰
18	Amhara	Ethiopia	0		0		0		–	Tzur et al ¹⁰
19	Annuak	Ethiopia	2		2		2.7		–	Behar et al ⁹
20	Maale	Ethiopia	0		0		0		–	Tzur et al ¹⁰

Map Ref.	Population	Country	p.S342 G	%G1 ^G	p.I384 M	%G1 ^M	p.N388/Y389	%G2	N	Source	References
21	Oromo	Ethiopia	0	0	0	0	0	0	76	–	Tzur et al ¹⁰
East Africa											
22	Luhya	Kenya	5.1	5.4	5.4	7.1	90	HapMap	Kopp et al ²		
23	Borana	Kenya	0	0	0	3	18	–	Ko et al ⁸		
24	Sengwer	Kenya	0	0	0	3	19	–	Ko et al ⁸		
25	Bantu-NE	Kenya	4.5	4.5	4.5	4.5	12	HGDP	Kopp et al ²		
26	Hadza	Tanzania	5	5	5	0	19	–	Ko et al ⁸		
27	Iraqw	Tanzania	5	5	5	3	19	–	Ko et al ⁸		
28	Sadawe	Tanzania	5	5	5	0	19	–	Ko et al ⁸		
Southeastern Africa											
29	MWI	Malawi	12	12	12	12	50	–	Tzur et al ¹⁰		
30	Sena	Mozambique	12.2	12.0	11.0	11.0	51	–	Tzur et al ¹⁰		
Southern Africa											
31	San	Namibia	0	0	0	1	7	HGDP	Kopp et al ²		
32	Motswana	Botswana	5.5	5.13	5.5	5.5	570	–	Winkler/Wester*		
33	Bantu-SA	South African	7.1	7	21.4	8	HGDP	Kopp et al ²			
34	Zulu	South African	5.3	5.0	5.5	113	–	Bhimma/Winkler*			
Total							2204				
Other world populations											
South and Central Asia											
Balochi		Pakistan	0	0	2.1	25	HGDP	Kopp et al ²			
Other		8 Populations	0	0	0	195	HGDP	Kopp et al ²			
Eastern Asia		18 Populations	0	0	0	231	HGDP	Kopp et al ²			
Europe (8 populations)		8 Populations	0	0	0	161	HGDP	Kopp et al ²			
Oceania (2 populations)		2 Populations	0	0	0	39	HGDP	Kopp et al ²			
Europe (8 populations)		8 Populations	0	0	0	161	HGDP	Kopp et al ²			
Native Americans		5 Populations	0	0	0	107	HGDP	Kopp et al ²			
North America											
African Americans		Mid-Atlantic United States	22.1	22.0	13.4	383	–	Kopp et al ²			

Map Ref.	Population	Country	%G1 ^G			%G1 ^M		%G2		N	Source	References
			p.S342	G		p.I384	M	p.N388/Y389				
African Americans		Southwest United States	19.7			19.7		NR		61	1000GP	1000GP ¹³
African Americans		–	22.6			22.2		13.4		2200	ESP6500	ESP6500 ¹²
African Americans		New York	20.9			20.4		15.3		148	–	Tzur et al ¹⁰
European Americans		–	0			0		0		4000	ESP65000	ESP6500 ¹²
European Americans		Utah	0			0		0		85	1000GP	1000GP ¹³
US Hispanic-New York City		New York	1.8			1.8		NR			–	Tzur et al ¹⁰
US Mexicans-Los Angeles		California	0			0		0		66	1000GP	1000GP ¹³

Abbreviation: NR, not reported.

* Unpublished data from R.B. and C.A.W. for Durban, South Africa. and C.W.W., M.E., and C.A.W. for Gaberone, Botswana.

Table 2***APOL1* Risk Alleles and Risk for Glomerular Disease Among African Americans**

	Results			References
	N	OR or RR	% with 2 RA	
Case-control studies				
HIV-associated nephropathy	54	29 (13–68.5)	72	Kopp et al ²
Primary FSGS	217	17 (11–26)	72	Kopp et al ²
Lupus collapsing glomerulopathy	26	5.4 (0.4–12.1)	50	Larsen et al ²²
Lupus with end-stage kidney disease	855	2.7 (1.8–4.2)	25	Freedman et al ²³
Sickle cell disease nephropathy	520	3.4 relative risk for proteinuria	45	Ashley-Koch et al ²⁴
Hypertension-attributed nephropathy	675	2.6 (1.8–3.6); 4.6 (3.1–6.8) in progressors	23	Lipkowitz et al ²⁵
Case-only biopsy series from HIV-positive patients				
HIV-associated nephropathy	60	–	62	Atta et al ²⁶
HIV+FSGS	35	–	63	Fine et al ²⁷
HIV immune complex kidney disease	31	–	3	Fine et al ²⁷

Abbreviations: AASK, African American Study of Kidney disease and hypertension; OR, odds ratio; RA, risk alleles; RR, relative risk. Associations of *APOL1* risk variants with specific kidney disease are shown, in descending order of 2 RA carriage. The study of sickle cell anemia compared the RR for proteinuria conferred by *APOL1* risk alleles. The study of lupus ESKD used lupus subjects lacking nephropathy as controls. Studies of pooled chronic kidney disease are omitted. The ORs with 95% confidence intervals in parentheses are shown if reported. For arterionephrosclerosis in the AASK study, progression was defined as urine protein/creatinine >0.6 g/g or serum creatinine >4 mg/dL (serum creatinine >3 mg/dL or end-stage kidney disease) during follow-up.