World Journal of Nephrology

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DOI: 10.5527/wjn.v4.i2.295

*World J Nephrol* 2015 May 6; 4(2): 295-306
ISSN 2220-6124 (online)




# African origins and chronic kidney disease susceptibility in the human immunodeficiency virus era

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Author contributions: Kasembeli AN, Duarte R, Ramsay M and Naicker S planned the review, wrote specific sections and reviewed the paper; Kasembeli AN was responsible for producing the first complete draft.
Supported by NIH Fogarty International Center Grant, No. 1D43TW008330-01A1; Millennium Promise Award, Non-communicable Chronic Diseases Leadership Training Program, NHLS Research Trust, Division of Nephrology Research Fund, University of the Witwatersrand, Johannesburg and FRC Individual grant, University of the Witwatersrand, Johannesburg.
Conflict-of-interest: None.

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Received: July 9, 2014
Peer-review started: July 10, 2014
First decision: October 27, 2014
Revised: January 6, 2015
Accepted: January 18, 2015
Article in press: January 20, 2015
Published online: May 6, 2015

## Abstract

Chronic kidney disease (CKD) is a major public health problem worldwide with the estimated incidence growing by approximately 6% annually. There are striking ethnic differences in the prevalence of CKD such that, in the United States, African Americans have the highest prevalence of CKD, four times the incidence of end stage renal disease when compared to Americans of European ancestry suggestive of genetic predisposition. Diabetes mellitus, hypertension and human immunodeficiency virus (HIV) infection are the major causes of CKD. HIV-associated nephropathy (HIVAN) is an irreversible form of CKD with considerable morbidity and mortality and is present predominantly in people of African ancestry. The APOL1 G1 and G2 alleles were more strongly associated with the risk for CKD than the previously examined MYH9 E1 risk haplotype in individuals of African ancestry. A strong association was reported in HIVAN, suggesting that 50% of African Americans with two APOL1 risk alleles, if untreated, would develop HIVAN. However these two variants are not enough to cause disease. The prevailing belief is that modifying factors or second hits (including genetic hits) underlie the pathogenesis of kidney disease. This work reviews the history of genetic susceptibility of CKD and outlines current theories regarding the role for APOL1 in CKD in the HIV era.

**Key words:** Chronic kidney disease; Genetics; African ancestry; Human immunodeficiency virus; APOL1; MYH9; Human immunodeficiency virus-associated nephropathy



**Core tip:** There are striking ethnic differences in the prevalence of chronic kidney disease, including human immunodeficiency virus (HIV)-associated nephropathy (HIVAN), in people of African ancestry suggestive of genetic predisposition. The APOL1 G1 and G2 alleles

are more strongly associated with the risk for HIVAN than the previously reported MYH9 E1 risk haplotype in individuals of African ancestry. The high prevalence of HIVAN among individuals of African ancestry could be a result of high frequencies of APOL1 risk variants as well as the prevalence of HIV-1 subtypes and modifying factors or second hits underlying the pathogenesis of kidney disease.

Kasembeli AN, Duarte R, Ramsay M, Naicker S. African origins and chronic kidney disease susceptibility in the human immunodeficiency virus era. *World J Nephrol* 2015; 4(2): 295-306 Available from: URL: http://www.wjgnet.com/2220-6124/full/v4/i2/295.htm DOI: http://dx.doi.org/10.5527/wjn.v4.i2.295

## INTRODUCTION

Chronic kidney disease (CKD) is a major public health problem worldwide[1]. Mortality due to CKD nearly doubled worldwide between 1990 and 2010, and is now positioned at 18$^{th}$ as a cause of death in the Global Burden of Disease Study[2] and at 5$^{th}$ position in South Africa[3]. An estimated 3.2 million people were on renal replacement therapy by the end of 2013, approximately 2522000 people undergoing dialysis treatment (haemodialysis or peritoneal dialysis) and 678000 people living with renal transplants[4] and it is also estimated that CKD incidence grows by approximately 6% annually[4]. There are striking ethnic differences in the prevalence of CKD such that, in the United States, African Americans have the highest prevalence of CKD[5]. Diabetes and hypertension, which have been considered the two leading causes of CKD, together with differences in clinical, social-demographic or lifestyle factors, are insufficient to account satisfactorily for the excess risk of end stage renal disease (ESRD) in African Americans[6,7]. Africa, the second largest and the world's second most populous continent, is approximately 30.2 million square km$^2$ and composed of 54 countries[8] and more than 1.1 billion people as of 2013, accounting for 15% of the world's population[9]. It has been postulated that, by 2030, approximately 70% of the patients with ESRD will be living in low income countries such as those in sub-Saharan Africa where majority of people live on less than one dollar-a-day[10,11]. The increased burden of CKD in Africa could be as a result of various communicable diseases such as leishmaniasis, schistosomiasis, infectious glomerulonephritis and importantly, human immunodeficiency virus (HIV) infection superimposed on non-communicable diseases such as hypertension and diabetes mellitus. These factors have resulted in the increase in CKD; several studies have shown that there is a four-fold increase in CKD in HIV uninfected individuals, compared to 18-50 fold increase in CKD in HIV positive individuals of African descent[12,13].

## HIV AND CHRONIC KIDNEY DISEASE

Acquired immune deficiency syndrome (AIDS)-associated nephropathy was originally reported in AIDS patients in the United States in 1984. Subsequently, asymptomatic HIV-infected individuals showed similar clinical and histological features, and the name was later changed to HIV-associated nephropathy (HIVAN)[14]. HIVAN is an irreversible form of CKD which is a pathologically distinct complication of HIV infection with considerable morbidity and mortality[15,16]. The odds of developing HIVAN have increased in recent years to fifty according to the United States Renal Data System[17]. There is a huge regional variation in the prevalence of HIV infection; globally, an estimated 35.3 million people were living with HIV as at 2012; in North Africa, approximately 260000 people are living with HIV; while in sub-Saharan Africa, which comprises two thirds of all people living with HIV, an estimated 25 million people are living with HIV[18]. CKD occurs in approximately 6.0%-48.5% of HIV positive patients in Africa[19]. About 24%-83% of these cases are classic HIVAN in South Africa[20-22]. HIVAN is a clinicopathological condition characterized by the presence of focal glomerulosclerosis with collapsing glomerulopathy and glomerular epithelial cell proliferation, together with microcystic tubular dilatation and interstitial inflammation[23]. Risk factors for HIVAN are older age, lower CD4 counts, high viral load, co-morbidity (such as diabetes mellitus, hypertension and hepatitis C co-infection)[24]. HIVAN is present predominantly in people of African ancestry, indicating a possible genetic predisposition[25,26]. Renal histology in HIV infected patients in South Africa is shown in Table 1. A 30-year review of 1848 renal biopsies by Vermeulen at Chris Hani Baragwanath Hospital in Johannesburg, South Africa found that focal segmental glomerulosclerosis (FSGS) comprised 29.6% of primary glomerulonephritis (GN), 24.4% of membranous GN, 23.8% of membranoproliferative GN, 10.3% of minimal change disease, 4.1% of mesangial proliferative GN and 2.7% of IgA nephritis; 19.7% of the biopsies were in HIV positive individuals (Vermeulen A, MMed, University of the Witwatersrand, 2014).

The mechanism by which HIV induces glomerular injury leading to the pathologic syndrome of HIVAN is not well understood, hence a number of theories have been postulated as to how HIV causes renal injury. First, a direct viral infection of podocytes, renal parenchymal cells, especially the visceral epithelial cells of the glomerulus, and the tubular epithelial cells and as a result, this elicits cytopathic effects including proliferation and apoptosis[27]. Secondly, HIV infects the lymphocytes and macrophages that enter the kidney, resulting in the release of inflammatory lymphokines or cytokines which promote injury and fibrosis[27]. In addition, there are studies that have demonstrated that *CCR5* and *CXCR4,* the two main HIV co-receptors, that mediate entry of HIV strains into susceptible

**Table 1 Spectrum of renal histology in human immunodeficiency virus in South Africa**

| Histology | Durban[21] | JHB[20] | Cape Town[22] | JHB[1] |
|---|---|---|---|---|
| **Biopsy numbers** | **30** | **99** | **192** | **364** |
| Classic HIVAN (%) | 83 | 27 | 24.4 | 32.7 |
| FSGS | | 3 | 32.8 | 11.3 |
| HIV Immune Complex Disease (%) (mostly with hepatitis B or C co-infection) | | 21 | 30.2 | 11.8 |
| Mesangial proliferative | | 6 | | |
| Membranoproliferative (type I and III) (%) | 7 | | | 2.7 |
| Lupus-like (%) | | | | 4.4 |
| IgA | | | | |
| Membranous (%) | 13.3 | 13 | 5.2 | 7.7 |
| Exudative-proliferative | | | | |
| HIV TTP/HUS (thrombotic microangiopathy) | | | | |
| Various glomerulonephropathies (%) (heterogenous group with different aetiologies) | 7 | 41 | 24 | 29.4 |
| Minimal change (%) | | 2 | | 3.3 |
| Immunotactoid | | | | |
| Amyloidosis | | | | |

[1]Adapted from Vermeulen Alda, MMed Research report, University of the Witwatersrand, 2014[83]. JHB: Johannesburg; HIVAN: Human immunodeficiency virus-associated nephropathy; TTP: Thrombotic thrombocytopaenic purpura; HUS: Haemolytic syndrome.

cells, are not expressed by intrinsic renal cells, but are expressed in circulating and infiltrating leukocytes at sites of tubulo-interstitial inflammation[28].

## GENETIC PREDISPOSITION TO CHRONIC KIDNEY DISEASE IN PATIENTS OF AFRICAN ANCESTRY

Genetic variation plays an important role in susceptibility to common forms of disease such as diabetes, hypertension and kidney disease, with marked differences in the prevalence and sometimes the presentation, according to ethnicity and ancestry. African Americans have four times the incidence of ESRD when compared to Americans of European ancestry, supporting a causal role for genetics in the aetiology of kidney disease[12,13,29]. These observations led to the use of ancestry informative population variation data to help explain this disparity. In 2008, two groups published papers back to back in Nature Genetics, heralding the discovery of genetic association of markers in the non-muscle myosin heavy chain 9 (*MYH9*) gene on chromosome 22 with non-diabetic ESRD[30] and FSGS[31] in African Americans (Figure 1 and Table 2). Both groups used genome wide admixture mapping approaches in their analysis, showing that increased African ancestry was correlated with increased susceptibility.

The transatlantic slave trade in the 16$^{th}$ to 19$^{th}$ centuries brought in an estimated 12 million individuals from Africa (mainly West Africa) to enslavement in America[32,33] and this was the driver for the introduction of African genetic variation to America. As a consequence of this population relocation, admixture occurred with Native Americans (Amerindians) and Europeans leading to mixed genomic profiles among the group now referred to as African Americans. African Americans have, on average, about 80% African ancestry, although there are regional differences across the country[34]. Differences in allele frequencies of common and rare variants have occurred as a result of random genetic drift, selection and other forces over thousands of years of separation of the ancestral populations, with Europeans having separated roughly 40000 years ago from African populations[35]. Computational approaches take advantage of ancestry informative markers (AIMs), which are single nucleotide polymorphisms (SNPs) that show marked allele frequency differences among the ancestral populations to infer the global ancestry of individuals. Studies utilizing AIMs have shown that American populations with African, Hispanic and Caribbean origins are admixed with varying substantial components of African continental ancestry[36]. This effect of admixture helped in identifying genetic regions that affect one ancestral population and not others, which drive phenotypic associations[37] and can be measured using mapping by admixture linkage disequilibrium (MALD), which quantifies the degree of ancestry of each locus[37-39]. MALD studies were used to identify genomic regions where admixed African American patients with CKD had an excess of African genomic markers compared to unaffected individual controls[30,31]. These studies identified CKD susceptibility loci in African Americans localised to a specific genomic region on chromosome 22q12 that contains more than 21 genes, and proceeded to pinpoint the association with non-diabetic and hypertensive CKD, to markers in non-muscle myosin heavy chain 9 (*MYH9*) gene.

The *MYH9* gene was an excellent biologically plausible candidate as it has a direct link to the structure of podocytes since it codes for a 1960 amino acid protein (Myosin IIA) expressed in the podocytes and widely-distributed cellular motor protein that is essential for cytoskeleton rearrangement, cell motility, division, and

**Table 2 Summary of the studies of *MYH9* and *APOL1* variants**

| Year | Population (ancestry) | Disease | Variant | Freq. | OR (95%CI) | Ref. |
|---|---|---|---|---|---|---|
| 2008 | African Americans | Hypertensive ESRD | *MYH9* E1 | 0.67 | 1.9 (1.25-2.87) | Kopp *et al*[31] |
| | | HIVAN | *MYH9* E1 | 0.67 | 5.3 (2.40-12.90) | |
| | | FSGS | *MYH9* E1 | 0.67 | 4.5 (2.92, 7.19) | |
| | European Americans | T2DM ESRD | *MYH9* E1 | 0.04 | NS | |
| | | FSGS | *MYH9* E1 | 0.04 | 9.7 (1.07, 463) | |
| 2008 | African Americans | Hypertensive ESRD | *MYH9* E1 | 0.3 | 2.1 (1.56, 2.74) | Kao *et al*[30] |
| | | Non-diabetic ESRD | *MYH9* E1 | 0.3 | 2.2 (1.73, 2.73) | |
| | | FSGS | *MYH9* E1 | 0.3 | 3.7 (2.11, 6.34) | |
| 2009 | African Americans | Hypertensive ESRD | *MYH9* E1 | 0.75 | 2.4 (NS) | Freedman *et al*[47] |
| | | Non-diabetic ESRD | *MYH9* E1 | 0.76 | 2.5 (NS) | |
| 2009 | African Americans | T2DM ESRD | *MYH9* E1 | 0.67 | 1.4 (NS) | Freedman *et al*[44] |
| 2010 | African Americans | Non-diabetic ESRD | *MYH9* E1 | NS | 2.0 (1.37, 2.92) | Behar *et al*[46] |
| | Hispanic Americans | Non-diabetic ESRD | *MYH9* E1 | NS | 3.7 (1.67, 8.20) | |
| 2010 | American Indians | Kidney dysfunction | *MYH9* SNPs | 0.43 | 1.04 (0.79, 1.36) | Franceschini *et al*[43] Strong Heart Family Study |
| 2010 | African Americans | Non-diabetic ESRD | *APOL1* G1 | 0.46 | 4.86 (2.35, 10.06) | Tzur *et al*[29] |
| | Hispanic Americans | Non-diabetic ESRD | *APOL1* G1 | 0 | 15.48 (4.00, 60.00) | |
| 2010 | African Americans | Hypertensive ESRD | *APOL1* G1/G2 | 0.41/0.21 | 7.3 (5.60, 9.50) | Genovese *et al*[13] |
| | | FSGS | *APOL1* G1/G2 | 0.47/0.25 | 10.5 (6.0, 18.4) | |
| 2011 | African Americans | HIVAN | *APOL1* G1/G2 | 0.54/0.28 | 29.2 (13.10, 68.50) | Kopp *et al*[12] |
| | | FSGS | *APOL1* G1/G2 | 0.55/0.25 | 16.9 (11.00, 26.50) | |
| 2014 | South African blacks | HIVAN | *MYH9* E1 | 0.83 | 2.10 (0.07-60.99) | Kasembeli *et al* (Unpublished observations) |
| | | | *APOL1* G1/G2 | 0.56/0.34 | 89.10 (17.68, 911.72) | |

NS: Not stated; SNPs: Single nucleotide polymorphisms; OR: Odds ratio; Freq: Frequencies; HIVAN: Human immunodeficiency virus-associated nephropathy; FSGS: Focal segmental glomerulosclerosis; T2DM: Type 2 diabetes mellitus; ESRD: End stage renal disease; APOL1: Apolipoprotein L1; MYH9: Non-muscle myosin heavy chain 9.

cell-cell adhesion[40]. As a result of these observations, researchers concluded that *MYH9* variants that are associated with susceptibility to CKD likely play a causal role in disease pathology[41]. The high frequency of the *MYH9* associated haplotypes in African populations led to speculations of selection in Africa (Figure 2)[42]. The ethnic specificity of the association was explored with different phenotypes and different populations (Table 2) and subsequent studies provided evidence for a contribution of *MYH9* variants in early stages of CKD as well as diabetic and hypertensive-related CKD in both African Americans and Europeans, but not in Native Americans[43-45]. However, biopsy-proven forms of CKD were lacking in some of these studies and therefore, as in the case of diabetic and hypertensive nephropathies, researchers suggested that the association with *MYH9* could also reflect the presence of non-diabetic and non-hypertensive CKD. This hypothesis was supported by association with *MYH9* SNPs that were strongly associated with these types of CKD[46].

The *MYH9* SNPs with the strongest associations were categorised into three haplotype groups termed as E, S and F[42,46] and E1 was defined as the risk haplotype (rs4821480, rs2032487, rs4821481 and rs3752462), being highly associated with CKD in individuals of African descent. E1 was then further found to be highly distributed in Africa as compared to other regions of the world (Figure 2)[42]. The *MYH9* E1 haplotype explained nearly the entire excess burden of major forms of CKD in African Americans with attributable risks of 100% and 70% for HIVAN and FSGS, respectively, and a significant percentage for hypertensive nephrosclerosis risk[31,40,47]. However, despite major scientific efforts, including *MYH9* re-sequencing experiments and detailed-intense genotyping, no mutations with a clear predicted functional effect could be identified that would impact kidney function and the field began to shift toward exploring neighbouring genes on chromosome 22.

Two research groups re-analyzed the chromosome 22q12 genomic region using data from International HapMap and 1000 Genomes Projects[29,48]. The data from these studies played a vital role in the discovery of candidate SNPs in the neighbouring apolipoprotein L1 (*APOL1*) gene, approximately 20 kb downstream from the 3' end of *MYH9,* that were statistically powered to explain an increased risk of CKD in individuals of African ancestry[13,29]. The studies yielded 7479 SNPs, four of which were non-synonymous mutations in the coding region of the genes in high linkage disequilibrium with the *MYH9* E1 risk haplotype. Two of these (rs73885319 and rs60910145) were missense mutations in the last exon (exon 7) of the *APOL1* gene, which result in amino acid substitutions: Ser342Gly and Ile384Met. These two missense mutations are referred to as the G1 alleles since they were in almost complete linkage disequilibrium ($r^2$ = 1.0) with each other, and are both highly associated with CKD susceptibility. Another SNP, rs71785313, was also found in exon 7 of *APOL1* and represents a six base pair deletion resulting in loss of two amino acids (Asn388-Tyr389del), and is referred to as the G2 allele. These three codon-changing variants in the *APOL1* gene, encoding apolipoprotein L1, were found to be in strong association with HIVAN odds

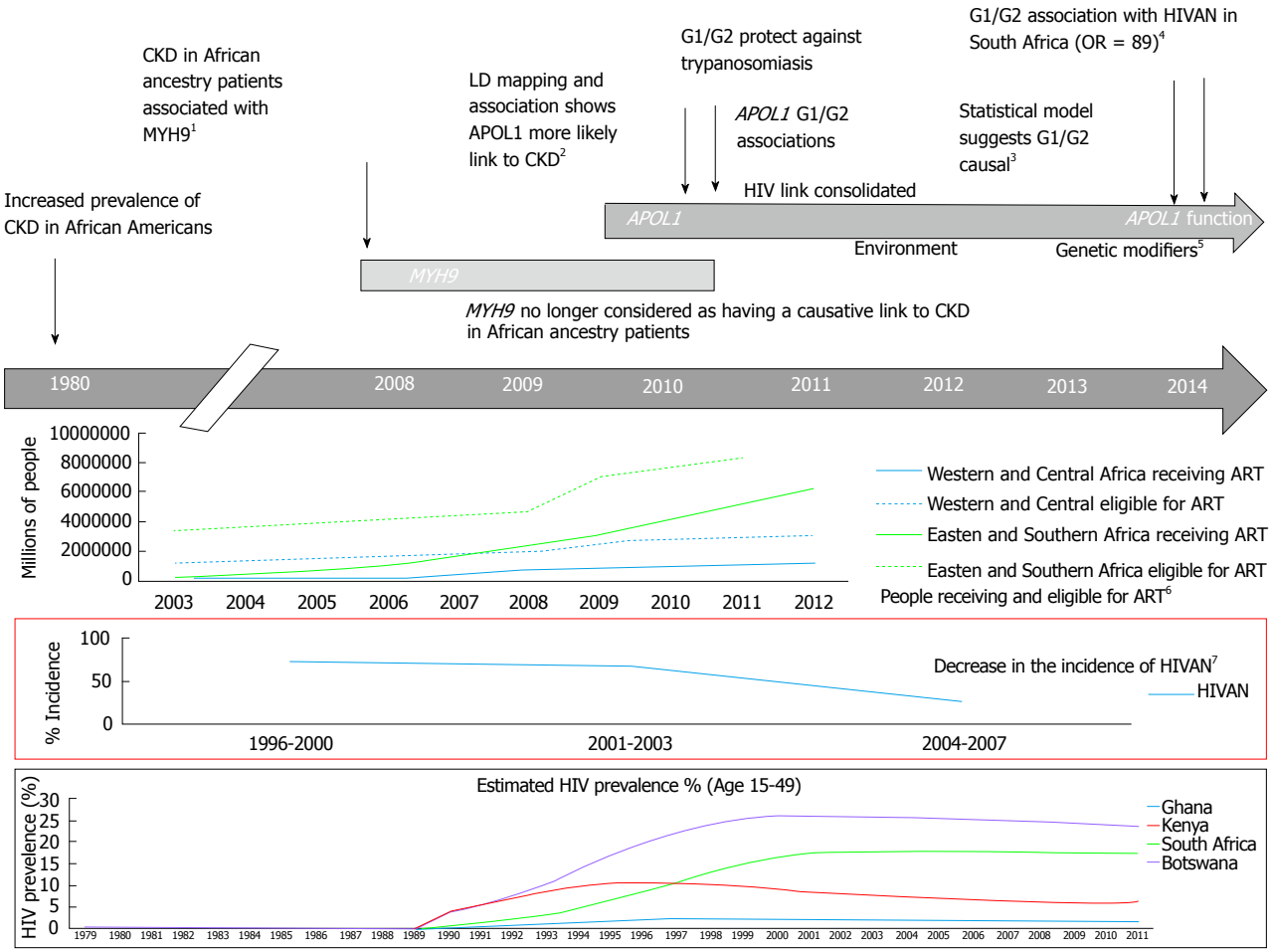


**Figure 1 Historical timeline reflecting the discovery of genetic association to chronic kidney disease in populations with African ancestry.** [1]Adapted from Kopp *et al*[31] and Kao *et al*[30]; [2]Adapted from Freedman *et al*[49], Genovese *et al*[13], Tzur *et al*[29]; [3]Adapted from Genovese *et al*[84]; [4]Adapted from Kasembeli *et al* (2014 unpublished observations); [5]Adapted from Freedman *et al*[64]; [6]Adapted from UNAIDS report on global AIDS epidemic[18]; [7]Adapted from USRDS 2012 Annual Data Report. APOL1: Apolipoprotein L1; MYH9: Non-muscle myosin heavy chain 9; ART: Antiretroviral therapy; CKD: Chronic kidney disease.

ratio (OR = 29), FSGS (OR = 17) and ESRD (OR = 7) in African Americans, for homozygotes or compound heterozygotes carrying two risk alleles[12,13,29]. They were also absent in individuals of European ancestry but common in African populations. The G1 and G2 alleles were strongly associated with the risk for CKD than the previously examined *MYH9* E1 risk haplotype in a sample of individuals of African ancestry. They are in perfect negative linkage disequilibrium, never occurring on the same parental chromosome, suggesting that these variants arose independently and due to their proximity and high linkage disequilibrium, they have remained mutually exclusive in almost all haplotypes observed[12,13]. The historical timeline reflecting the discovery of genetic association to CKD in populations with African ancestry is shown in Figure 1. The link with increased susceptibility to kidney dysfunction in the presence of HIV infection[15,16] is now well established and the association of *APOL1* risk alleles with HIVAN is of particular concern in sub-Saharan Africa, where the risk allele frequency is high (Figure 2). *APOL1* association with CKD and the postulated mechanism of action and the functional role of *APOL1* in kidney disease are explored further in the next sections.

## *APOL1* ASSOCIATION WITH CKD IN INDIVIDUALS OF AFRICAN ANCESTRY

The coding variants (G1 and G2) are suggested to be causally related to CKD and provide an explanation for selection of *APOL1*-associated CKD risk polymorphisms as a protective measure against Trypanosomiasis, an infectious disease that was common in Africa. A study by Genovese *et al*[13], (2010), comparing 205 African Americans with biopsy-proven FSGS with 180 African Americans without kidney disease as controls was performed, using SNPs from the 1000 Genomes Project belonging to Yoruba as proxies to the African American population. These SNPs revealed evidence of a strong association within a 10 kb region in the exon 7 of the *APOL1* gene. The strong signal was found to be at non-synonymous coding variants, rs73885319 (S342G) and rs60910145 (I384M) which were in perfect linkage disequilibrium ($r^2$ = 1.0). The frequency of these variants was 52% in patients and 18% in

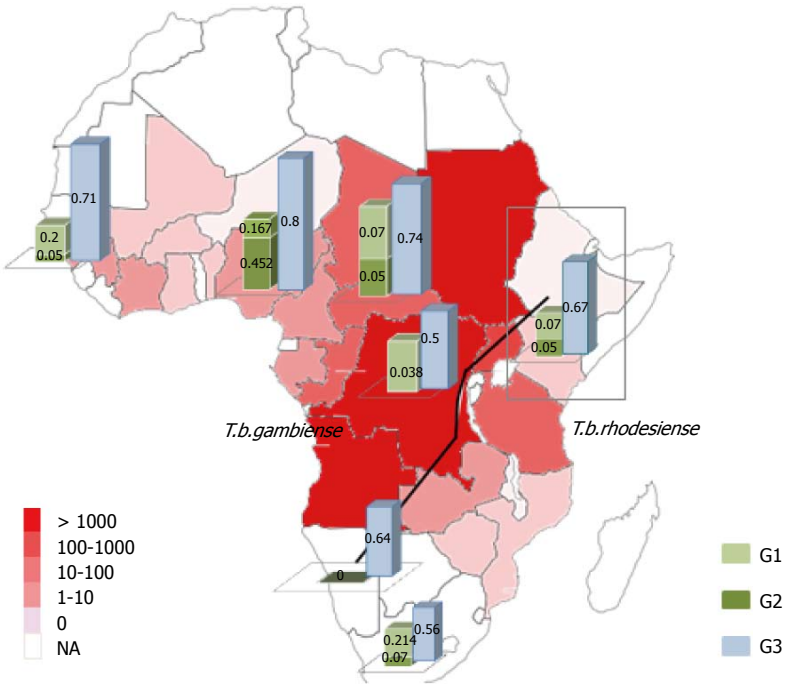


**Figure 2 Distribution of Human African Trypanosomiasis (T.b *gambiense* and T.b *rhodesiense*), MYH9 E1 and APOL1 G1 and G2 risk alleles in Africa[12,42].** The frequency of distribution of *APOL1* risk variants in Africa are represented by bar charts and overlap the areas distribution of Human African Trypanosomiasis. The numbers reflect the reported cases of Trypanosomiasis from the WHO, 2010. T.b: *Trypanosoma brucei*.

controls. They further controlled for the effects of these two variants and found a second strong *APOL1* signal, 12 base pairs from I384M. This signal is a 6-base pair deletion represented by rs71785313 which removes two amino acid residues (Asparagine-N and Tyrosine-Y). The frequency of this variant was 23% in patients and 15% in controls. The odds ratio (OR) of association for carrying at least one risk (G1-G2) allele was 10.5 (95%CI: 6.0-18.4). Controlling for both G1 and G2 did not result in significant association with *MYH9.* However, controlling for *MYH9* variants maintained significant *APOL1* signal at G1 and G2. Kopp *et al*[12], (2011), in a larger FSGS and HIVAN cohort confirmed the association but this time, a greater association was observed in HIVAN (OR = 29.2, 95%CI: 13.1-68.5, $P = 6 \times 10^{-22}$) compared to FSGS (OR = 16.9, 95%CI: 11.0 to 26.5, $P = 1.3 \times 10^{-48}$). The authors reported that 50% of African Americans with two *APOL1* risk alleles would develop HIVAN if not on antiretroviral therapy. A study in an indigenous South African black cohort showed an independent high association with HIVAN susceptibility for these G1 and G2 variants of 89-fold, 95%CI: 17.68-911.72, $P = 1.2 \times 10^{-14}$ (Kasembeli *et al*, unpublished observations). In all these studies, there was strong evidence for a contribution of *APOL1* variants to CKD (Figure 1 and Table 2).

The observed mode of inheritance of the *APOL1* risk variants was fully recessive in both FSGS and HIVAN cohorts. However, there have been instances where mild dominant effects (OR of 1.26 for one risk allele and OR of 7.3 for 2 risk alleles) have been observed in larger cohorts of hypertensive-associated CKD and geographically matched control subjects[13]. We therefore cannot fully exclude this mild dominant inheritance because this could be explained by yet "undiscovered variants" or by sporadic mutations that might occur in patients with recessive model. Furthermore, there could be a possibility of additional rare variants in *APOL1, MYH9* or other neighbouring genes that could be involved in CKD susceptibility since extended linkage disequilibrium exists in this region as a result of selective pressure[49].

## POSITIVE SELECTION FOR *APOL1*-ASSOCIATED CKD RISK VARIANTS AS A RESULT OF TRYPANOSOMIASIS EPIDEMIC IN AFRICA

It has been shown that harbouring of *APOL1* risk variants protects against Trypanosomiasis disease [Human African Trypanosomiasis (H.A.T)], otherwise known as sleeping sickness, that was epidemic in Africa many years ago and still affects millions of Africans today. This effect explains the high frequencies of these variants in the general African American and indigenous African population (Figure 2)[12,42]. The *APOL1* G1 and G2 alleles show distinct distributions among various African and African-derived populations and evidence shows these mutations to be maintained in these populations. In Yoruba from Nigeria in West Africa, the frequency is greater than 45% for G1 (Figure 2) while in African Americans the G1 frequency is approximately 20%. The battle between host and pathogen (*Trypanosoma* species), resulted in development of *APOL1* mutations (G1 and G2) that provided positive selective advantage to carriers at the expense of increased risk for CKD (Figure 3).

There are three main *Trypanosoma* species; *Trypanosoma brucei brucei, Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense*.

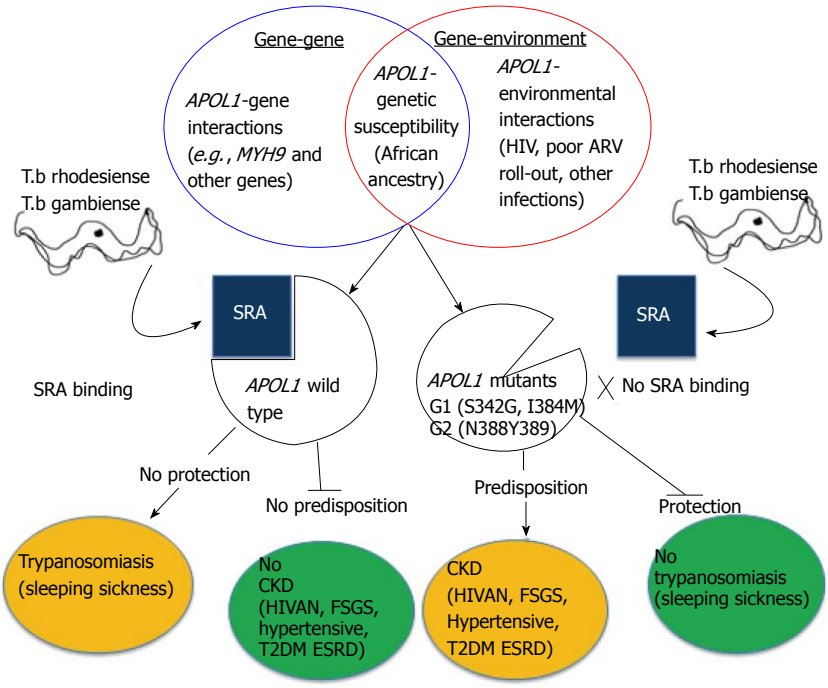


**Figure 3 Gene-Gene, Gene-Environment steering contribution to APOL1 associated CKD and the positive selection of APOL1 associated CKD variants as a result of Trypanosomiasis.** SRA: Serum resistant associated protein; HIV: Human immunodeficiency virus; T.b: Trypanosoma brucei; APOL1: Apolipoprotein L1; MYH9: Non-muscle myosin heavy chain 9; HIVAN: Human immunodeficiency virus-associated nephropathy; FSGS: Focal segmental glomerulosclerosis; T2DM: Type 2 diabetes mellitus; ESRD: End stage renal disease; CKD: Chronic kidney disease.

*Trypanosoma brucei brucei* is unable to infect humans because of the complex, trypanolytic factor (TLF) comprising of apolipoprotein L1, high density lipoprotein (HDL) particles, haptoglobin-related protein and apoliprotein A1 that is present in the human serum. This confers innate protection against *Trypanosoma brucei brucei.* However, both *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense* have evolved a mechanism to evade lysis by the TLF leading to infection, hence sleeping sickness (Figure 3)[50,51]. Apolipoprotein L1, a protein product of *APOL1* gene is usually part of TLF circulating in the blood. The *APOL1* gene is a member of the *APOL* gene family which is composed of six genes in humans (*APOL1, APOL2, APOL3, APOL4, APOL5* and *APOL6*), grouped within 619kb on chromosome 22[52]. This protein has five functional and structural domains: a secretory domain, pore forming domain, B-cell lymphoma 2 homology domain 3, membrane addressing domain, leucine zipper domain and serum resistant-associated interacting domain (SRA), listed from the N-terminal to C-terminal respectively.

The trypanolytic function of apolipoprotein L1 is the most widely studied function of apolipoprotein L1[13,53]. The secretory domain allows it to be expressed as a circulating protein, which makes it the only circulating *APOL* protein[53-56]. *Trypanosoma brucei rhodesiense* and *Trypanosoma brucei gambiense* evade the TLF lysis by expressing SRA protein that binds to the C-terminus domain of the apolipoprotein L1, in the process neutralizing its lytic activity[57,58]. However, *APOL1* variants G1 and G2, powerfully associated with CKD arose to modify the C-terminus SRA binding site of the *APOL1* gene resulting in a mutated apolipoprotein L1 that evades neutralization by the *Trypanosoma* SRA protein[58]. By so doing, apolipoprotein L1 exercised its trypanolytic activity, conferring an adaptive advantage in the endemic regions of Africa (Figure 3). This explains the distribution of G1 and G2 risk variants in Africa.

Genovese *et al*[13] reported that both G1 and G2 variants restored the lytic activity of human serum and this provides the selective advantage to carriers of two *APOL1* risk variants against sleeping sickness. These findings corroborated the evidence of the recent evolution of *APOL1* which occurred in the last 10000 years and also suggesting that these variants were selected for within Africa because they conferred protection against lethal trypanosomiasis while at the same time increasing susceptibility to CKD (Figure 3)[49]. A more recent study in a South African black population (Kasembeli *et al*, unpublished data, 2014) has found the odds to have almost doubled. The prevalence of HIVAN in Africa is variable, 24%-83% in South Africa, while in the United States, it is highest in the African American population (15.5%). This is eight-fold greater than that of HIV-infected European Americans[59]. This high prevalence of HIVAN among individuals of African ancestry could be, not only as a result of high frequencies of *APOL1* risk variants, but also the prevalence of HIV-1 subtypes circulating in Africa. For instance, HIV-1 subtype C is highly virulent, accounting for approximately 50% of all HIV infections worldwide and 98% of HIV infections in South, West and East Africa, with corresponding higher viral loads[60,61]. Another more important reason could be because sub-Saharan African countries are resource limited, and therefore roll-out of antiretroviral therapy (ART) may have been delayed, giving more room for the development of HIVAN among individuals carrying two *APOL1* risk variants. An effective roll-out of ART has been shown to reduce the occurrence of HIVAN[22,62,63]; Figure 1. Therefore, there is need for HIV screening,

surveillance, and strict implementation of World Health Organization (WHO) recommendations for ART initiation to reduce the burden of HIVAN and other forms of HIV-related CKD in Africa. At present, WHO ART guidelines 2013 for the treatment of HIV infection in Africa suggest that ART be instituted for individuals with WHO clinical stage 3 and 4 disease and in all HIV positive individuals with CD4 counts < 500 cells/μL.

## GENE-ENVIRONMENTAL MODIFIERS OF *APOL1* SUSCEPTIBILITY

*APOL1*-environmental interactions play a vital role in CKD susceptibility in individuals of African ancestry (Figure 3). These could be social demographic status, lifestyle or presence of other communicable diseases and most importantly, HIV infection coupled with poor ART roll-out. Environmental exposure to HIV was initially thought to trigger HIVAN. However, observations in African American family studies showed that relatives of HIVAN patients, in the absence of HIV infection, suffered ESRD due to other aetiologies[64]. This illustrates that there could be other environmental factors that drive the process. As described, patients with HIVAN harbouring two *APOL1* risk alleles that are untreated or undertreated for HIV infection will suffer rapid progression to ESRD[12]. In striking contrast, HIV patients without the *APOL1* risk genotype are protected from HIVAN even when HIV infection is not properly controlled. This effect is well illustrated in the Ethiopian population who appear to be protected from HIVAN since their genomes lack the *APOL1* risk variants. A study by Behar *et al*[65], in HIV infected individuals of Ethiopian origin reported complete absence of HIVAN. This led to the emphasis of skewed ethnic distribution, inter-individual variability and/or familial aggregation of HIVAN suggesting that host genetic susceptibility plays a major contributing factor. This study genotyped 676 African individuals from 12 populations, including 304 Ethiopians, for mutations in the *MYH9* and *APOL1* risk clusters. The frequency of the G1 and G2 *APOL1* risk variants was zero[65]. However, there was an increasing trend in frequency of the risk variants proceeding towards the west and south in Africa (Figure 2). This led researchers to conclude that the risk of developing HIVAN is not a African-wide problem but rather restricted to Western, Central and Southern Africa, and absent in regions of the North and North-East parts of Africa including Ethiopia. Since sleeping sickness was not an epidemic in Southern Africa, a possible explanation for the increase in prevalence of *APOL1* risk variants could be the result of migration of the bantu-speaking populations from West Africa and East Africa[66,67].

In the United States there has been a steady decline in the incidence of HIVAN with the introduction of HAART, in spite of stable frequencies of the risk variants[68]. Risk factors for progression to ESRD in HIVAN are severity of renal dysfunction, percentage of sclerotic glomeruli[25,69], lack of viral suppression[26,70], 2 *APOL1* risk alleles[63,71], while use of renin angiotensin system blockers were reported to be protective[25]. HIV-infected individuals with non-HIVAN pathology and two *APOL1* risk alleles had an almost 3-fold risk of ESRD, in spite of effective ART-suppression of viral load and use of renin-angiotensin aldosterone blockers; baseline kidney function was the strongest predictor of progression to ESRD in this study[71]. Investigators reviewing the African American study on Kidney Disease and Hypertension (AASK) and The Chronic Renal Insufficiency Cohort (CRIC) found that *APOL1* risk variants in black patients were associated with higher rates of ESRD and progression of CKD[72].

Thus HIV is considered a risk factor for HIVAN when presented with the appropriate genetic susceptibility. Either genetic risk or viral infections alone do not cause the kidney disease. Instead it is the geneenvironment interaction that is fundamental for the pathogenesis. The rapidly changing natural history of *APOL1*-associated HIVAN provides further support that HIV is an environmental risk factor[68]. Additional viral environmental modifiers have been proposed. The John Cunningham (JC) polyoma virus has been shown to maintain a reservoir in the uroepithelium of the kidney after infection and has been proposed to interact with the genetic risk posed by *APOL1* variants[73]. Divers *et al*[73] studied the relationship between the JC virus and genetic risk for kidney disease hypothesising that the presence of the *APOL1* risk variants may predispose individuals to JC infection and that this second hit may act as an additional environmental factor increasing kidney disease risk. However, paradoxically, the reverse scenario was observed where the presence of the high risk *APOL1* variants in the presence of JC virus resulted in less kidney disease. The JC virus in the kidney was postulated to either protect against other nephropathic viruses or alter cellular function as protection against other sources of glomerular injury.

## GENE-GENE INTERACTIONS AS MODIFIERS OF *APOL1*-ASSOCIATED NEPHROPATHY

Whilst nephrology research in African ancestry populations has been hampered by the lack of large genome wide- association studies, a number of gene-gene interaction studies have been conducted on pooled GWAS data in non-diabetic ESRD in African Americans and non-nephropathy controls. Results of a gene-gene interaction analysis identified several SNPs that interacted with *APOL1* risk variants (Figure 3)[74]. *MYH9* has been shown to be one of the genes linked to *APOL1* to cause CKD susceptibility. Other studies have also shown a possibility of other genes interaction with *APOL1* gene. In a replication study, eleven SNPs were validated and three genes, podocin (NPHS2; rs16854341); serologically defined colon cancer

antigen 8 (SDCCAG8; rs2802723) and SNP "near bone morphogenetic protein 4" (BMP4; rs8014363) were significant. These interactions were quantified and all show effects on *APOL1* association[75,76]. These three genes show expression in podocytes and are linked to renal disease characterised by FSGS. It has thus been postulated that they play a role in inducing podocyturia and glomerular damage.

## *APOL1*-ASSOCIATED CKD: THE FUTURE

Since there is evidence of *APOL1* association with non-diabetic forms of CKD and the role of selection in the increase in frequencies of the risk variants, it is necessary to move beyond the statistical tests of association to molecular cellular characterization to evaluate the effects of these risk variants in CKD. It has been postulated that cellular and physiologic activities of apolipoprotein L1 include involvement in autophagic and apoptosis pathways[52,77-79]. There is a general agreement that *APOL1* expression occurs in podocytes[80]. But whether there is apolipoprotein L1 expression in the tubular cells, glomerular endothelial cells, and the tunica intima and media of the renal blood vessels is uncertain. Currently, there is no definitive mechanism by which *APOL1* variants cause kidney injury but several possibilities have been proposed. Firstly, apolipoprotein L1 isoform expressed in the kidney cells may be retained in the cells and cause cell destruction *via* the apoptotic pathway since they share structural and functional similarities with proteins from the BcL2 family[77,78]. Secondly, *APOL1* as part of TLF, is directed to lysosomes to induce programmed cell death *via* the autophagic response[13,56,81]. Thirdly, circulating apolipoprotein L1 may also be important in the pathogenesis of CKD since the presence of G1 and G2 could lead to dysfunctional HDL particles leading to inflammation of vascular endothelial cells, with arteriolar nephrosclerosis[49]. There is a proven race specific relationship between *APOL1* genotype and HDL cholesterol concentration and kidney function[82]. In Han Chinese and European American populations, there was a higher HDL level in association with higher eGFR. The inverse association was observed in West Africans and African Americans. However, a significant effect was observed only in African Americans with *APOL1* risk variants (but not in West Africans). These observations have led to the view that the mechanism underlying *APOL1* nephropathy most likely involves HDL cholesterol. In addition, circulating *APOL1*, may be available for uptake by podocytes after passage across the glomerular filtration barrier and exercising their effect on the podocytes. Future studies should define the role of *APOL1* in the pathogenesis of kidney disease.

## LESSONS LEARNED FROM CKD POPULATION GENETICS

The remarkable advances in molecular genetics have enabled researchers to unravel the underlying genetic susceptibility to kidney disease in African Ancestry populations. Identification of region of 22q12.3 using MALD studies and identification of *APOL1* risk variants have raised the possibility of a personalised approach to treat several forms of kidney disease that are prevalent in African populations. As regards HIVAN, the priority for the African continent should be targeting of the modifying trigger of the disease, HIV infection, through effective treatment and prevention campaigns. Greater advances in understanding the mechanisms underlying *APOL1* pathogenesis, the identification of modifiable environmental factors and interacting genes offer the promise of novel preventive, prognostic and therapeutic measures to treat *APOL1* associated forms of kidney disease in the genetically susceptible and therefore vulnerable African descent individual.

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